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Nanotechnology in cancer drug delivery and selective targeting

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Abstract
Numerous investigations have shown that both tissue as well as cell distribution profiles of anticancer drugs can be controlled by their entrapment in submicronic colloidal systems (nanoparticles). The aim behind this approach is to increase antitumor efficacy and to reduce systemic side-effects. The biological application of nanoparticles is a developing branch of nanotechnology that raises new possibilities in the diagnosis and treatment of human cancers. The use of nano technology in cancer treatment offers possibilities including destruction of tumors with minimal damage to healthy tissue and organs. This review provides information regarding tumor targeting with conventional or long-circulating nanoparticles. The in vivo fate of nanoparticles, after intravascular or tumor administration and the mechanism involved in tumor regression is discussed. Nanoparticles are beneficial for the selective delivery of oligonucleotides to tumor cells. Moreover, certain types of nanoparticles shows capacity to reverse MDR resistance, which is a major problem in conventional chemotherapy. The use of nanoparticles will allow simultaneous tumor targeting and drug delivery in a unique manner. Ultimately, the advantages include enhancing solubility of hydrophobic drugs, circulation time prolongation, minimizing nonspecific uptake, preventing undesirable off-target and adverse effects, improving intracellular penetration, and allowing for specific cancer targeting.

Keywords: nanotechnology, cancer drug

1. Introduction
Cancer is the most serious fatal diseases in today's world that kills people every year. It can affect any organ of people from any place. Due to its complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. Many approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects [1]. Treatment for cancer includes surgical removal, chemotherapy, radiation, and hormone therapy. Chemotherapy delivers anticancer drugs systemically to patients for controlling the proliferation of cancerous cells. Due to nonspecific targeting by anticancer agents, many side effects occur and poor delivery of those agents cannot bring out the desired outcome in most of the cases. Development of cancer drug involves a very complex procedure that is associated with advanced polymer chemistry and electronic engineering. The main challenge of cancer treatment is to differentiate the cancerous cells and the normal body cells. Hence, the main objective becomes engineering the drug in such that it can identify the cancer cells to diminish their growth and proliferation [2]. Conventional chemotherapy cannot target the cancerous cells selectively without interacting with the normal body cells. So they cause serious side effects including organ damage which results in impaired treatment with lower dose and ultimately low survival rates [3].
Nanotechnology is the science that deals with the size range from a few nanometers (nm) to several hundred nm, depending on their desired use [4]. It offers numerous benefits to overcome the limitations of conventional treatment approaches. It is promising both in cancer diagnosis as well as treatment as it can enter the tissues at molecular level. Cancer nanotechnology is being interestingly evaluated and implemented in cancer treatment indicating a major advance in detection, diagnosis, and treatment of the disease. Various researches are carried out to discover more accurate nanotechnology based cancer treatment to minimize the side effects of the conventional formulations [5, 6]. Nanoparticles are now designed to assist therapeutic agents to pass through biologic barriers, to mediate molecular interactions, and to identify molecular changes [7, 8].

2. Limitations of conventional chemotherapy
Conventional chemotherapeutic agents act by destroying rapidly dividing cells, which is the main property of neoplastic cells. That is why chemotherapy also damages normal healthy cells that divide rapidly like cells in the bone marrow, macrophages, digestive tract, and hair follicles [1].The main limitation of conventional chemotherapy is that it is not specific to the cancerous cells and results in side effects including myelosuppression (decreased production of white blood cells causing immunosuppression), mucositis (inflammation of the lining of the digestive tract), alopecia (hair loss), organ dysfunction, and even anemia or thrombocytopenia. These side effects can impose dose reduction, treatment delay, or discontinuance of the given therapy [9, 10]. Cell division may be effectively ceased near the center in solid tumours making chemotherapeutic agents insensitive to chemotherapy. Therefore, chemotherapeutic agents fails to penetrate and reach the core of solid tumors and thus unable to kill the cancerous cells [11].
Traditional chemotherapeutic agents gets washed out from the circulation being engulfed by macrophages. So they remain in the circulation for a very short time and cannot interact with the cancerous cells causing the chemotherapy completely ineffective. The poor solubility of the drugs is a

problem of concern in conventional chemotherapy making them unable to penetrate the biological membranes [3]. Another problem is associated with P-glycoprotein, a multidrug resistant protein which is overexpressed on the surface of the cancerous cells, prevents drug accumulation inside the tumor, acting as the efflux pump, and mediates the development of resistance to anticancer drugs. Thus making the administered drugs unsuccessful or fails to bring the desired output [12].

