Review Article

Polymeric Nanocarriers for Combined Drug Delivery and Targeting in Cancer Therapy

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ABSTRACT

Nanotheranostics is a novel, fast growing field that combines the advantages of treatment as well as diagnosis via a single nanoscale carrier. The ability to combine both therapeutic and diagnostic capabilities into single package makes it an exciting prospect for the development of novel nanomedicine. Nanotheranostics can deliver drug, while simultaneously perform the monitoring therapy. So there is a decrease in the potential of over or under-dosing patients. Polymeric nanoparticles show a higher intracellular uptake and accumulation and a more significant cytotoxicity to cancer cells when compared to a free drug. Polymer-based nanomaterials, in particular, have been used extensively as carriers for both therapeutic and bio imaging agents and thus hold great promise for the formulation of multifunctional theranostic formulations. Nobel metal such as gold and platinum and some biocompatible polymers like poly lactic acid and poly ethylene glycol are the major nanocarriers that have been used. A fluorophore, MRI contrast agent or a radio nuclei can be used as a an imaging agent, and is incorporated into the polymer along with a potent drug. In certain cases the drug itself acts as an imaging agent which provides a new platform for the researchers. Therefore, we review recent advances in polymer-based systems for nanotheranostics, with a particular focus on their applications in cancer treatment.

Keywords: Cancer therapy, Imaging agent Nanoconjugates, Nanotheranostics

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INTRODUCTION

The term "Theranostics" depict any "material that combines the steps of therapy and diagnostic imaging" into one step process. The field of nanotheranostics [1] has been useful to physicians to simultaneous monitor drug distribution an release and evaluate its therapeutic efficacy. Polymer-based nanomaterials [2] or nanocarriers, which possess excellent biocompatibility, biodegradability, and structural versatility. Biopolymers naturally degrade into safer materials (like carbon dioxide and water) over time in the body, and are typically nontoxic except at extremely high concentrations. Polymers such as Poly Ethylene Glycol (PEG), poly(D,L-lactic acid), poly(D,L-glycolic acid), and poly(ε-caprolactone) have already been approved for clinical use in macro formulations.

Polymer-based platforms have been studied exclusively for cancer therapy which offers many advantages. In particular, polymeric nanoparticles are able to enhance drug efficacy compared with free drugs due to improved drug encapsulation and delivery, prolonged circulation half-life, and sustained or triggered drug release [3]. Polymeric nanoparticles are also able to cummulate at a specific disease location through passive targeting by the Enhanced Permeability and Retention (EPR) effect, or by active targeting by the incorporation of targeting moieties specific for a receptor or cell surface ligand at the required site. Polymer drug conjugates, dendrimers, liposomes, etc are some of the examples for the nanocarriers and the structural arrangement containing imaging agents are shown below (**Fig.1**).

