Editorial Article

NANOTECHNOLOGY FOR TARGETED DELIVERY IN CANCER THERAPEUTICS

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ABSTRACT

Recent advances in nanotechnology has shown tremendous promise to revolutionize cancer therapeutics by generating new therapies that might allow more efficient targeted delivery of anticancer agents to kill cancerous cells or tumors and imaging agents for diagnosis of various cancers. But, before application of nanoparticle-based targeted delivery systems, significant challenges related to clinical toxicities should be taken in to consideration. This review highlights various new therapies in the context of advances in nanotechnology related to cancer therapeutics.

Keywords: Nanotechnology, nanoparticle, targeted delivery, cancer therapy

INTRODUCTION:

Cancer is a leading cause of death worldwide. It is a complex and critical disease, occurring as a result of progressive accumulation of genetic and epigenetic changes[1-2]. The most important defining feature of cancer is the rapid growth of abnormal cells, which can invade adjoining parts of the body and spreads to other organs. Since the previous decade, the fast growing research on therapeutics has shown promising possibilities for achieving the dream of every oncologist.

Despite outstanding recent advancement in the therapeutic cock-tail, significant challenges still remain present in the field of cancer therapeutics. Unfortunately, commonly used cancer chemotherapy have presented unsatisfactory results, as the therapy is deleterious to patient health by making patients more susceptible to other diseases and often cause death by weakening the immune system of the patient body. Major challenges in cancer chemotherapy are related to toxicity on healthy proliferating cells and multi-drug resistance (MDR) against anticancer agents. The life threatening side-effects caused by nonspecific tissue distribution of the anticancer agents have restricted the systemic high dose strategy[3]. Cancer cells except those having intrinsic resistance are sensitive to chemotherapy in the beginning; but, often develop acquired resistance upon repeated chemotherapy cycles[4]. The resistance initiated by an anticancer agent extends cross-resistance to a wide range of drugs having different chemical structures and cellular targets[4-5].Once the resistance develops, systemic high dose administration of anticancer agents becomes ineffective and the resistance is further stimulated. Thus, there is a crisis in fighting against cancer. The effectiveness of a cancer therapy is understood by its ability to reduce and eliminate tumors without damaging healthy tissues. Therefore, a distinct capacity to target tumors with limited effect on healthy tissues is the most essential for the success of cancer therapy and the ultimate goal of it is to maximize survival period and quality of life of cancer patient. These facts put the accent on the need for new generation of more effective and safe therapies for the treatment of various cancers.

With current parallel breakthroughs in molecular understanding of various diseases and controlled manipulation of materials at the nanometric scale, nanotechnology offers marvelous promise in therapy, prevention and diagnosis of various complex diseases including cancer[6]. Thus, a budding interest in nanotechnology has been generated remarkable number of advancements in recent years with a main focus on current cancer therapy. The fusion of this two disciplines has given rise the new field -"nano-oncology" providing cancer researchers with various new and innovative ways to diagnose and treat cancers[1]. Nanotechnology offers great promise to improve therapeutic effectiveness and safety profile in the treatment of cancers through site specificity, their ability to limit multi-drug resistance (MDR) and efficient delivery of anticancer agents[7]. A wide variety of nanoparticle-based systems are available for cancer detection, diagnosis and treatment include liposomes, polymeric micelles, nanosystems, nanoshells, fullerene-based derivatives, carbon nanotubes, dendrimers, quantum dots, gold nanoparticles, solid lipid nanoparticles, nanowires, paramagnetic nanoparticles, etc.[7-8]. The ability of nanoparticles in cancer treatment has dual significance. Firstly, nanoparticles play as drug carriers[9]. Secondly, they can absorb different wavelengths of light than the body, and when exposed to appropriate wavelengths, nanoparticles heat up without heating the body. Thus, nanoparticles selectively kill cancerous cells[10].

