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# DENDRIMERS: A NOVEL DRUG DELIVERY SYSTEM

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**ABSTRACT:** The field of Dendrimers has recently emerged as the most commercially viable technology of this century because of its wide-ranging potential applications in many fields such as: healthcare, electronics, photonics, biotechnology, engineering products, pharmaceuticals, drug delivery, catalysis, electronic devices, environmental issues and nanotechnologies. This is due to the ease of integration of these unique globular molecules with more mature areas of chemistry. The review aims majorly on the structure, types, preparation, properties, types, applications and in cancer therapy. Advances in dendrimer delivery systems, biodegradable dendrimers, and release from dendrimers can be applied to drug delivery in addition to other applications. It also focuses on the development of dendrimers into cancer drug carriers and the recent advances in the controlled degradation of dendrimers along with targeting dendrimers to mono-clonal antibodies, finally determining its robustness.

**KEYWORDS:** Dendrimers, Dendron, EPR effect, Biocompatibility

## INTRODUCTION

Dendrimers are synthetic 3D macromolecule structure with tree like branches or arms that provides high degree of surface functionalities and versatility. They may be often referred as polymers. Fritz Vogtle et. al synthesized the first cascade molecules. The word Dendrimer originated from two words, the Greek word *Dendron*, meaning tree and *neros* meaning part. It was not until 1984 that the first family of hyperbranched polymers was developed by Tomalia and his team, who described the iterative coupling of ethylene diamine(EDA) to a central ammonia core to produce a series of branched macromolecules named "starburst dendrimers."[1] Newkome et. al called them arborols from the Latin word *arbor* also meaning a tree. They considered them also as monodisperse polymers with specific size, high degree of molecular uniformity, porosity, solubility and highly functional terminal groups on the surface.[2] Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.[3]

## STRUCTURE

Dendrimers are built from a starting atom such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reaction to produce a chemical branching structure. As the process repeats, successive layers are added, and the spheres

can be expanded to the size required by the investigator. The result is a spherical macromolecular structure similar to albumin and globulin.

Dendrimers possess distinguished architectural components.

1. An initiator core.
2. Interior layers (generations) composed of repeating units radically attached to the interior core.
3. Exterior (terminal functionality) attached to the outermost interior generations.

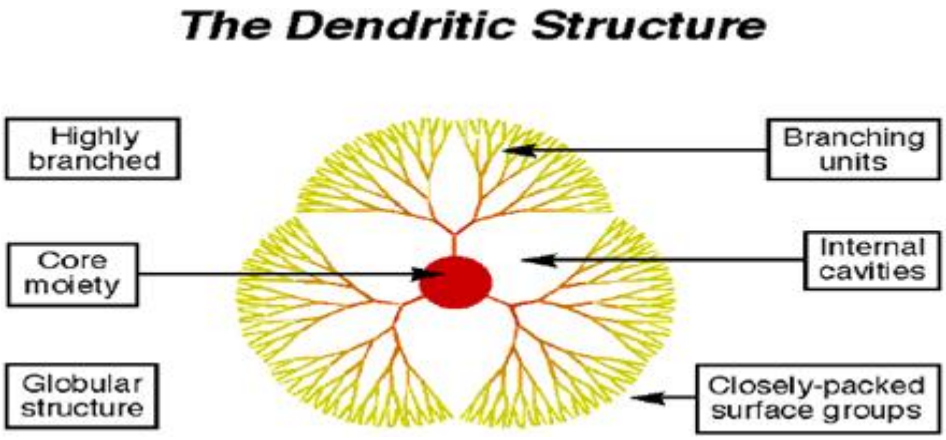


Fig No: 1 Structure of Dendrimer[4]

## TYPES OF DENDRIMERS[5]

**1**. Pamam Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10 (a molecular weight of over 9,30,000 g/mol) have been obtained (by comparison, the molecular weight of human haemoglobin is approximately 65,000 g/mol).

PAMAM dendrimers are commercially available, usually as methanol solutions. *Starburst dendrimers* is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the starlike pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

**2.** Pamamos Dendrimer

Radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

**3.** PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle. These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines.

PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. It stands for Poly (Propylene Amine). In addition, these dendrimers are also sometimes denoted "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

**4.** Tecto Dendrimer

These are composed of a core dendrimer, surrounded by dendrimers of several steps to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state, drug delivery, reporting location to reporting outcomes of therapy.

**5.** Multilingual Dendrimers

In these dendrimers, the surface contains multiple copies of a particular functional group.

**6 .**Chiral Dendrimers

The chirality in these dendrimers are based upon the construction of a constitutionally different but chemically similar branches to chiral core.

**7.** Hybrid Dendrimers Linear Polymers

These are hybrids (block or graft polymers) of dendritic and linear polymers.

**8 .**Amphiphilic Dendrimers

They are built with two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

**9.** Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

**10.** Multiple Antigen Peptide Dendrimers

It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications,
*e.g*. vaccine and diagnostic research.

**11.** Fréchet-Type Dendrimers

It is a more recent type of dendrimer developed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalisation, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media.

## METHOD OF PREPARATION

1) Divergent Method:

Divergent dendrimer synthesis is a technique that effectively grows the dendrimer structure from the initiator core to the periphery in a stepwise fashion by iterative addition of monomer units. Specifically, it is initiated by coupling of a monomer unit to a multifunctional initiator core where the dendrimer generation increases by successive addition of the building blocks to the surface of the parent dendrimer.

Tomalia and co-workers used this strategy to couple *N*-(2-aminoethyl) acrylamide monomers to an ammonia core to develop PAMAM-$NH_2$ dendrimers.[1] Each branching unit is synthesized in a two step sequence starting with exhaustive Michael addition of the acrylate ester to the ammonia core followed by amidation with excess EDA. The first step produces a half-generation, and the addition of the diamine yields the full generation.

2) Convergent Method:

The convergent approach to dendrimer synthesis was developed to address the deficiencies of the divergent method. Convergent synthesis begins with the dendrimer surface units coupled to additional building blocks to form the branching structure, thus constructing dendrons from the periphery toward the central focal point. Each dendron is then coupled through its focal point to a multifunctional core to produce the complete dendrimer.

Unlike divergent synthesis, convergent reactions are simple to purify since the desired dendrons are substantially different from the reaction byproducts, thus eliminating the need for highly efficient reactions. While the number of synthetic steps is similar for both convergent and divergent techniques, the convergent approach has fewer non-ideal growth events, which leads to improved mono-dispersity of the final dendrimers.[6]

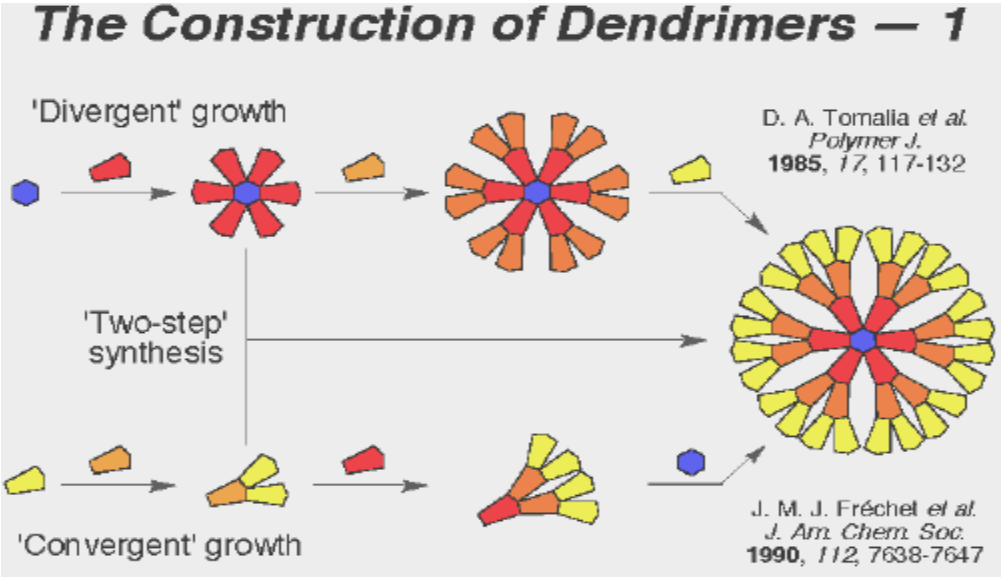


Fig no.: 2 Preparation of Dendrimers[7]