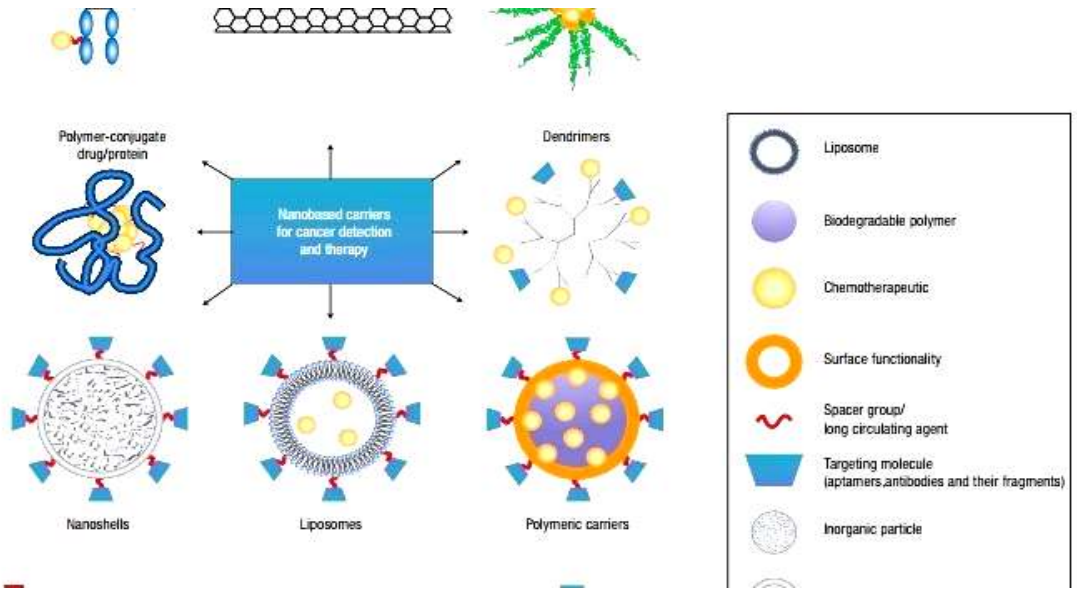

Figure 1: Schematic Diagram of Nano carriers with Diagnostic Agent

Depending on the contrast agent involved, polymer-based nanotheranostics can be imaged using a wide variety of techniques, such as fluorescence imaging, radionuclide imaging (e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT)), magnetic resonance imaging (MRI), and ultrasound imaging (**Table 1**).

Table 1: **Overview of Commonly used Imaging Modalities**

Imaging modality	**Imaging agent**	**Spatial resolution**	**Advantages**	**Disadvantages**
MRI	Gadolinium, Iron oxide, Manganese oxide, 19F labeled compounds	10–100 μm	Clinical translation; high resolution; no radiation; no depth limit; quantitative results	High cost; long imaging used in patients with no metallic implant
PET	18F, 64Cu, 11C, 15O-labeled Compounds	1–2 mm	Clinical translation; high sensitivity; unlimited penetration; image biochemical processes; quantitative results	high cost; radiation; low resolution
SPECT	111In chelates	1–2 mm	Clinical translation; high sensitivity; unlimited penetration relatively lower cost; quantitative results	radiation; low resolution
Optical imaging	Fluorochrome, Photoproteins	1–5 mm	High sensitivity; no radiation; high-throughput screening for target confirmation and compound optimization; multichannel imaging	limited clinical translation; low resolution; low depth penetration
Ultrasound	Nano/microbubbles	50 μm	High resolution; low cost; ease of operation; no radiation; quantitative results	low depth penetration

In general, a polymer-based theranostic material is comprised of at least three main components: (i) a polymer component which offers stability and biocompatibility, (ii) a therapeutic agent (small –molecule drug or siRNA), and (iii) an imaging agent (i.e., MRI contrast agent, radionuclide, fluorophore, etc.)(**Fig. 2**). In some cases, the therapeutic component can also act as the imaging component, an example is doxorubicin (DOX), which have an inherent fluorescence. These components can be arranged in different ways depending on the need of delivery. Many formulations now also incorporate targeting ligands as a fourth component to enhance specific delivery to the tumor site.