The Background of Nanotechnology:

The field of nanotechnology was first predicted by Richard P Feynman (Nobel laureate in Physics, 1965) in 1959 with his famous lecturer entitled, "There's plenty of Room at the Bottom"[11]. The prefix 'nano' derives from Greek word for 'dwarf'. Nanoparticles can range in size from 1 to 100 nm. One nanometer (nm) is equal to one-billionth of a meter ($1 \text{ nm} = 10^{-9} \text{ m}$). An appropriate practical definition of nanotechnology that is unconstrained by an arbitrary size limitation is proposed by Bawa[12] as "the design, characterization, production and application of structures, devices and systems by controlled manipulation of size and shape at the nanometric scale (atomic, molecular and macromolecular scale) that produces structures, devices, and systems with

at least one novel / superior characteristic or property". This progressive continuous influx of novel technology platforms lead the potential to a positively healthcare impact at various important levels like detection of molecular changes responsible for disease pathogenesis, imaging and diagnosis of various diseases, drug delivery, multifunctional systems for combined therapeutic and diagnostic applications, vehicles to report the *in vivo* efficacy of a therapeutic agent and nanoscale enabling technologies which will accelerate scientific discovery and basic research. Nanoparticles can enter into smallest capillary vessels due to their ultra-tiny volume size and avoid rapid clearance by phagocytes, so that, their duration in the blood stream is greatly prolonged. They can penetrate cell and tissue gaps to arrive at the target organs. They are able to show controlled release properties due to their biodegradability, pH, ion and temperature sensibility of materials[13]. Presently, nanoparticles have been widely used to deliver antibiotics, anticancer agents, radiological agents, vaccines, proteins, polypeptides, antibodies, genes, and so on. Over the years, nanoparticle-based drug delivery and imaging systems have shown huge potential in biological, medical, pathological, and pharmaceutical applications.

Nanoparticle-Based Targeted Delivery Systems in Cancer Treatment:

The nano-range dimensions imbue nanoparticles with advantageous unique physical properties that facilitate immense possibilities in cancer therapeutics. Several new nanotechnologies, mostly based on nanoparticles, can facilitate delivering anticancer and imaging agents to kill cancerous cells in cancer therapy and cancer diagnosis respectively (Table 1).

Table 1: Various nanoparticle-based delivery systems with their therapeutic and diagnostic uses in cancer therapy.

Nanoparticle-based delivery systems	Therapeutic and diagnostic uses
Liposomes	Controlled and targeted drug delivery; Targeted gene delivery
Polymeric Micelles	Controlled and targeted drug delivery
Nanosystems	Tumor targeting
Nanoshells	Tumor targeting
Fullerene-based Derivatives	As targeting and imaging agent
Carbon Nanotubes (CNTs)	Drug, gene and DNA delivery; Tumor targeting
Dendrimers	Targeted drug delivery
Quantum Dots (QDs)	As targeting and imaging agent
Gold Nanoparticles (GNPs)	Targeted delivery and imaging agent
Solid Lipid Nanoparticles (SLNs)	Controlled and targeted drug delivery
Nanowires	As targeting and imaging agent
Magnetic nanoparticles	As targeting and imaging agent

Liposomes:

Liposomes are small artificial spherical vesicles composed of non-toxic phospholipids and cholesterol, which self-associate into bilayers to encapsulate drugs, genes and other biomolecules on aqueous interior (Figure 1)[14].

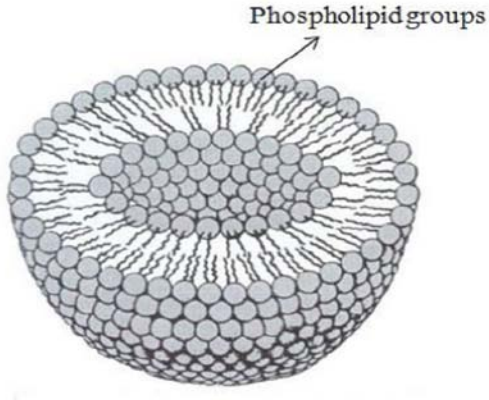

Figure 1: Liposome formed by phospholipids.

Liposomes are within the size-range of 25 nm to 10 μm, depending on their preparation method[15] various therapeutic agent loaded liposomes are being tested extensively as targeted delivery for fighting against cancers[16].

Liposomes of certain sizes, typically less than 400 nm, can rapidly penetrate tumor sites from the blood, but are kept in the blood stream by the endothelial wall in healthy tissue vasculature[17] Liposomes use over expressions of perforation in cancer nanovusculature to produce effective therapeutic concentrations of anticancer agents at the tumor site[18]. They have ability to limit and / or reduce some common side-effects like nausea, headache, vomiting, and hair loss. Several kinds of nanoscale liposomes, which are widely employed in cancer therapeutics, listed in Table 2.

Table 2: Nanoscale liposomes used in cancer therapeutics.