**Table No. 1 PROPERTIES OF DENDRIMERS**

| Sl.No | PROPERTY | DENDRIMERS |
|---|---|---|
| 1 | Structure | Compact, Globular |
| 2 | Synthesis | Step-wise growth |
| 3 | Structural control | Very high |
| 4 | Architecture | Regular |
| 5 | Shape | Spherical |
| 6 | Crystallinity | Non-crystalline |
| 7 | Aqueous solubility | High |
| 8 | Non-polar solubility | High |
| 9 | Viscosity | Non-linear relationship with molecular weight |
| 10 | Reactivity | High |
| 11 | Poly-dispersity | Mono-disperse |

**DENDRITIC DRUG DELIVERY**:

Encapsulation of Guest Molecules

1. Internal Cavities Hosting Encapsulated Guest Molecules

The flexible branches of a dendrimer, when constructed appropriately, can provide a tailored sanctuary containing voids, wherein drug molecules can be physically trapped.[8] Encapsulation of hydrophilic, hydrophobic, or even amphiphilic compounds as guest molecules within a dendrimer,[9] can be enhanced by providing various degrees of multiple hydrogen bonding sites or ionic interactions.[10]

A wide variety of molecules have been successfully encapsulated inside dendrimers. Drugs like 5-fluorouracil,[10] 5-amino salicylic acid, pyridine, mefanimic acid and diclofenac, paclitaxel,[11] docetaxel,[12] 10-hydroxycamptothecin, have been successfully encapsulated. Together, these results showed that encapsulation is a general strategy for the delivery of low molecular weight compounds by dendrimers. This method is anticipated to of particular value when display of the bioactive molecule on the surface of the dendrimer induces unwanted immunogenicity or reduces biocompatibility.

**Dendrimer as a catalytic nanoreactor ensuring mass transfer**

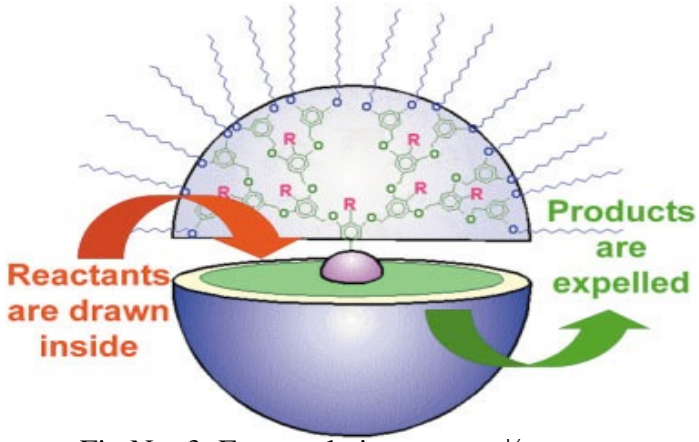


Fig No.:3 Encapsulation process[15]

2. Dendrimers for Gene Transfection

The delivery of extremely large macromolecules, such as plasmid DNA for on-viral gene therapy, is counter-intuitive because the encapsulation of a ‘‘guest’’ molecule many times the molecular weight of the dendrimer itself appears impossible. Nonetheless, experimental evidence had demonstrated that gene delivery strategies also benefit from the participation of dendrimers.[14] For example, the fractured form of PAMAM, known as SuperfectTM, is now a commercially-available transfection agent for in vitro applications .[15]

Typical approaches to optimize dendritic gene delivery for in vivo use have involved the surface modification of a PAMAM backbone, either with arginine or hydroxyl groups. Improved gene delivery with a novel PAMAM-PEG-PAMAM triblock copolymer, show that construction of dendrimers composed of new building blocks is warranted the success of these applications is likely to depend on the continuing development of novel materials for dendrimer synthesis.