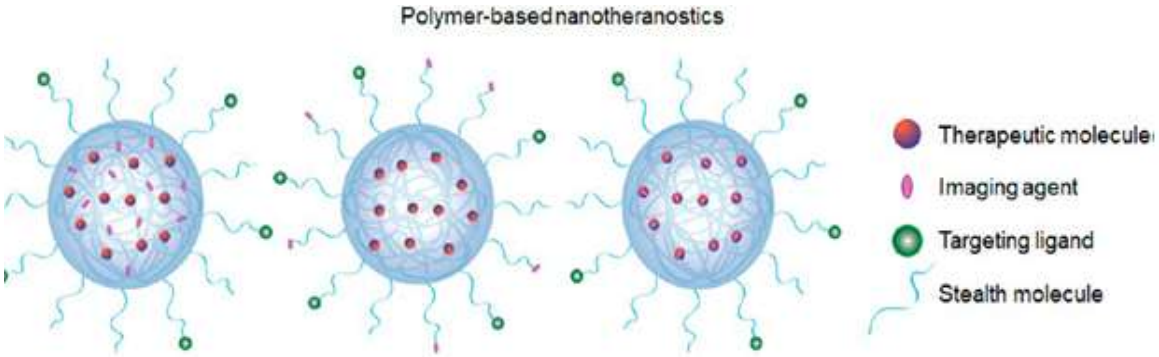

Figure 2: Illustration of A Polymer-Based Nano theranostic Agent

A variety of polymeric nanoparticle carriers like polymer conjugate complexes, nanospheres, micelles, and dendrimers have been developed to facilitate the delivery of drugs to cancerous sites and have shown great efficacy against various types of cancers.
Conjugation of drug molecules to the polymer backbone allows reuse, drug loading and control over release kinetics. Self-assembled nanospheres, micelles, and dendrimers loaded with therapeutic agents offer sustained and controlled release through surface or bulk erosion, drug diffusion through the polymer matrix, or environmental activation or stimulation. By a combination of an imaging agent along with the encapsulated drug within a polymeric nanoparticle, researchers have been able to cumulate analysis data of drug distribution and release at the target site in real time ie, while the drug being administered to the body.

MODIFICATIONS OF CURRENT THERAPY

The most typical cancer treatments in clinic include chemotherapy, radiotherapy and surgery. Theranostics extensively aim to reduce the severe side effects of chemotherapy and radiotherapy, as well as to avoid the high risk , large trauma and complications of surgery.

CHEMOTHERAPY

It is the treatment of disease by the use of chemical substance especially the treatment of cancer by cytotoxic and other drug. So far, a few cancer nanomedicines have gained approval from FDA, such as Doxilfor clinical ovarian cancer therapy, Thermo DOX for liver cancer clinical therapy. Prodrugs may be employed in theranostic systems, sometimes to reduce the drug toxicity by activating the toxic attack to cells only at tumor sites. For example, the platinum(IV) pro-drugs are very popular option because of their wide availability. Cancer treatment with a single drug often causes themulti-drug resistance (MDR) by cancer cells, which may be solved by theranostics with convenient and efficient methods [4].

One way to overcome MDR is the combination of anticancer drugs with P-glycoprotein (Pgp) reversing agents, which prevent pumping the chemotherapeutic drugs out of cancer cells through over-expressed Pgp. Masking the positive charge of antitumour drug is the key to overcome the MDR. DOX adsorbed on the surface of polymeric nanoparticles might show a higher intracellular uptake and accumulation and a more significant cytotoxicity to cancer cells than the free drug. Another strategy is to apply the

combination of mixed anti-cancer drugs loaded on nanocarriers, so a synergistic anticancer performance may take effect. According to a study, silica nanorattles [5] entrapped with Pseudomonas aeruginosa exotoxin 40 (PE 40) and docetaxel exhibited improved anti-cancer efficacy.PE 40 restrains the SSS protein (Synthetic serum substitute protein) synthesis through ribosylation of elongation factor 2 (EF-2), while docetaxel inhibits mitosis, leads to a synergetic anticancer effect.

RADIOTHERAPY

The treatment of disease with ionizing radiation also called radiation therapy. In radiation therapy high energy rays are often used to damage cancer cell and stop them from growing and dividing. Radiation therapy (RT) is an integral part of current treatment strategies of many sarcomas.

Radiation directly damages DNA strings in the cell nucleus and thus results in the inhibition of cell proliferation. Nanoparticles with strong photoelectric absorbance capacities are employed as the radiation dose-enhancing agents. Gold nanoparticles have been found to be able to mediate radiosensitization because of the greater absorption and deposition of energy in surrounding tissues from photoelectrons, Auger electrons, and characteristic X-rays [6]. Polyethylene glycosylation modified gold nanoparticles (P-GNPs) have been demonstrated to prolong their circulation time in blood for RT[7]. The gold- and superparamagnetic iron oxide

Nanoparticles (SPION)-loaded polymeric micelles also showed excellent radiotherapeutic outcomes [8]. Examples of SPION are in (**Table 2**). For instance, Bismuth nanoparticles were coated with Mesoporous Sillica Nanoparticle (MSN) and illustrated with significant tumor eradication. For terminal cancer patients, RT can relieve the symptoms [9]. RT may induce many complications, and even cause the loss of organ functions.