Liposomes	Drugs	Indications
Doxil	Doxorubicin	Kaposi sarcoma in AIDS
Mycet	Doxorubicin	Combinational therapy of recurrent breast cancer
Caelyx	Doxorubicin	Refractory kaposi sarcoma, ovarian cancer, recurrent breast cancer
DaunoXome	Daunorubicin citrate	Kaposi sarcoma in AIDS
OncoTCS	Vincristine	Non-Hodgkin's lymphoma
NX211	Lurtotecan	Ovarian cancer
Platar	Platinum compounds	Solid tumors

Polymeric Micelles:

Polymeric micelles, actually supramolecular, self-assemblies of block copolymers, are spherical, colloidal nanoscale particles with unique core-shell structure (Figure 2).

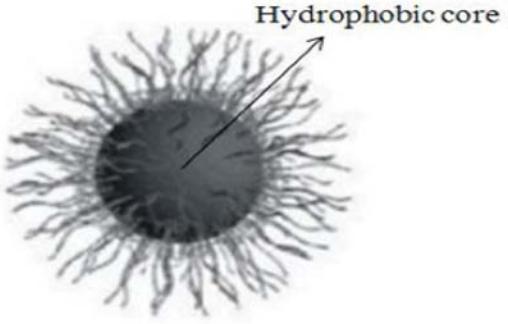

Figure 2: Polymeric micelles.

The inner core of polymeric micelles serves as a nanocontainer for hydrophobic molecules surrounded by an outer shell of hydrophilic flexible tethered strands of polymers[19]. For the formation of polymeric micelles, drugs can be partitioned in the hydrophobic core and the micelle core acts as a drug reservoir. The outer hydrophilic layer forms a stable dispersion in aqueous media, which can be administered intravenously. Polymeric micelles have demonstrated high durability in the blood stream and effective tumor accumulation after their systemic administration[19-20]. To support prolonged systemic circulation, polymeric micelles are designed to be biocompatible and thermodynamically stable in physiological solution[21]. The better thermodynamic stability of polymeric micelles indicates low critical micelle concentration (CMC), which prevents *in vitro* rapid dissolution[19, 22.] They are currently recognized as one of the most promising nanocarrier system for drug and gene delivery in the treatment of cancers. Polymeric micelle-based anticancer drug delivery has several benefits over other anticancer drug delivery systems like drug solubility, prolonged half-lives, efficient drug loading without any chemical modification of the parent drug, evading defenses, selective accumulation at the tumor site, and lower toxicity. They might show a tumor-infiltrating ability as well as controlled release of drugs, which is likely to be important for the complete eradication of tumor mass. Like liposomes, polymeric micelles can be modified using piloting ligand molecules for targeted delivery to specific cancer cells and pH-sensitive drug-binding linkers can be added for controlled drug delivery[12, 23]. Multifunctional polymeric micelles may be designed and developed to facilitate simultaneous drug delivery and related imaging in cancer therapeutics[23].

Nanosystems:

Novel nanosystems can be programmed to alter their structure and properties during the drug delivery process, providing more efficient extra- and intra-cellular delivery of encapsulated anticancer agents. This is achieved by molecular sensors that respond to physical and / or biological stimuli, including changes in pH, enzymes, temperature or red-ox potential. Biological drugs can be delivered with programmed nanosystems including DNA, SiRNA and other nucleic acids[24].

Nanoshells:

Nanoshells are another attractive platform for cancer diagnosis and cancer therapy. They are mainly metal-based nanoparticles. Nanoshells have a core of silica with a top layer of gold (Figure 3)[25].

Figure 3: Nanoshell.

By changing the thickness of the gold layer, the alteration in optical absorption properties of these nanoshells is possible when radiated with near-IR laser. The near–IR laser illuminates the tissue and the light will be absorbed by nanoshells to generate intense heat. Thus, nanoshells get active to destroy only the cancerous cells and tumors thermally without damaging the surrounding healthy cells[26]. Antibodies and/or therapeutic anticancer agents can be attached to their surfaces, enabling those nanoshells to target cancerous cells or tumors[8]. The gold nanoshell-antibody complex can be used to ablate breast cancer cells. Gold nanoshells have been used in rapid immunoassays, capable of detecting analyte within complex biological media without any sample preparation. Aggregation of antibody-nanoshell conjugates with extinction spectra in the near-IR is monitored spectroscopically in the presence of analyte[27].

Fullerene-based Derivatives:

Fullerene-based derivatives are recently proposed in nanopharmaceutical formulations and have found various applications in cancer therapy[28-29]. They are crystalline particles in form of carbon atoms. The most abundant form of fullerenes is Buckminster fullerenes (C 60) with 60 carbon atoms and arranged in a spherical structure with truncated icosahedron shape, resembles that of a soccer ball (bucky ball), which contains 20 hexagons and 12 pentagons (Figure 4).