**Gene Transfection process[16]**

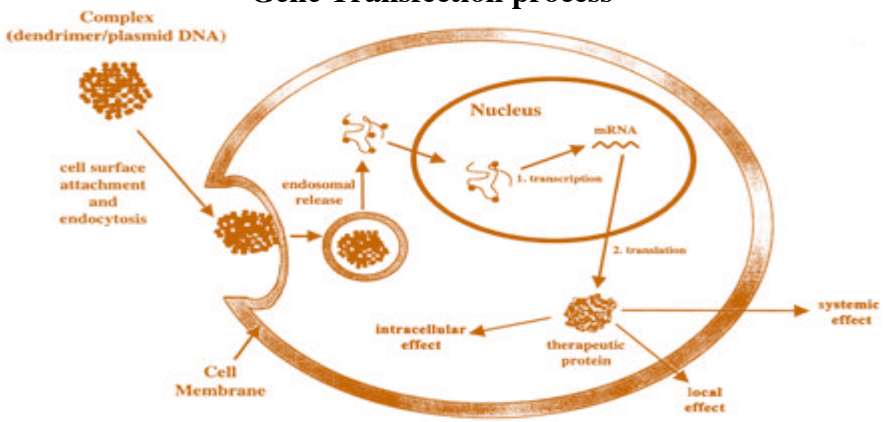


Fig No.: 4

3. Release of Encapsulated ‘‘Pro-drugs’’

Once a dendrimer carrying an encapsulated drug reaches the intended site of action, the guest molecule must be released to gain bioactivity. Indeed, a concern is that the active drug would ‘‘leak’’ out prematurely, thereby reducing the amount available for the intended therapeutic intervention, or more ominously, result in systemic toxicity. The release of encapsulated guest molecules was relatively faster, occurring over a few hours, apparently through hydrolytic degradation of the dendrimer in aqueous conditions. At present, additional control of delivery rates by instantaneously releasing its entire drug payload upon reaching its cellular target is valuable.[17]

4. Dendrimer Conjugates- as Vaccines

Most low molecular weight substances are not immunogenic, consequently, when it is desired to raise antibodies against small molecules, they must be conjugated to a macromolecule. In the past, natural proteins have commonly been used as carriers to generate antibodies to small molecules, now an alternative strategy using dendrimers has been demonstrated. In particular, unmodified PAMAM dendrimers that fail to elicit an antibody response on their own become haptenized upon protein conjugation and generate a dendrimer-dependent antigenic response.[18]

A specific example of this technique is provided by the dendrimeric presentation of antigenic HIV peptides, which proved superior to other multimeric presentation strategies, such as conjugation to dextran. Finally, although carbohydrate-conjugated dendrimers) are typically non-immunogenic, antibodies can be successfully elicited against cancer-specific oligosaccharides displayed on a dendritic scaffold, offering a method for generation of a new class of cancer vaccines.

## APPLICATIONS

1. Catalysis

There are many examples of using dendrimers in organo-metallics[19-20] such as ferricenic sandwich[21-22] with impressive re-dox catalysis properties. The area of catalysis is fixing the catalyst in the periphery, or scaffolding, or on the core of dendrimers.

2. Biomedicals

The formation of particulate systems with well defined sizes and shapes is of eminent interest in certain medical applications such as drug delivery,[23] gene transfection[24] and imaging.[25-29] The bioactive agents may be encapsulated into the interior of the dendrimers or chemically attached/physically adsorbed onto the dendrimer surface.

3. Electronic devices

Organic electronic devices (e.g., organic integrated circuits, organic thin-film transistors, organic solar cells, organic field quenching devices, organic light-emitting transistors, light-emitting electrochemical cells, organic optical detectors, organic photoreceptors, organic laser diodes, and organic electroluminescent devices) are described as linear or branched dendrimer compounds incorporating a specify component and serve as hole-injecting, hole-transporting, electrontransporting, or hole-blocking materials.[30-31]

4. Environment

Dendrimer molecules are new class of polymers. These polymers are assembled around the center of a single molecule. As the layers build outwards from this core molecule, dendritic nature of the growing structure emerges. Large regions resemble the smaller Ys formed by triplets of monomers. Chemists can manipulate the characteristics of the interior and the outer surface. These polymers have many applications, such as environmental defence[32-35] labeled dendrimer acting as host molecules.