Table 2: Polymer-Based Theranostic Systems Containing Superparamagnetic Iorn Oxide Nanoparticle (SPION) for Anticancer Drug Delivery

Polymer	Drug
Pluronic-based polymer curcumin	DOX, Paclitaxel
PEG-PMAA-poly(glycerol monomethacrylate)block copolymers	Paclitaxel
EG-PGA-PEG-acrylate	DOX
PEG-PGA –PEG –acrylate	DOX 140 PVA 5-FU,DOX,Ceftriaxone

IMMUNOTHERAPY

It is the prevention or treatment of disease with substance that stimulate the immune response. Recently, immunotherapy has emerged as a promising treatment for advanced cancers, because it acts on the immune system, rather than the tumor itself. Some immunotherapeutic drugs, such as immune checkpoint inhibitors (Anti CTLA4 and anti PD1agents) and T cells, hold great promise for clinical treatment, and have been approved by FDA [10]. The antigen, immune adjuvant and nucleic acid vaccine loaded in nanomaterials have been demonstrated to improve their immunotherapeutic efficacy [11]. The nano platforms influence the activity of immune cells, damage the cancer cells easily andalter the immune response nonspecifically. For example, Gold nanoparticles conjugated with repetitive and homogenous antigens were able to stimulate immune responses in an in vitro setting, even without adjuvants [12].

BIOCOMPATIBLEPOLYMERS UTILIZED IN CANCER NANOTHERANOSTICS

Poly Ethylene Glycol (PEG) is the most popular polymeric material studied for drug release with improved drug stability and minimized immunogenicity. Copolymers of PEG and other polymers such as polyesters (e.g. Poly Lactic Acid (PLA), poly (lactic glycolic acid) (PLGA), and polycaprolactone (PCL)), have been extensively studied as drug delivery systems (DDS) for therapeutic and imaging agents. For example, Peng et.al [13]. Incorporated IR-780 iodide (a near-infrared (NIR) dye) and 188-Rhenium into

PEG-PCL micelles for simultaneous NIR fluorescence and nuclear imaging and photothermal therapy (PTT) of cancer, which provides surveillance of tumor accumulation, distribution, as well as kinetics of drug release[14].

For instance, after being labelled with 19F, pH-responsive nanogels with a poly(2-[N,N-diethylamino]ethyl methacrylate) (PEAMA) core and PEG tethered chains, showed great potential as magnetic resonance spectroscopic imaging (MRSI) nanoprobe which facilitate in endosomal release and intracellular delivery of doxorubicin as well as cytoplasmic delivery of siRNA, representing these pH-responsive smart nanogels as powerful candidates for cancer diagnosis and therapy. Also, PK1, apolymer-drug conjugate of *N*-(2-hydroxypropyl) methacrylamide (HPMA), drug linker a tetrapeptide spacer for cleavage by lysosomal enzymes) and intercalating agent doxorubicin, which was the first passively tumor accumulated polymeric prodrug that entered clinical trials, had been successfully radiolabeled to facilitate its pharmacokinetic studies. In another study, by conjugating 111 in with HPMA copolymer, which was also functionalized by two v3–binding peptides (i.e. RGD fk and RGD4C), significantly enhanced contrast at the tumor sites could be observed under scintigraphic imaging [15].