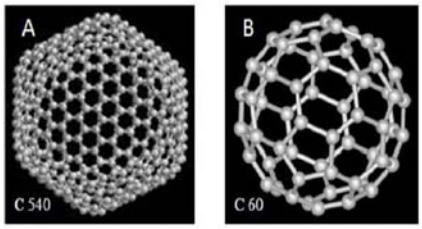

Figure 4: Fullerene-based derivatives; (A: fullerene C540, B: fullerene C60).

Other fullerenes are C70, C76, C78, C84, C86, C540 etc[30]. Fullerene cages are about 0.7 to 1.5 nm, in diameter and

the cage structure of fullerene is ideal for attaching anticancer agents or even radiological agents to increase treatment efficacy for killing as well as diagnosis of cancerous cells. Their good stability make them unique candidates for safely delivering highly toxic substances to tumors[29]. Both empty and metallofullerenes have low *in vitro* and *in vivo* cytotoxicity. Endohedral metallofullerenes have shown their potential application in diagnosis. Water solubilized forms of metallofullerenes like $M@C_{82}(OH)_{30}$ are being used as magnetic resonance imaging (MRI) contrast agents, X-ray contrast agents, and radiopharmaceuticals. Another metallofullerene derivative, $^{166}Ho^{3+}@C_{82}(OH)_{30}$ has been extensively studied as radioactive tracer for imaging and killing for cancerous cells[30]. The advantage of fullerene-based therapies over other targeted therapies is likely to be fullerene potential to carry multiple drug pay-loads such as taxol and other chemotherapeutic agents[8].

Carbon Nanotubes (CNTs):

Carbon nanotubes consist of exclusively carbon atoms arranged in a series of condensed benzene rings rolled-up into tubular architecture (Figure 5).

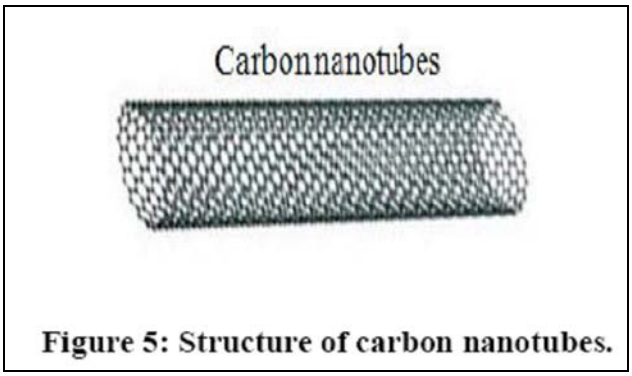

Figure 5: Structure of carbon nanotubes.

Carbon nanotubes belong to the family of fullerenes, the third allotropic form of carbon along with graphite and diamond, have been recently developed to use in cancer therapeutics[31]. Tumor targeting carbon nanotubes have been synthesized covalently attaching multiple copies of tumor specific monoclonal antibodies (MABs), radiation ion chelates and various fluorescent probes[32]. The surface of carbon nanotubes can be modified with proteins for cellular uptake. Then they are heated up upon absorbing near-IR light wave. When exposed to near-IR light carbon nanotubes quickly release excess energy as heat (~70ºC), which can kill cancerous cells[28]. The approach of coating the surfaces of tiny carbon nanotubes with MABs is used towards developing a biosensor for breast cancer detection, by functionalizing the carbon nanotubes with antibodies that are specific to cell surface receptors of breast cancer cells. They often further potential of killing cancerous cells over a wide area that may serve the biological cell-signaling pathway, thus promoting cancer remission.

Dendrimers:

Dendrimers were first described by Vogtle et al[33]. They are perfect monodisperse macromolecules with regular and highly branched 3-D architecture. Dendrimers consist of a series of chemical shells, namely an interior small core; interior layers (generations) composed of repeating units, radically attached to the interior core and exterior (terminal functionality) attached to the outermost interior generations (Figure 6)[34].