5. Sensors

The structures and properties of dendrimers evolved interest in interfacing the nanoscale dendrimers in the particular area of chemistry and biological sensing. Covalent bond formation is most important in dendrimer formation, followed by metal-ligand coordination bond formation and non-covalent bond formation.[36-38] Rapid progress of the nanotechnological and advanced nanomaterials production offers wide range of applications for detection of environmental contaminants. Their integration into functional analytical devices, applications as electrode materials and gas sensing nanoprobes, in biosensors and as capture probes in immunomagnetic fields.

6. Nanotechnology

Dendritic polyglycerol represents hyper branched polymer characterized by the combination of a stable, biocompatible polyether scaffold, high-end group functionality and a compact, well-defined architecture. These characteristics can be used to generate new materials properties and for biomedical applications to molecularly amplify or multiply effects or to create extremely high local concentrations of drugs, molecular labels, or probe moieties.[39]

Nanostructures with uniform and well-defined particle size and shape are of eminent interest in biomedical applications because of their ability to cross cell membranes and to reduce the risk of premature clearance from the body. Many commercial small molecule drugs with anticancer, anti-inflammatory, and antimicrobial activity have been successfully associated with dendrimers such as poly(amidoamine) (PAMAM), poly(propyleneimine) (PPI or DAB) and poly(etherhydroxylamine) (PEHAM) dendrimers.[40]

## Dendrimers in Cancer Diagnosis and Treatment[41]

Cancer epitomizes the challenges faced during drug delivery: an anticancer drug must be able to seek out subtle changes that distinguish a transformed cell from the other 200 or so types of healthy cells found in the body and then provide a sufficiently high dose of a toxic agent to selectively kill the cell while not harming its healthy neighbours. Therefore, dendrimers can be endowed with many favorable properties for drug delivery. They can successfully meet the formidable tasks of diagnosing and treating of malignant disease.

### A.Accumulation at the Sites of Tumors

In cancer chemotherapy, the desirable size-based features are reinforced by the enhanced permeability and retention (EPR) effect that improves the delivery of macromolecules to tumors. The EPR effect is based on unique pathophysiological features of a solid tumor, such as extensive angiogenesis resulting in hyper-vascularization, limited lymphatic drainage, and increased permeability to lipids and macromolecules. These features, which help ensure adequate nutrient supply to meet the metabolic requirements of rapidly growing tumors can be turned to the tumor's disadvantage by the use of nano-sized therapeutic agents.

### B. Demonstration of EPR Effect on Liposomes

The EPR response was subsequently demonstrated for similarly-sized liposomes, thereby establishing that this effect was largely a function of particle size and did not solely depend on the chemical or biophysical properties of the macromolecule. Specifically, in one study, optimal tumor delivery occurred for liposomes having a size distribution between 70 and 200nm in diameter. An independent study showed efficacy for liposomes loaded with daunorubicin in the same size range; specifically, those with 142nm in diameter exhibited an inhibitory effect against Yoshida sarcoma whereas smaller (57–58 nm) and larger (272nm) liposomes had weaker or no effect.

Over time, cautionary notes were raised that tempered initial enthusiasm for exploiting the EPR effect for cancer treatment. For example, the porosity of the vasculature in tumors can be highly variable even with a single vessel that can be leaky to one size of particle in one region but not in another. The ability to match exact and uniform sizes needed to target an individual tumor – is highly tractable with dendrimers because selection of an exactly-sized entity is possible compared with the large size distributions that plague liposome and most polymeric materials.[42]