POLYMER AND NOBLE METAL NANOCONJUGATES

The unique optical property of noble metal nanomaterials (e.g. gold and silver NPs), also known as surface Plasmon resonance[16,17], can be precisely tuned by changing nanomaterials size, shape, and surface characteristics. Their application in cancer detection is limited by the penetration depth of light in visible and near-infrared range .These NPs can provide high contrast to soft tissues due to their high density, acting as promising contrast agents imaging of solid tumors in X-ray computed tomography (CT). By adjusting the morphological properties of noble metal nanomaterials (e.g. size, shape, and shell thickness) the nanomaterials (e.g. nanorods, nanopyramids, nanocages, and nanoshells). It can be tuned to absorb visible-to-near-infrared wavelength light for photothermal therapy [17].

Gold NPs not only played an important role in PTT, but also acted as fluorescence quenching components of activatable optical contrast agents [18]. To increase the sensitivity for early detection of tumor regression, gold NPs were incorporated into the PEAMA core of pH responsive theranostic nanogel, which had a fluorescein isothiocyanate (FITC)-labeled Asp-Glu-Val-Asp (DEVD) peptide at the end of its tethered PEG chain. The fluorescence of FITC molecules was initially quenched by Gold NPs. During the apoptosis process, cysteine protease caspase-3 was activated, specifically recognizing and cleaving DEVD peptide sequence, eventually leading to the dispersion of FITC molecules into solution exhibiting fluorescence for imaging. So far, Cyt Immune Sciences have developed a series of active-targeting drug-loaded gold NPs through the conjugation of PEG and tumor necrosis factor alpha (TNF-) [19].

POLYMER AND SEMICONDUCTOR NANOCONJUGATES

Nanoparticles with semiconductor cores are usually referred as quantum dots (QDs). Their optical properties arise from the quantum confinement of excitons in all three spatial directions, their absorption and emission spectra can be fine-tuned by changing the size of Nano Particle core. QDs provide a significant advantage over organic chromophores for their bright fluorescence without photo bleaching, which is preferable for long-term, repeated imaging. QDs' application in cancer detection and diagnosis is largely limited by the penetration depth of light in visible and near-infrared range.

The synthesis of QDs usually involves heavy metals such as cadmium (Cd), which are highly toxic in human bodies, limiting the use of QDs. Entrapping QDs into polymeric NPs or coating QDs with SiO2, are required to reduce the toxicity of QDs [20,21]. For example, Deepagan and co-workers developed a multifunctional PEG-coated PLGA NPs by simultaneously encapsulating Mn2+-doppedZnS QDs and anticancer agent camptothicin (CPT). Cetuximab, an anti-EGFR (epidermal growth factor receptor) antibody, was then conjugated to

the surface of PLGA NPs via (1ethyl-3-[3-dimethylaminopropyl]carbodiimide)-(N-Hydroxysuccinimide) (EDC-NHS) reaction for the targeting of EGFR overexpressed cancer cells. Owing to the bright fluorescence of ZnS QDs, in vitro targeting efficiency and cellular uptakeof modified PLGANPs could be directly evaluated by fluorescence imaging, indicating a significantly higher anticancer activity [21].

POLYMER AND CARBON NANOTUBES NANOCONJUGATES

Carbon nanotubes (CNTs) consist of graphitic sheets rolled up into cylindrical shape. The electronic properties of CNTs can be changed from metallic to semiconducting by altering the arrangement of the hexagon rings along the tubular surface. Recently, due to their high surface area and internal volume, both single-walled and multi-walled CNTs have been studied for the loading and delivery of therapeutic and imaging agents through stacking. CNTs as nanovectors for cancer treatment is that they can combine the techniques of chemotherapy, gene therapy, photothermal therapy with current clinical imaging techniques. CNTs as nanocarriers is limited by their biological toxicity and poor solubility inmost organic or aqueous solutions .

Surface modification of CNTs with soluble and biocompatible polymers (e.g. poly (vinylcarbazole), poly (styrene sulfonate), and PEG) is useful in the development of CNTs nanotheranostics. Recently, Chenet al. established a novel nano platform based on Ferric Oxide-filled CNTs (Fe3O4-CNTs) and hybrid SiO2-coatedCdTeQDs (HQDs) for cancer-targeted imaging and magnetically guided drug delivery [22]. Although the in vitro data of Hela cells demonstrated the potentials of using this nanoplatform for target-specific diagnosis and therapy, in vivo studies are required to verify its diagnostic and therapeutic efficacy before this nano platform proceeds to clinical trials.