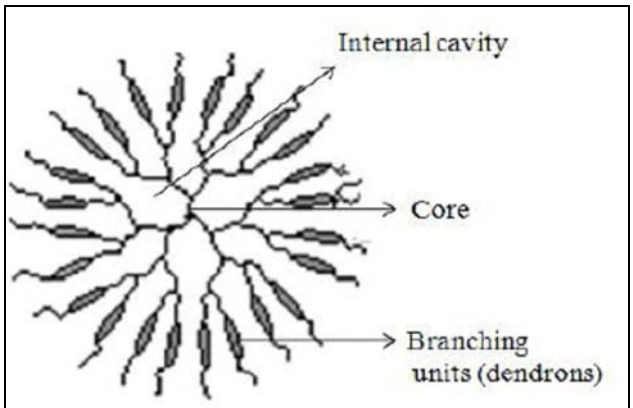

Figure 6: Structure of dendrimer.

The emerging role of dendrimers for anticancer therapies and diagnostic imaging has highlighted the advantages of these well-defined materials as the newest class of macromolecular nanoscale delivery devices[35]. Dendrimers used in drug delivery and imaging are usually 10 to 100 nm in diameter with multiple functional groups on their surfaces rendering them an ideal carrier systems for targeted drug delivery. Scientists and researchers have fashioned dendrimers into an effective and sophisticated anticancer therapy machines carrying 5 important chemical tools: (i) a molecule designed to bind cancerous cells and tumors, (ii) fluorescence upon locating genetic mutations, (iii) to assist in imaging tumor shape using X-rays, (iv)carrying therapeutic agents released on demand and (v) signaling when cancerous cells are finally dead[8]. Antibody-dendrimer conjugates have been used for radiolabelling with minimum loss of immunoreactivity[36]. Research on dendrimer-based delivery applications shows that anti-PSMA antibody (J 591) when conjugated with a dendrimer containing fluorocrome, can be used for targeting prostate cancer and imaging[37]. Again, the controlled surface modification followed by the conjugation of folate and fluoresin moieties on the surface of dendrimer, is shown to yield molecules capable of tumor targeting through folate receptors[28, 38].

Quantum Dots (QDs):

Quantum dots, semiconductor nanocrystals have emerged with promising applications for early detecting of cancers and determining the efficacy of tumor therapies[39]. They are ranging from 2 to 10 nm in diameter and possessing unique tunable targeting properties. Quantum dots can be prepared from semiconductor materials by electrochemistry or by colloidal synthesis. The common quantum dots are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), indium arsenide (InAs) etc[14]. Depending on their size, they can excite at appropriate wavelengths. They can absorb white light and re-emit it within nanoseconds with different combinations of particles. Thus, various quantum dots can emit different fluorescent light (400 to 1350 nm)[39]. They are used as

fluorescent probes in diagnostic imaging and therapeutics. Quantum dots can be conjugated to a ligand (Figure 7).

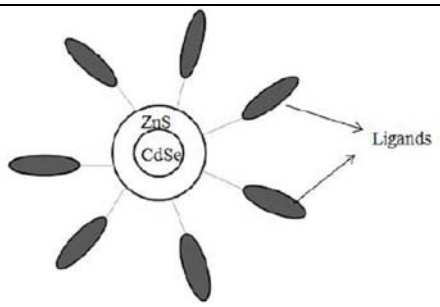

Figure 7: Ligand conjugated ZnS-capped CdSe quantum dot.

In 1998, Smith et al[40] demonstrated ZnS-capped CdSe quantum dots coated with mercaptoacetic acid could bond to blood transferrine *in vivo*. This fluorescent complex was absorbed by tumor cells. Gao et al.[41] demonstrated *in vivo* cancer targeting and imaging in living animals by quantum dot-tagged prostate cancer cells. In this study, systemic injection of multifunctional quantum dot probes were used to achieve sensitive and multicolor fluorescence imaging of cancerous cells. But unfortunately, under some conditions, quantum dots become cytotoxic[42]. Modification of quantum dots by PEG glycation and micelle encapsulation may limit cytotoxicity[43]. Research on quantum dots is continuing to find biocompatible and effective quantum dots.

Gold Nanoparticles (GNPs):

Gold nanoparticles have recently emerged as an attractive candidate in cancer therapy as targeted delivery systems. They have been also used as contrast agents *in vitro* based on their ability to scatter visible light. Gold nanoparticles exploit unique physical and chemical properties for transporting and unloading pharmaceuticals[44]. They are inert and non-toxic and have shown to have 600 times more absorption in cancer cells than normal human cells. The ability of gold nanoparticles to bind strongly with various biological molecules has been utilized to target tumors by tagging. Researchers have developed gold nanoparticles-based ultra-sensitive detection systems for DNA and protein markers associated with many forms of cancers using these[8]. It was demonstrated that systemically delivered gold nanoparticles-tumor necrosis factor (GNP-TNF) accumulated in tumors in a subcutaneous model of colon cancer[1].