**Schematic representation of EPR effect**[43]

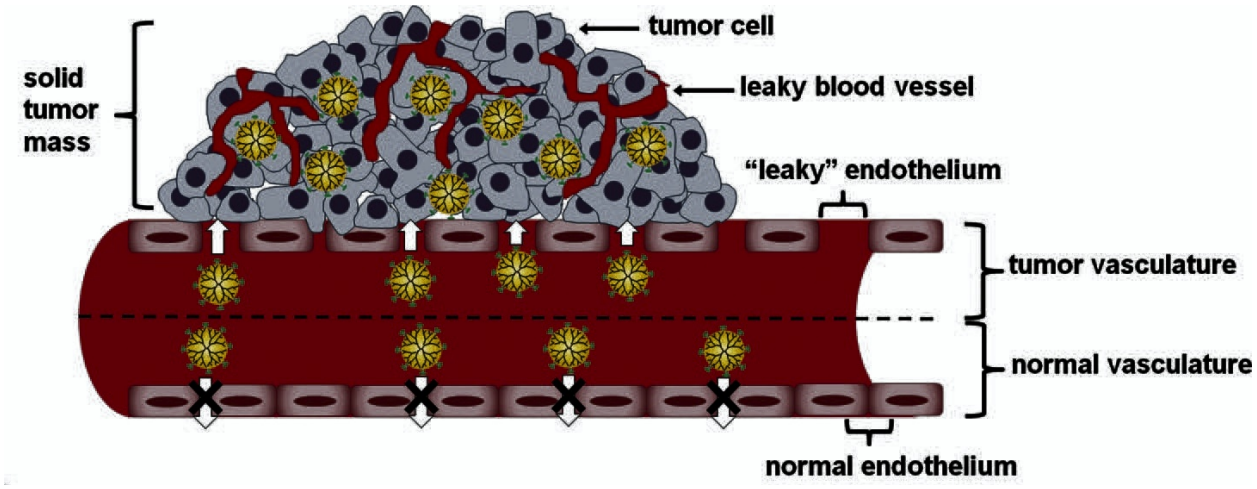


Fig No.: 5

**A. Selective Target Biomarkers**

Targeting Methods

Dendrimers can achieve passive EPR-mediated targeting to a tumor simply by control of their size and physicochemical properties.

1.Targeting Cancer cell

The localised nano-particle in the close vicinity of a cancer cell, can be immediately useful for diagnostic purposes or for the delivery of radioisotopes capable of killing any cell within a defined radius. In general, most delivery strategies require that the anticancer agent directly attached to, or be taken up by, the target cell. The ability to append more than one type of functionality to a dendrimer allows the inclusion of ligands intended to bind specifically to cancer cells in the design of a multi-functional drug-delivery nanodevice. Although, a wide range of targeting ligands have been considered, including natural biopolymers such as oligopeptides, oligosaccharides, and polysaccharides such as hyaluronic acid, or polyunsaturated fatty acids.

2. Targeting by Folate

Folate is an attractive small molecule for use as a tumor targeting ligand because the membrane-bound Folate Receptor (FR) is over expressed on a wide range of human cancers, including those originating in ovary, lung, breast, endometrium, kidney and brain.[44] Folate is an exemplary small molecule tumor-targeting agent as well as monoclonal antibodies directed against tumor associated antigens. As a small molecule, it is presumed to be non-immunogenic, it has good solubility, binds to its receptor with high affinity when conjugated to a wide array of conjugates, including protein toxins, radioactive imaging agents, MRI contrast agents, liposomes, gene transfer vectors, antisense oligonucleotides, ribozymes, antibodies and even activated T-cells.

Upon binding to the folate receptor, folate-conjugated drug conjugates are shuttled into the cell via an endocytic mechanism, resulting in major enhancements in cancer cell specificity and selectivity over their non-targeted formulation counterparts. Recently, folate has been enlisted in an innovative dendrimer-based targeting schemes.

3.Targeting by Monoclonal Antibodies

Of the many strategies devised to selectively direct drugs to cancer cells, perhaps the most elegant is the use of monoclonal antibodies that recognize and selectively bind to tumor associated antigens (TAAs). TAA-Targeting Monoclonal Antibodies have been exploited as delivery agents for conjugated ‘‘payloads’’ such as small molecule drugs and prodrugs, radioisotopes, and cytokines Current prospects remain mixed but hopeful, optimistically, progress marked by commercial interest with companies providing their immunotherapeutic drug candidates with flashy trademarked names, such as ‘‘Armed Antibodies TM.’’[45]

**RECENT ADVANCES** [46]

1. Targeting on HIV infected macrophages in vitro

Monocytes and macrophages are believed to disseminate HIV throughout the human body. The targeting of these cells, therefore, is crucial to treating HIV. Tuftsin is a macrophage activator tetrapeptide, and is known to bind specifically to macrophages and monocytes. In this work, Dutta et al. prepared efavirenz loaded, Tuftsin conjugated 5$^{th}$ generation poly(propyleneimine) dendrimers (PPI) inorder to study their targeting potential and anti-HIV activity in vitro.