POLYMERAND METAL OXIDE NANOCONJUGATES

Magnetic metal oxide NPs, especially iron oxide NPs, have attracted much attention for their potentials in imaging, cell labeling, drug delivery, gene delivery. Ferromagnetic and ferromagnetic NPs are super paramagnetic, showing high magnetization if only an external magnetic field exists. This unique property makes them the most prominent probes for MRI. Another problem for the application of magnetic NPs in cancer treatment is that after intravenous injection, magnetic NPs are converted to complex by immune cells, and then accumulate in reticuloendothelial systems (RES) organs, such as liver, spleen, bone marrow and lymph nodes.

To overcome that coating with amphiphilic polymers and conjugation of target-specific motifs) have been developed which impart water solubility as well as tumor-targeting properties for metal oxide nanoparticles. Metal oxide NPs usually need a particle coating for agent loading therefore, the conjugation or coating of magnetic metal oxide NPs with polymers is often indispensible for these NPs' use as cancer nanotheranostics, [21] Shi et al. developed a novel nanotheranostics comprised of several key components: 1) magnetic NPs for MRI and hyperthermia, 2) QDs for fluorescent imaging, and 3) PLGA coating for the simultaneous loading of chemotherapeutic drug (paclitaxel (PTX)), QDs, and magnetic NPs, as well as the subsequent conjugation of tumor-specific antibody (anti-prostate specific membrane antigen (anti-PSMA)) for cancer cell targeting[22].

LIPOSOMES

Liposomes are small bilayer vesicles enclosing aqueous compartment that can be produced using amphiphilic phospholipids and cholesterol. Liposomes are spherical, vary in size most are 400nm or less. The nanosized diagnostic agents such as iron oxide nano particles, quantum dots and gold nanoparticles can be entrapped within the theranostics liposomes and the therapeutic agent can be either encapsulated in the core or embedded in the lipophilic bilayer shell. The advanced theranostic liposomes are conjugated with molecular biomarkers for targeting effect.

To overcome opsonization by the immune system and fast elimination from blood circulation, stealth liposomes i.e, PEG coated liposomes, were formulated with stability and longer half life in blood

[22,23]. Liposomes surface-coated with D-alpha-tocopheryl polyethylene glycol-1000 succinate (TPGS) and loaded docetaxel and evaluated for possibility against brain tumor by in vitro cell line studies with PEGylated liposomes, conventional nude liposomes(without TPGS coating) and TPGS coat liposomes. The TPGS-coated liposomes showed higer efficacy than PEGylated liposomes. TPGS coated theranostics liposomes containing docetaxel and quantum dots with and without targeting moieties. The higher cellular uptake and cytotoxicity of targeted theranostic liposomes was observed in camparison to non-targeted liposomes [23].

MICELLES

The micelles are another safer alternative for parenteral administration of poorly water soluble materials. The stability of the micelles depends on strong cohesive force between drug and polymer core as well as cross linking of the shell or core. They are generally prepared by direct dissolution method and organic solvent method. Therapeutic or diagnostic agents can be loaded into hydrophobic core of micelles and the outer hydrophilic layer with targeting agent. This can then be administrated intravenously. The theranostic micelles of particle size less than 50nm diameter avoid renal exclusion reticuloendothelial cell permeability in solid tumors Micelles are efficient platform for cancer drug delivery. Polymeric micelle was designed and prepared for simultaneous magnetic resasonance imaging (MRI) and micelles are self assembling colloidal structure with a hydrophobiccore and hydrophilic shell.