3. Nanotechnology in cancer targeting

Nanotechnology was able to make a great revolution in selective cancer targeting. Nanoparticles are designed through various modifications such as changing their size, shape, chemical and physical properties and hence program them for targeting the desired cells. They are able to target the neoplastic cells either through active or passive targeting.

3.1 Active Targeting

In active targeting, nanoparticles containing the chemotherapeutic agents are designed such that they directly interact with the defected cells. Targeting agents are usually attached with the surface of nanoparticles for molecular recognition. Designed nanoparticles target the cancerous cells either by ligand-receptor interaction or antibody-antigen recognition [13]. Nanotechnology based targeted delivery system has three main components: (i) an apoptosis-inducing agent (anticancer drug), (ii) a targeting moiety-penetration enhancer, and (iii) a carrier. Different substances are used to construct a nanoparticle. Commonly used materials include ceramic, polymers, lipids, and metals [14]. Natural and synthetic polymers and lipids are mainly used as drug delivery vectors [15]. Particles containing chemotherapeutic agents are engulfed by phagocytes and rapidly cleared by the reticuloendothelial system (RES). Many strategies were developed to sustain the nanoparticles in blood stream one of which is the alterating the polymeric composition of the carrier. Nanoparticles are coated with hydrophilic polymers to prevent washing out and remain in the bloodstream for a longer time that can sufficiently target cancerous cells. Hydrophilic polymer coating on the nanoparticle surface helps in repelling plasma proteins and escapes from being opsonized and cleared. This is called as “cloud” effect [16]. Usually used hydrophilic polymers are polyethylene glycol (PEG), poloxamines, poloxamers, polysaccharides etc [17, 18]. Cancerous cells are having some unique properties which differentiate them from the healthy cells at molecular level. Some receptors are over expressed on the surface and make the distinguishing feature. Attaching of the complementary ligands on the surface of nanoparticles helps them to target only the cancerous cells. Once the nanoparticles bind with the receptors, they undergo receptor-mediated endocytosis or phagocytosis by cells, resulting in cell internalization of the encapsulated drug [4].

Specific Receptor Targeting

Folate receptors are over expressed in many neoplastic cells which acts as a target for certain anticancer therapies. Using this concept, researchers are designing the surface of nanoparticles with folic acid [19]. Folic acid targeted daunomycin-HPMA conjugates were found to increase both the number of survivors and the survival time of tumor-bearing mice.Folic acid may be highly effective in enhancing the efficacy of other polymer-bound cytotoxins [20]. Some other preparations include nanoparticles to which folate was conjugated covalently using surface carboxyl groups as well as conjugation of folate to hydrazine modified poly-lactic acid nanoparticles. Isobutyl-cyanoacrylate (IBCA) nanocapsules were prepared and coated with folate that showed a significantly increased efficacy of nanocapsules targeted to the tumor [7]. Nanoparticles are wiely being investigated to target the transferrin receptors for binding and cell entry, as these are overexpressed by certain tumor cells to increase their iron uptake. Transferrin (Tf) can be conjugated to a variety of materials for cancer targeting which include Tf-chemotherapeutic agent, Tf-toxic protein, Tf-RNases, Tf-antibody, and Tf-peptide[21,22]. Tf-lytic hybrid peptide can selectively target cancerous cells. The intravenous administration of Tf-lytic peptide significantly inhibited tumor progression.