Solid Lipid Nanoparticles (SLNs):

Solid lipid nanoparticles hold significant promise in cancer treatment. They are particles of submicron size (50 to 1000 nm) made from lipids that remain in a solid state at room as well as body temperature. Since early 1990's, a number of solid lipid nanoparticle-based systems for the delivery of anticancer agents have been successfully formulated and tested. Various anticancer agents like doxorubicin, daunorubicin, idarubicin, pacltitaxel, camptothesins, etoposide, etc have been encapsulated using this nanotechnological approach[45]. Several obstacles frequently encountered with anticancer agents, such as a high incidence of drug resistant tumor cells can be partially overcome by delivering them using solid lipid nanoparticles[45].

Nanowires:

Nanowires are glowing silica wires in nanoscale, wrapped around single strand of human hairs. They are about five times smaller than virus and several times stronger than spider silk[8]. Nanowire based arrays have significant impact for early diagnosis of cancer, and cancer treatment. The nanowire-based delivery enables simultaneous detection of multiple analytes such as cancer biomarkers in a single chip, as well as fundamental kinetic studies for biomolecular reactions[46]. Protein coated nanowires have potential applications in cancer imaging like prostate cancer, breast cancer and ovarian malignancies.

Magnetic nanoparticles:

Magnetic nanoparticles are able to target cancerous cells and have potential use in cancer therapeutics. The magnetic effect of magnetic nanoparticles is due to super paramagnetic iron oxides, typically Fe_2O_3, and Fe_3O_4, which do not retain their magnetic property when removed from the magnetic field[47]. Their paramagnetic characteristics have made them good candidate the destruction of tumors *in vivo* through hypothermia. Polymer coating on the surface of magnetic nanoparticles prevents their cytotoxicity and allows them to move freely in the organism without any reaction or adhesion[47].

Clinical Toxicities of Nanoparicle-Based Delivery Systems: A Challenge for Nanotechnology:

In spite of rapid scientific advances in the field of nanotechnology, significant challenges are remaining present before the application of nanoparticle-based delivery in clinical setting. Unfortunately, there has not been extensive research conducted to evaluate the clinical toxicities of nanoparticles. Curtis et al.[48] hypothesized possible mechanisms of clinical toxicities of nanoparticles-

1. Toxicity of nanoparticles may be due to their small size as suggested by studies of ultra-fine particles in the respiratory tract[48]. They are also able to pass biological barriers and they have propensity to agglomerate. Thus, they may affect absorption, distribution and excretion of these nanoparticles[49].
2. Shape may also be an important factor that determines toxicity. e.g., carbon nanotubes[49.]
3. Nanoparticles can create and / or scavenge reactive oxygen species (ROS) and free radicals[50].
4. Nanoparticles might also trigger immune responses e.g., antibody specific to fullerenes, dendrimers and protein dendrimer conjugates have shown strong immunogenic responses[51]. However, there is a growing concern about the role in possible allergic reactions[49].

Understanding of physicochemical, molecular and physiological process of nanoparticles is imperative for nanoparticle-based delivery to become a reliable and

sustainable treatment modality. Many preclinical studies have demonstrated a reduced toxicity profile, when incorporating and delivery of immunosupressants like rapamycin and cyclosporine etc, as well as anticancer agents like geldanamycin etc, into various nanocarriers in rodent studies[52]. The safety of patients and clinicians, who will handle these nano-deliveries in the treatment of cancer in future are of primary concern. Clinical protocols must be established on the handling and delivering nanoparticle-based delivery effectively.

CONCLUSION:

Nanoparticle-based targeted delivery systems such as liposomes, polymeric micelles, nanosystems, nanoshells, fullerene-based derivatives, carbon nanotubes, dendrimers, quantum dots, gold nanoparticles, solid lipid nanoparticles, nanowires, magnetic nanoparticles, etc hold great potential to increase the cure-rate of cancer patients, while minimizing side effects. In future, various multifunctional novel nanoparticle-based targeted deliveries may be designed and developed to facilitate simultaneous targeted drug delivery and related imaging in cancer therapy. As we look to what is on the horizon for cancer therapeutics during the upcoming decades, we are optimistic that an increasing number of novel nanoparticle-based deliveries for therapeutic and diagnostic applications in cancer treatments will emerge. We expect that with continued support, cancer therapeutics will be an important beneficiary of nanotechnology for years to come.

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