



Recent Progress in Antitumoral Nanotechnology

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Abstract

The last advances in applications of nanotechnology in antitumoral prevention, detection and treatment during the last decade are reviewed. Drug delivery and negative side effects are the seminal challenges in order to get more effective cancer therapies. In this context, nanotechnology provides a quite versatile platform to deal with it. Herein is discussed the recent state-of-the-art of nanotechnology, which includes: metal nanoparticles, quantum dots, micelles, nanoencapsulation, polymeric nanoparticles, liposomes, ceramic-based carriers, dendrimers, nanoshells, and carbon nanotubes. Finally, the review discusses the advantages and challenges for the application of nanotechnology in antitumoral therapy.

Keywords

Nanotechnology, Nanoparticles, Antitumoral, Cancer therapy.

Introduction

Cancer arises when a group of cells begin to grow abnormally disregarding the division rules of normal cells. Because of their uncontrolled growth and proliferation, these cancer cells establish an autonomous tumor tissue. Metastasis, the spreading of malignant tumor cells, is the main cause of cancer lethality. Cancer is a leading cause of morbidity and mortality worldwide. In cancer therapy, undoubtedly the first and the most important step is diagnosis [1]. It is obvious that the earlier the cancer diagnosis, the better the chance for successful treatment and survival. Thus, the detection time frame has an enormous effect on a patient's prognosis, nanotechnology bring new hope to the arena of cancer detection research, owing to nanoparticles' unique physical and chemical properties, giving them the potential to be used as a synthetic scaffold for imaging probes in the detection and monitoring of cancer. Nanoparticle (NPs) is defined as an aggregate of atoms bonded together with a radius between 1 and 100 nm [2]. Materials of this size are especially interesting because of their physical and chemical properties (e.g., lower melting points, higher specific surface areas, specific optical properties, mechanical strengths, and specific magnetizations) differs significantly from those observed in bulk materials and this properties that might prove attractive in various field applications [3]. NPs can be based

on polymers, metals, oxides, etc., and according to the characteristic desired, not only depends of precursor salts, but also it will depend of the synthesis method. As a result, strict control of the nanoparticles morphology is therefore required in order to obtain NPs of desired properties. The synthesis of NPs can be by top-down, which is the breakdown method; an external force is applied to a solid that leads to its break-up into smaller particles. The other way to produce NPs and the most used is the bottom-up; which is departed from atoms of gas or liquids based on atomic transformations or molecular condensations [3,4] and includes chemical and physical routes. One of the interesting field applications can be found in nanomedicine, where NPs can improve diagnosis, treatment, drug delivery system, bio tagging or labeling, etc [5-8]. Particularly, NPs have received great attention in antitumoral treatment and currently research have shown that different metal and metal oxide NPs are effective in cancer therapy and diagnosis [9]. These NPs have antitumor activity by themselves or in combination with other therapies [10]. The most commonly studied NPs include Gold NPs [5], iron oxide NPs [11], quantum dots [12], polymeric NPs [13], carbon nanotubes [14] and liposomes [15].