Luteinizing Hormone-Releasing Hormone Receptor. Luteinizing hormone-releasing hormone (LHRH) is being used in many ongoing researches as a targeting moiety (ligand) to LHRH receptors that are over-expressed in the plasma membrane of various types of cancer cells like breast cancer, ovarian cancer, and prostate cancer [23, 24]. The particles were particularly designed to dissolve the drug in a cell's internal fluids, controlling the release rate. For selective targeting, the nanoparticles were “decorated” on the outside with targeting molecules called aptamers, tiny chunks of genetic material. The aptamers specifically recognize the surface molecules on cancer cells. In addition, the nanoparticles also contained polyethylene glycol molecules to keep them away from being rapidly destroyed by macrophages [25].

A tracking agent, two-photon dye ASPI-SH, was attached to the surface of the iron oxide. Silica was added to form the structure of the silica shell before additional silica shell grown by tetraethylorthosilicate hydrolysis. The targeting agent LHRH was coupled to the silica shell through carbon spacers so as to prevent stearic hindrance during the interaction of the targeting agent with its complementary molecule on cells. In a study after the administration of the nanoparticles, the patients were exposed to a DC magnetic field. The selective interaction, internalization, and so forth were investigated by using LHRH receptor expressing cells on oral epithelial carcinoma cells. Data clearly showed that the nanoparticles selectively interacted with the specific cell types [7].

Asialoglycoprotein (ASGP), another receptor which is overexpressed in hepatoma, is utilized in cancer targeting by nanoparticles for anticancer drug delivery. In a study the nanoparticles were conjugated with galactosamine (GAL) through an amide linkage to enhance hepatoma HepG2 cell uptake by targeting ASGP receptors. Immunofluorescence analysis utilizing a rhodamine-123 probe, encapsulated in the hydrophobic core of the gal-nanoparticles, revealed the high degree of selectivity of the nanoparticles to hepatic tumors with enhanced cellular uptake through receptor-mediated endocytosis resulting in subsequent release of the encapsulated paclitaxel inside the cytoplasm. Those nanoparticles inhibited the growth of the cells with a consequent decrease in systemic toxicity compared to free paclitaxel.

A dual-particle tumor targeting system was developed for selectively inhibiting angiogenesis in hepatoma. Nanoparticle, encapsulating ganciclovir conjugated with galactosamine, was the first component and an enhanced

permeability and retention (EPR) mediated targeting nanoparticle containing an HSV thymidine kinase (TK) gene was the second component of the dual-particle tumor targeting system. It was stated that thymidine kinase would digest ganciclovir to produce cytotoxic effects after cancer cells internalization of the first and second nanoparticles together. Thus it kills the targeted cancer cells [7].

a) Antibody Mediated Targeting

Many tumor cells show unusual antigens due to their genetic defects, that are either inappropriate for the cell type, environment, or temporal placement in the organisms' development. The immune responses educed by tumor antigens are not so strong because they are recognized as own cells. Highly specific monoclonal antibodies (mAbs) are used to strengthen the immune response and to intensify the immune system's antitumor capacity. These antibodies target proteins that are abnormally expressed in neoplastic cells and are essential for their growth. Nanoparticles conjugated with an antibody against a specific tumor antigen are developed for selective drug delivery [6]. Most of the mAbs are produced by the clones of a single hybridoma cell. After binding with tumor antigens, mAbs can destroy cancer cells through a variety of approaches which include directly inducing apoptosis, blocking growth factor receptors, and anti-idiotype formation. They can indirectly eradicate cancer cells by activating complement mediated cellular toxicity and antibody dependent cell mediated cytotoxicity [7]. Antibody engineering has recently came with the outcome of antibody production that contains animal and human origins such as chimeric mAbs, humanized mAbs (those with a greater human contribution), and antibody fragments. Antibodies can be used in their original form or as fragments for cancer targeting. However, the presence of two binding sites (within a single antibody) gives higher binding opportunity and makes it advantageous to use the intact mAbs. Moreover, a signaling cascade is initiated to kill the cancer cells when macrophages bind to the Fc segment of the antibody. The Fc portion of an intact mAb can also bind to the Fc receptors on normal cells resulting in increased ability to evoke an immune response and liver and spleen uptake of the nanocarrier. Stability in long-term storage is their additional advantage. On the other hand, antibody fragments including antigen-binding fragments (Fab), dimers of antigen-binding fragments (F(ab′)2), single-chain fragment variables (scFv), and other engineered fragments are considered safer with reduced nonspecific binding [4, 26, 27]. The efficacy of antibodies can be increased by conjugating a therapeutic agent directly to it. mAbs can act as the highly specific probes when they are attached to nanoparticles to aid in targeted delivery of various antitumor cytotoxic agents[4]. Binding affinity and selectivity to cell surface targets by engineering proteins can also be increased through the detection of a specific conformation of a target receptor.