Several aspects were studied:

a. Drug loading and entrapment efficiency
b. Cytotoxicity
c. Cellular uptake
d. Anti-HIV activity

a.Drug loading and entrapment efficiency

The entrapment of efavirenze (EFV) in the tuftsin conjugated polymer (TuPPI) was found to be 0.87g of EFV per gm of TuPPI. This corresponds to an entrapment efficiency of approximately 49%. The entrapment efficiency of PPI (that is, dendrimer without the tuftsin conjugate) was found to be 37%. The increase in entrapment efficiency of TuPPI with respect to PPI may be due to the increased amount of function groups available for complexation as well as steric hindrance due to the conjugation at the terminal amino groups. As may be expected, the increase in entrapment efficiency also correlated with a decrease in the rate of *in vitro* drug release. While the PPI dendrimer almost completely released the drug in 24 hours, the TuPPI derivative prolonged the release rate up to 144 hours.

b.Cytotoxicity

These studies were carried out, which found no cytotoxicity in the case of EFV and tuftsin up to a concentration of 5.0 ng/mL. EFV loaded PPI exhibited cytotoxicity at a concentration above 0.625 ng/mL, which was attributed to the presence of free primary amine groups, as cationic dendrimers are known to be cytotoxic.

c.Cellular uptake studies

These studies showed that while the uptake of PPI was higher compared to that of free EFV, the cellular uptake of TuPPI was significantly greater than PPI. At 1 h, the uptake of TuPPI was 34.5 times higher than that of free EFV.

d.Anti-HIV Activity

The uptake in HIV infected macrophages was significantly higher than in uninfected cells for TuPPI, whereas HIV infection made no statistical difference in the uptake of free EFV and PPI. As a consequence of enhanced cellular uptake , reduced toxicity and inherent anti-HIV activity, EFV-loaded TuPPI was found to have significant anti-HIV activity, more so than the free drug alone.

2. Plasmid and Doxorubicin co-delivery targeting tumor

In this recent work, a PEGylated PAMAM dendrimer with a tumor-targeting moiety was used as a platform to deliver both a tumor necrosis factor-related apoptosis-inducing ligand and doxorubicin, a common anticancer drug. This is an example of combination cancer therapy, which has shown promising results indicating that therapies often have a synergistic effect on one another, making their combined effect greater than the sum of their individual contributions. This co-delivery system was evaluated both in vitro with tumor cells, and in vivo using a mouse model.

The components of the co-delivery system were analysed and the in vitro analysis showed that full co-delivery system was most effective at inducing apoptosis.

Tumor-targeted medicative co-delivery system of genes and chemotherapeutic drugs exhibits multi-functions for combined therapy. It successfully delivers both genes and chemotherapeutic drugs to target cells, thus inhibiting tumor growth and reducing general toxicity.

3. Design, Synthesis, and Biological Evaluation of a Robust, Biodegradable Dendrimer:

The Frechet group has often been at the forefront of dendrimer research, and in this work they describe a new PEGylated dendrimer that combines the biocompatibility of 2,2-bis(hydroxymethyl) propanoic acid (bis-HPMA) dendrimers with the robustness of polyamide dendrimers to make a new hybrid dendrimer scaffold.

By improving solubility and blood circulation time of small molecule drugs, and by promoting accumulation in tumor tissue by the EPR effect, dendrimer carriers have increased the efficacy of chemotherapeutic agents Biodegradability is an important feature , however, to ensure that the dendrimer carrier does not persist in the body longer than is beneficial. To that end, polyesters are attractive because of their biodegradability, however, their hydrolytic susceptibility makes the synthesis of drug conjugates challenging. Polyamide and polyamine dendrimers are more robust, but consequently do not easily degrade in the body

## CONCLUSION:

The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight, there by offering scaffold for drug delivery. An increasingly large number of drugs being developed today are facing problems of poor solubility, bioavailability and permeability.

Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also, as a research progresses, newer applications of dendrimers will emerge and the should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

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