Gold Nanoparticles

Gold nanoparticles AuNPs have unique physical, chemical, optical

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and electronic properties, which can be used in multidisciplinary research. There are different methods to synthesize AuNPs, and the chemical synthesis is the easiest and less toxic way. Among the conventional methods to obtain AuNPs, the citrate reduction is the most popular, because this method is simple, cheap, and can be used to prepare large quantities of NPs [16]. AuNPs have especially been attractive due to optical properties, which are conferred when sized AuNPs are excited with a wavelength much smaller than that of the incident light, then an electric field is formed in the particle, which at a certain wavelength induce a resonance of the free electrons across the particle, this is known as surface plasmon resonance (SPR), then the particle absorbs and scatters the electromagnetic radiation intensely [17]. The resonance frequencies are strongly dependent on the gold nanoparticle size, surface and agglomerations [18,19]. The plasmon resonance properties of AuNPs have been explored for applications in nanomedicine with emphasis on cancer, which can enhance biological labeling, detections, targeted therapy, diagnostic and sensing [20-23]. Also, AuNPs can be used as drug-delivery carriers due to biocompatibility and immunogenicity [24]. For instance, Figueroa *et al.* [25], have developed a gold nanoparticle (AuNP) polyamidoamine (PAMAM) conjugates for use as non-viral transfection agents. AuPAMAM conjugates were prepared by cross linking PAMAM dendrimers to carboxylic-terminated AuNPs via EDC and sulfo-NHS chemistry. The results showed that increasing the amine to carboxyl ratio during conjugation of PAMAM onto AuNPs yielded the optimal vector with respect to colloidal stability and transfection efficiency *in vitro*. AuPAMAM conjugates present attractive candidates for non-viral gene delivery due to their commercial availability, ease of fabrication and scaleup, high yield, high transfection efficiency and low cytotoxicity. Additionally, a study about biocompatibility and cancer therapeutic applications using glycoprotein (GA) functionalized AuNPs containing *ab*-emitting Au-198 were used in compromised immunodeficient (SCID) mice that present human prostate tumor xenografts. The results showed significant tumor regression and effective control in the growth of prostate tumors over 30 days. Three weeks later after administration of GA-198AuNPs, tumor volumes for the treated animals were 82% smaller when compared with tumor volume of control group. The results provide further evidence on the therapeutic efficacy and concomitant *in vivo* tolerance and nontoxic features of GA-198AuNPs [26]. Moreover, the study of AuNPs as radiation sensitizer in cancer therapy shows that the highest radio sensitization enhancement factor was AuNPs of 50 nm (1.43 at 220 kVp) compared to AuNPs of 14 and 74 nm (1.20 and 1.26, respectively) [22]. Plasmonic photothermal therapy (PPTT) and Photo-thermal therapy (PTT) are a minimal-invasive therapy in which photon energy is converted into heat to kill cancer. Due to its plasmonic properties, AuNPs have been widely used to enhance this treatment thereby making them superior contrast agents for PTT [27,28]. In this sense, Mackey *et al.* [29], utilized theoretical calculations as well as experimental techniques *in vitro* to determine the optimum gold nanorod (AuNR) size, it was compared the plasmonic properties and the efficacy as photothermal contrast agents of three different sizes of AuNRs. Examining three different AuNRs (38 × 11, 28 × 8, and 17 × 5 nm), was determined that the 28 × 8 nm AuNR is the most effective in plasmonic photothermal heat generation. The 28 × 8 nm AuNR was found to be the most effective photothermal contrast agent for PPTT in human oral squamous cell carcinoma.

Magnetic Nanoparticles

Iron and its compounds are widespread in nature and can be readily synthesized in the laboratory [30]. Nowadays, the synthesis and utilization of iron oxide nanoparticles with unique properties has been widely studied because of their potential applications in many fields such as physics, chemistry, environmental, biology and medicine, particularly, due to magnetic properties and biocompatibility such as

magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$). Magnetic properties are principally sensitive to the particles size, when size of particle decreases; it can exhibit superparamagnetic phenomena due to each particle can be considered as a single magnetic domain [31]. For that reason, the synthetic route to get NPs is highly important, many different synthetic procedures have been developed, but based in bottom-up synthetic procedures, the most common are: co-precipitation, microemulsion, and sonochemical synthesis [32]. Super paramagnetic nanoparticles (SPMN) are biocompatible and offer a high potential for several biomedical applications. Therefore, SPMN have been attracted much attention in a great variety of applications in biological and medicine, such as biosensing, drug delivery, hyperthermia, cell labeling and as contrast agents [33-35]. The foregoing, based on their inducible magnetization, this magnetic NPs can be directed to a defined location and heated in presence of an external magnetic field [35].

Recently, superparamagnetic nanoparticles have attracted a lot of attention in diagnosis and therapies for cancer treatment. Some studies have shown that the use of SPMN to diagnose tumor malignancy accurately and in early stages would minimize the cost in clinical practices. A study of fabrication and characterization of thermally cross-linked superparamagnetic ironoxide nanoparticles (TCL-SPION) was developed in order to detect tumors *in vivo*. When the Cy5.5 TCL-SPION was administered to mice with Lewis lung carcinoma tumor by intravenous injection, the tumor was unambiguously detected in T2-weighted magnetic resonance images as a 68% signal drop as well as in optical fluorescence images within 4 h, these results indicate a high level of accumulation of the nanomagnets within the tumor site [36].