A new method for the preparation of hollow protein nanoparticles containing ganciclovir which encapsulates a hepatic cancer therapeutic gene, thymidine kinase (HSV1tk), derived from simple herpes virus. The nanoparticles were modified by displaying a hepatitis B virus surface-antigen to own hepatocyte recognition ability and particle formation ability. Through the hepatic cancer targeting directly deliverd the gene. The therapeutic effect of the HBsAg-HSV1tk hollow protein nanoparticles specific to hepatic cancer was also confirmed. They also developed a method of encapsulating cytotoxic drug, containing a cancer treating gene, within nanoparticles modified to display an antibody used for specific targeting of human squamous carcinoma cells. The nanoparticles were modified to express an antibody that recognizes the epidermal growth factor receptor, expressed by the cancer cells. Animal studies confirmed that the transfer and expression of the gene was very specific to the human squamous carcinoma and highly effective in treatment [7]. Wartlick *et al*. developed biodegradable nanoparticles based on gelatin and human serum albumin in which the surface of the nanoparticles was modified by covalent attachment of the biotin-binding protein NeutrAvidin, enabling the binding of biotinylated drug targeting ligands by avidin-biotin complex formation. HER2 receptor, a member of the epidermal growth factor receptor family, is overexpressed in certain types of cancer (breast cancer). HER2 receptor specific antibody trastuzumab (herceptin) was conjugated to the surface of these nanoparticles for targeting HER2-overexpressing cells. Confocal laser scanning microscopy showed an effective internalization of these nanoparticles by HER2-overexpressing cells through receptor-mediated endocytosis [28].

Nanoparticles can be designed to enhance Fas ligand expression, a type-II transmembrane protein which induces apoptosis when bound with its receptor, on the surface of Fas receptor-expressing leukemia cells. Fas ligand-receptor interactions play a significant role in the regulation of the immune system and the progression of cancer [29, 30]. Fas agonist CH-11, a monoclonal antibody to the Fas receptor, is conventionally used to target the cancer cells. The mAb rituximab (Rituxan) was approved in 1997 for the treatment of patients with non-Hodgkin's lymphoma.

b) Antiangiogenesis

Angiogenesis is described as the growth of new blood vessels from preexisting vessels. Tumors cannot grow more than 2 mm in diameter without angiogenesis [31]. Cancerous cells produce abnormal amounts of angiogenic growth factors resulting in an excessive angiogenesis overwhelming the effects of natural angiogenesis inhibitors giving rise to leaky and tortuous vessels that are in a constant state of inflammation Studies on breast cancer showed that the degree of metastasis, tumor recurrence, and shorter survival rates are correlated with angiogenesis [32, 33]. Antiangiogenesis therapy is designed based on two mechanisms: drugs which prevent the formation of new blood vessels that supply to the tumor (e.g., TNP-470, endostatin, and angiostatin) or drugs that destroy the existing blood vessels (e.g., combretastatin) [34]. The objective of antiangiogenic therapy is to delay both primary and metastatic tumor growth by blocking the supply of essential nutrients and the removal of metabolites causing stunted tumor growth thereby avoiding tumor spread as well as enhancing the shrinkage of tumors [35]. Antiangiogenic drugs either act directly by targeting endothelial receptors or indirectly by targeting angiogenic cytokines [36-38]. Active targeting of the tumor vasculature by nanoparticles is achieved by targeting the VEGF receptors (VEGFRs), integrin receptors, and other angiogenic factors. Integrins, which mediate the attachment between a cell and its surroundings, are the main component in angiogenesis process and their increase in number enhances the survival, growth, and invasion of both tumor and endothelial cells [38, 39]. Integrin antibody has been widely used as a targeting