A treatment of hepatocellular carcinoma (HCC)[24]. The ranostic micelles were assembled using poly(lactic acid)–poly(ethyleneglycol) poly(L-lysine)-diethylene triamine penta acetic acid(PLA-PEG-PLL-DTPA) and PLA- PEG –PLL Biotin [25]. The HCC therapeutic paclitaxel(PTX)was encapsulated in the cores and Gold ions for imaging were chelated to the Diethylene Triamine Penta Acetic acid (DTPA) moieties. Biotinylated alpha-fetoprotein (AFP) antibodies were linked to the micelle surface bya biotin-avidin reaction to form targeted Gd/PTX-loaded micelles (TGPM).TGPM significantly increased tumor imaging intensity (more than 3 times) and prolonged imaging time (from 1 to 6 h). TGPM exhibited higher anti-tumor efficiency than Taxol and GPM. These results indicate that TGPM has great potential in HCC theranostics.

CARBON NANOMATERIALS

Carbon nanomaterials, or nano-carbons, have particular use in a large variety of fields including biomedicine because of their highly-enriched distinctive physical and chemical properties (**Fig. 3**). Based on their bonding structures, nano-carbons may be classified into sp^2-carbon nanomaterials and sp^3-carbon nanomaterials. Typical sp^2-carbon nanomaterials include zero-dimensional (0D) fullerene, one-dimensional (1D) carbon nanotubes (CNTs), and two-dimensional (2D) graphene). Many nano-carbons, including CNTs, graphene derivatives, Cdots, and NDs, show interesting inherent optical properties such as fluorescence, making them useful contrast agents in optical imaging and sensing. The excellent electrical properties of CNTs and graphene, allow them to be extensively used in a wide range of biosensing platforms. Sp^2-carbon nanomaterials especially single-walled carbon nanotubes (SWNTs) and graphene with all carbon atoms exposed on their surfaces, exhibit ultra-high surface area available for efficient drug loading and bioconjugation [24]. CNTs and graphene derivatives with strong optical absorbance in the near-infrared region are also useful for photothermal ablation of cancer.

DENDRIMERS

Dendrimers are synthetic nanomedicine that comprises a highly branched spherical polymer. Dendrimers used in nanotheranostics are usually 10 to 100nm.Dendrimers can be synthesized starting from the central core toward the periphery (divergent synthesis) or in a top-down approach starting from the periphery (convergent synthesis). The name has actually deliver from the greek word “Dendrone” meaning “Tree”, which indicates their unique tree-like branching architecture. They are characterized by layers between each cascade point popularly known as “Generations”. The

complete architecture can be distinguished in to the inner core moiety followed by radially attached generations that possess chemical functional group at the exterior terminal surface as given in (**Fig. 4**) [25].