moiety on nanovectors for anti-angiogenesis therapy due to its pleitropic upregulation in many tumor settings. Some of them have passed several clinical trials [40-43]. Tumor angiogenesis was successfully detected in rabbit and mouse models by perfluorocarbon nanoparticles conjugated to various contrasting agents (Gadolinium, Gd, or fluorine isotope 19, ^{19}F) and linked to an integrin antibody [40-42]. The use of peptides as the targeting agents resulted in increased intracellular drug delivery in different murine tumor models [44, 45]. An approach to target integrin overexpression involves using a synthetic peptide containing the recognition site for integrins, namely an arginine-glycine-aspartic acid (RGD) sequence [41]. The first angiogenesis inhibitor for colorectal cancer therapy, bevacizumab (Avastin), an anti-VEGF mAb that inhibits the growth factor of new blood vessels, was approved in 2004 [4, 46]. Prokop and his team developed a method of preparing biocompatible nanoparticle that can be used as drug delivery vehicles. They were designed to retain and deliver Antiangiogenic compounds over an extended period of time for targeting tumor vasculature. Nanoparticles were formulated comprising a hydrophilic core of sodium alginate, cellulose sulfate, and Antiangiogenic factors such as thrombospondin (TSP)-1 or TSP-517 which was crosslinked with dextran polyaldehyde with calcium chloride or conjugated to heparin sulfate with sodium chloride. In addition, luciferase (bioluminescent agent) or polymeric gadolinium (contrast agent) was placed within the polyanionic core. The hydrophilic shell surrounding the core additionally contained spermine hydrochloride, poly (methylene-co-guanidine) hydrochloride, and pluronic F-68, calcium chloride, and a targeting ligand conjugated to an activated polyethylene glycol or crosslinked to dextran polyaldehyde. Targeted nanoparticles were evaluated by monitoring luciferase in a murine model [7].

3.2 Passive Targeting

Nanoparticles also target cancer through passive targeting. As apoptosis is stopped in cancerous cells, they continue to suck nutritious agents abnormally through the blood vessels forming wide and leaky blood vessels around the cells induced by angiogenesis. Leaky blood vessels are formed because of basement membrane abnormalities and decreased numbers of pericytes lining rapidly proliferating endothelial cells [47]. So, the permeability of molecules to pass through the vessel wall into the interstitium surrounding tumor cells is increased. The size of the pores in leaky endothelial cells falls between 100 to 780 nm [48-50]. Thus nanoparticles below this size can easily pass through the pores which results in facilitating the efflux of nanoparticles to cluster around the neoplastic cells [51, 52]. Nanoparticles can be targeted to specific area of capillary endothelium, to concentrate the drug within a particular organ and perforate the tumor cells by passive diffusion or convection. Lack of lymphatic drainage eases the diffusion process. The tumor interstitium is composed of a collagen network and a gel like fluid. The fluid has high interstitial pressures which prevent the inward flux of molecules. Tumors also lack well-defined lymphatic networks having leaky vasculature. So, drugs that enter the interstitial area may have extended retention times in the tumor interstitium. This feature is called the enhanced permeability and retention (EPR) effect and facilitates tumor interstitial drug accumulation [53, 54]. Nanoparticles can accumulate easily as well as selectively by enhanced permeability and retention effect and then diffuse into the cells [55].

4. Cellular uptake, ph dependent drug delivery, and prevention from lysosomal degradation

Active or passive targeted nanoparticles have difficulties in releasing drugs in the neoplastic cells since lysosomal enzymes rapidly destroy both the nanoparticles and drugs inside the cells. After getting internalized, the colloidal carriers usually reach the lysosomal compartment, where hydrolytic enzymes degrade both the carrier and its content. Therefore, the intracellular distribution of the carrier is modified when the encapsulated drug is a nucleic acid. Because pH around of tumors cells is more acidic, carriers that change solubility at lower pH can be used to target and release drugs. The extracellular environment of solid tumors is acidic and there is an altered pH gradient across their cell compartments. Nanoparticles sensitive to the pH gradients are promising for cancer drug delivery. A pH-responsive nanoparticle consists of a shell and a core which makes them respond to the pH gradient and changes its solubility pattern. The core-shell polymer nanoparticles are designed with their lower critical solution temperature (LCST) being dependent on the ambient pH 7.4. At low pH, in and around of tumor cells the resulting change in LCST causes the core-shell nanoparticles to deform and precipitate in an acidic environment, triggering the release the chemotherapeutics. A targeting molecule is additionally conjugated to the shell of the nanoparticles which can recognize tumor cells [56]. A study reported a new strategy for preparing a pH sensitive sustained release system for cancer treatment. The system utilizes solid hydrophobic nanospheres containing anticancer drugs which are encapsulated in a pH sensitive microsphere. It also includes a bioadhesive material into the solid hydrophobic matrix of the nanospheres. The nanosphere hydrophobic matrix was formed by dispersing paclitaxel into the hot melt of candelilla wax. The microsphere of pH sensitive matrix was created by adding the drug/wax mixture into an aqueous solution containing a pH dependent anionic polymer that is stable at pH 7.4 but solubilized at pH 6 and lower. The prepared suspension was spray dried to produce a free flowing dry powder which consists of 10% paclitaxel. The nanospheres are able to release the drug over an extended period of time by dissolving/swelling the microsphere at a lower pH which is typically found in cancerous tissue [7]. Recently, researchers developed a system which either fuse with the plasma membrane or have a pH-sensitive configuration that changes conformation in the lysosomes and allows the encapsulated material to escape into the cytoplasm[57].Biodegradable nanoparticles were formulated from the copolymers of poly(d,l-lactide-co-glycolide) for their rapid endolysosomal escape. The system works by selective reversal of the surface charge of nanoparticles (from anionic to cationic) in the acidic endolysosomal compartment causing the nanoparticles to interact with the endolysosomal membrane and escape into the cytosol. These nanoparticles are able to deliver wide ranged therapeutic agents, including macromolecules such as DNA at a slow rate, for sustained therapeutic effect. For using nanotechnology in cancer treatment, researchers developed thermoresponsive, pH-responsive, and biodegradable nanoparticles by grafting biodegradable poly (d,l-lactide) onto N-isopropyl acrylamide and methacrylic acid. It is sufficient for a carrier system to concentrate the drug (hydrophobic, that crosses the plasma membrane easily) in the target tissue.

5. Hyperthermia

Healthy cells are capable of surviving exposure to temperatures up to 46.5°C. Irreversible cell damage occurs to the cancerous cells at temperatures from approximately 40°C to about 46°C due to the disorganized and compact vascular structure for which they are less stable which means surrounding healthy cells are more readily able to spatter heat and maintain a normal temperature. This process is called hyperthermia which is used for the purpose of damaging protein and structures within cancerous cells and in some cases, which causes tumor cells to directly undergo apoptosis. Nanoparticles are utilized for a variety of purposes in hyperthermia-based treatments which include serving as the active thermotherapeutic agents, sensitizers and are also used for targeting purposes like antibody enhanced targeting to increase efficacy and to reduce hypothermia-associated side effects. Nanoparticles can locate and specifically target the deep-seated tissues and organs. Magnetic fluid hyperthermia is a well-practiced old method for cancer treatment. Small magnetic particles are used which respond to an externally applied magnetic field by heating up. In addition to specific targeting, nanoparticles also have another benefit. Cells that have picked up some of the particles cannot get rid of them, and every daughter cell will have one half of the amount of particles present on the mother cell.