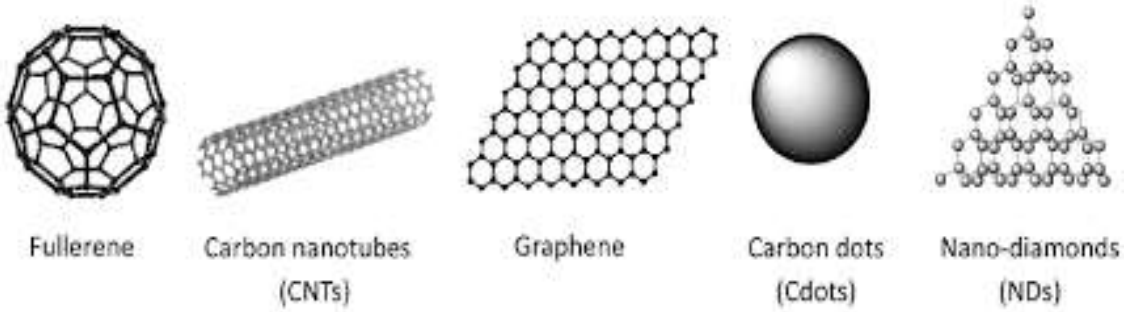

Figure 3: Various Carbon Nanomaterials

Various dendritic platform such as polyamidoamine (PAMAM), Poly (propyleneimine) (PPI),poly-L-Lysine ,melamine, poly (ether hydroxyl lamine) (PEHAM), Poly(esteramine) (PEA)and polyglycerol have been synthesized and explored as drug delivery vehicles. Dendrimers have received considerable attention in biological application due to their high water solubility, biocompatibility, polyvalency and precise molecular weight. These features make them an ideal carrier fir drug delivery and targeting applications. Recently, a dendrimer based prodrug has been developed for paclitaxel (p-gp efflux substrate) that has focused on enhancement of permeability and transportation of drug across cellular barriers. The highly functional lauryl-modified G3 PAMAM dendrimer-paclitaxel conjugates demonstrated good stability under physiological conditions and 12-fold greater permeability across Caco-2 cell and porcine brain endothelial cell monolayers than paclitaxel alone [25].

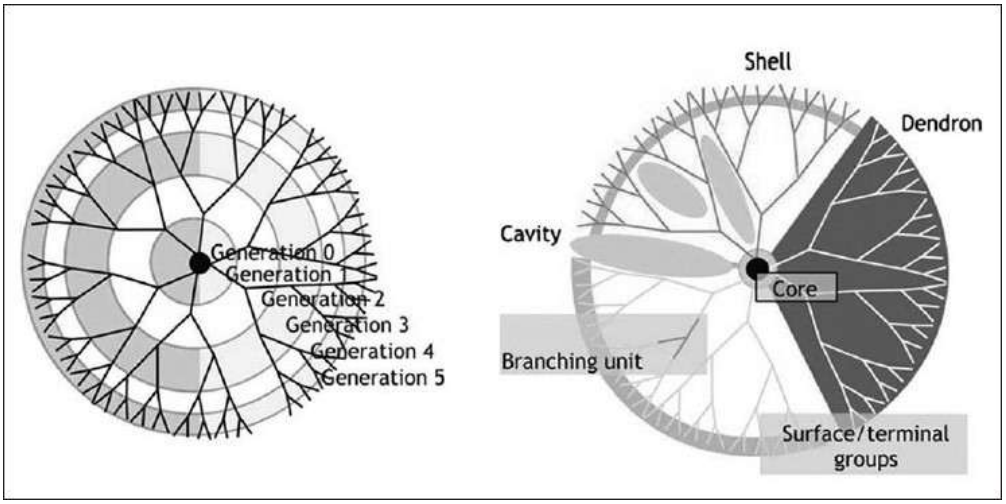

Figure 4: **Structure of Dendrimers Showing Different Generations**

CONCLUSION

With the ability to provide concurrent therapy and imaging, nanotheranostics have great potential and applicability in medicine and biomedical research. Polymers offer many benefits in their use, including biocompatibility, tailorability, and low cost. They can be used to encapsulate normally insoluble compounds, and they protect their cargo from degradation until they have reached their target location. Of course, there could be concerns about nanoparticle toxicity, as still not much is known about behavioral platform of NP. The size and surface properties of nanoparticles, for example, can affect

biodistribution and circulation via mechanisms such as nonspecific protein adsorption, macrophage interaction, and disturbance of biological barriers.

As an example for (biodistribution and circulation), highly positively or negatively charged nanoparticles altered the integrity of the blood-brain barrier in rats, while neutral or slightly negatively charged nanoparticles did not. Polymeric nanoparticle formulations are also often relatively polydisperse, making it difficult to thoroughly characterize them to meet regulatory requirements. Additionally, it is possible for the long circulation of polymeric nanocarriers to induce toxicity or hypersensitivity reactions. As a result, careful toxicological testing and analysis is necessary for each new nanostructure. However, researchers are currently engineering increasingly sophisticated architectures with multiple therapeutic and imaging modalities to overcome these limitations. While theranostic nanoparticles have yet to be utilized in a clinical setting, the considerable advances made in cancer nanotheranostics will likely have far-reaching applications in other important fields such as cardiology and tissue engineering. Multifunctional polymeric nanoparticles can enable targeted cancer therapy and imaging and can also facilitate monitoring of the therapeutic effect. However, further in vivo work will be required to thoroughly investigate the safety and efficacy of these novel theranostic platforms prior to clinical application.

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