A method of manufacturing nanoparticles for targeted delivery of thermotherapy in cancer treatment was developed. The prepared ferromagnetic nanoparticles were coated with biocompatible material like poly (methacrylic acid-co-hydroxy-ethylmethacrylate) using free-radical polymerization. A stabilizing layer was formed around the magnetic particles by an ionic surfactant, sodium bis-2-ethylhexyl sulfosuccinate. For selective targeting, antibodies were attached to the surface of coated magnetic particles. The thermotherapeutic magnetic composition containing single-domain magnetic particles attached to a target specific ligand was inductively heated using a magnetic field. High efficiency of the bioprobes was determined in animal model.

6. Combining drugs with different physical properties

Several studies have shown that combination therapy is more effective than a single drug for many types of cancer. Drugs having different physical properties could not be combined into a single particle before. It was always been difficult to get the right amount of drug to the tumor. A new method was developed in which nanoparticles and drugs with different physical properties were incorporated which had been impossible with previous drug delivering nanoparticles. Earlier generations of nanoparticles mean encapsulation in a polymer coating by which drugs with different charges or different affinity could not be carried together. The new technique, called "drug-polymer blending," allows the researchers to hang the drug molecules like pendants from individual units of the polymer, before the units assemble into a polymer nanoparticle. They developed nanoparticles with hydrophobic docetaxel and hydrophilic cisplatin. After loading the drugs into the nanoparticle, the researchers added a tag which binds to a molecule called prostate-specific membrane antigen (PSMA), that is a type 2 integral membrane glycoprotein present on the surfaces of most prostate cancer cells. This allows the nanoparticles to bypass healthy tissues and reduce the side effects caused by most chemotherapy drugs. As a result, they go directly to their target region. The new technique facilitated them to precisely control the ratio of drugs loaded into the particle. They were also able to control release rate of the drugs after they entered the tumor cells [58].

7. Advantages of nanoparticle therapy over conventional chemotherapy in cancer treatment

- The use of nano technology in cancer treatment offers some exciting possibilities including the possibility of destroying cancer tumors with minimal damage to healthy tissue and organs as well as the detection and elimination of cancer cells before they form tumors.
- Nanoparticles confers several advantages over that of free drugs, including their capability to carry high payloads of drugs, with prolonged half-life and reduced toxicity of the drugs, and increased targeting efficiency.
- Using targeted nanoparticles to deliver chemotherapeutic agents in cancer therapy offers many advantages to improve drug/gene delivery and to overcome many problems associated with conventional chemotherapy. For example, nanoparticles via either passive targeting or active targeting have been shown to enhance the intracellular concentration of drugs/genes in cancer cells while avoiding toxicity in normal cells.
- Their advantages include enhancing solubility of hydrophobic drugs, prolonging circulation time, minimizing nonspecific uptake, preventing undesirable off-target and side effects, improving intracellular penetration, and allowing for specific cancer targeting
- Although targeted nanoparticles have emerged as one strategy to overcome the lack of specificity of conventional chemotherapy, there are also potential risks and challenges associated with this novel strategy. For instance, some cancer cell types would develop drug resistance over the drug treatment course, thereby rendering drugs released from the targeted nanoparticles to be ineffective. Combined therapies, such as the use of targeted nanoparticles for delivering both chemotherapeutics and gene therapeutics, might be effectively delivered and specifically targeted to cancer cells and tissues to overcome this drug resistance and to stop the tumor growth. Another strategy to overcome this drug resistance is to develop multifunctional targeted nanoparticles.

8. Targeting Agents

Nanocarriers are used as targeting agents for cancer therapy comprising anticancer drugs, targeting moieties, and polymers. There are a variety of nanocarriers such as liposomes, dendrimers, micelles, carbon nanotubes, nanocapsules, nanospheres, and so forth. Therapeutic agents can be entrapped, covalently bound, encapsulated, or adsorbed to the nanoparticles [4, 7]. Liposomes are composed of lipid bilayers where the core can be either hydrophilic or hydrophobic depending on the number of lipid bilayers [59, 60]. Liposomes having a single lipid bilayer contain an aqueous core for encapsulating water soluble drugs, whereas other liposomes having more than a single bilayer entrap lipid soluble drugs [60-61]. They are readily cleared by the macrophages and are therefore coated with inert polymers for stabilization in the physiological conditions. Liposomes are commonly coated with polyethylene glycol (PEG) [14, 16, 62-64]. In vivo study shows that liposomes coated with hyaluronan (HA) improves circulation time and enhances targeting to HA receptor-expressing tumors [65, 66]. Both active and passive

targeting can be achieved with liposomal drug delivery. Liposomal nanoparticles can conjugate with either antibodies or ligands for selective drug delivery [67, 68].They possess some advantages that they are biodegradation, nonantigenic and have a high transport rate [69]. They can also be designed for pH sensitive drug delivery or thermotherapy. Dendrimers are branched three dimensional tree-like structures with a multifunctional core. They are synthesized from either synthetic or natural elements such as amino acids, sugars, and nucleotides. Dendrimers can be prepared by controlled polymerization of the monomers maintaining desired shape and size. Multiple entities including both hydrophobic and hydrophilic molecules can be conjugated to dendrimers due to their exclusive branching point [60]. They can also be loaded with drugs using the cavities in their cores through hydrophobic interactions, hydrogen bonds, or chemical linkages. Dendrimers are capable of delivering genes, drugs, anticancer agents etc [60]. Micelles are spherical structures where molecules with a hydrophobic end aggregate to form the central core and the hydrophilic ends of other molecules are in contact with the liquid environment surrounding the core. Micelles are effective carrier for the delivery of water insoluble drugs carried in the hydrophobic core. Nanospheres are composed of a matrix system in which drug is evenly distributed by entrapment, attachment, or encapsulation. The surface of these nanoparticles can be modified by the addition of ligands or antibodies for targeting purposes. On the other hand, nanocapsules are like vesicles that have a central core where a drug is confined and a core is surrounded by a polymeric membrane. Targeting ligands or antibodies can be attached to the surface [16, 59]. Fullerenes (also called bucky balls) and nanotubes are a family of molecules composed of carbon in the form of a hollow sphere or ellipsoid tube [60]. Atoms may be trapped inside fullerenes while antibodies or ligands are bound to the surface for targeting. Carbon nanotubes are modified to make them water-soluble and functionalized as they can be linked to a variety of active molecules such as peptides, proteins, nucleic acids, and therapeutic agents. Nanotubes can be single walled or multiwalled [59]. Suitable polymers for nanoparticle preparation include poly (alkyl cyanoacrylates), poly (methy lidenemalonate), and polyesters such as poly (lactic acid), poly(glycolic acid), poly(e-caprolactone), and their copolymers. Poly (-caprolactone), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers are most extensively researched due to their biocompatibility and biodegradability [57, 70].

9. Conclusion

Nanotechnology has already revolutionized cancer therapy in many aspects and is radically changing the treatment pattern. It has made a great impact on selective recognizing of the cancerous cells, targeted drug delivery, and overcoming limitations of the conventional chemotherapies The side effects of the traditional chemotherapies can greatly be removed by these novel active or passive targeting which can substantially increase the survival rate. Targeted nanoparticles have provided an effective platform for a better and more specific delivery of cancer therapeutics. These targeted nanoparticles would be able to detect cancer cells, visualize their location in the body, deliver drugs to these cells only, circumvent drug resistance, kill cancer cells while sparing normal cells with minimal side effects, monitor treatment effects in real time, and provide feedback whether the patients respond well to the treatments to stop the treatment in time. The role and scope of targeted nanoparticles for drug delivery in cancer therapy is growing, and the development of effective multifunctional targeted nanoparticles will not be far in the future. Current nanotechnology based drug delivery systems for cancer treatment, which are already marketed and under research and evaluation, include liposomes, polymeric micelles, dendrimers, nanospheres, nanocapsules, and nanotubes.The formulations based on nanotechnology already been marketed are DOXIL (liposomal doxorubicin) and Abraxane (albumin bound paclitaxel).

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