SPMN can be used alone or with surface modification. SPMN could play an important role in the development of hyperthermia for treatment of tumors *in vivo*. Size and surface modification of MNPs enable a safe application to the tumor and high heating efficiency by Neel relaxation, which promises good therapeutic success [37]. It is important to highlight that SPMN with functionalized surface coatings can conjugate chemotherapeutic drugs or be used to target ligands/proteins, making them useful for drug delivery, targeted therapy, magnetic resonance imaging, transfection, and cell/protein/DNA separation [38,39].

Recently some studies have demonstrated that catalytic activity of SPMN can improve the anticancer drug efficacy. This is because SPMN in presence of hydrogen peroxide generate reactive oxygen species (ROS) [40,41]. In fact, Huang *et al.* [11], have reported that pH-responsive SPION-micelles can synergize with β -lap to improve cancer therapy. These SPION-micelles, selectively release iron ions inside cancer cells, which interact with hydrogen peroxide generated from β -lap in a tumor-specific, in an NQO1-dependent manner. Through Fenton reactions, these iron ions escalate the ROS stress in β -lap-exposed cancer cells, thereby greatly enhancing the therapeutic index of β -lap. It was suggested that the incorporation of SPION-micelles with ROS-generating drugs could potentially improve drug efficacy during cancer treatment [11].

Quantum Dots

Quantum dots (QDs) are semiconductor nanocrystals, which due to their unique photophysical, mechanical, electrochemical, and catalytic properties have attracted great attention for applications, particularly in electronics, optoelectronic, biology and medicine [42,43]. QDs properties are size-dependent due to the quantum confinement effect [44]. The absorption onset and fluorescence emission shift to larger energy while decreasing size [45]. In other words, QDs could vary in color from green-yellow to orange-red and luminesce from blue to yellow, where shorter wavelength, higher energy, electronic transitions correspond to smaller crystal size [46]. It is important to control in a relatively simple manner the variation of

core size and compositions, and through variation of surface coating [44], which will depends of the QDs synthesis. The most common way to obtain QDs is by bottom-up processes [42]. Particularly, wet chemical method, which mainly follow conventional precipitation method with careful control of parameters for a single solution or mixture of solution [42].

For medical applications QDs could provide a versatile nanoscale scaffold, whereby it can design multifunctional QDs with both imaging and therapeutic functions. The narrow emission and broad absorption spectra of QDs makes them well suited to excellent multiplexed bioimaging, cell tracking, and diagnostic applications [47,48], specially for cancer treatment. Nowadays, due to QDs advantages, there are several studies related with applications in cancer treatment. The folate receptor is over expressed in a broad spectrum of malignant tumors that makes it an attractive target for selective delivery of imaging agents to tumor cells [49]. Nanoparticles containing QDs entrapped in a lipid shell, and then post-loaded with a folate-lipid conjugate for targeting in mouse and human tumor cells expressing the folate receptor were studied. As result it was found that only folate-targeted lipodots were taken up by tumor cells. Confocal depth scanning showed substantial internalization, which confirms the specificity of targeted folate lipodots. Besides, binding and internalization were inhibited by free folate, and no uptake was found in a folate-receptor negative cell line [49].

The biocompatible luminescent properties of QDs, have allowed to develop a highly stable aqueous suspensions of Silicon QDs using phospholipid micelles, in which the optical properties of Si nanocrystals are retained. These luminescent micelle-encapsulated Si QDs were used as luminescent labels for pancreatic cancer cells [50]. Another applications of QDs are as chemosensors Lemon *et al.* [43], designed optical chemosensors that feature a quantum dot and an analyte-responsive dye. It was reported that chemosensors is non-invasive, and allows the dynamical monitoring of pH, oxygen, and glucose, within the tumor microenvironment by using multiphoton imaging.

Polymeric Nanoparticles

It is possible to overcome the limitations of the nanotechnology's applications in medicine, such as toxicity and instability, by anchoring biocompatible polymers on the surfaces of diagnostic nanomedicines [51,52]. The surface modification of nanoparticles with hydrophilic polymers reduces the interfacial energy in an aqueous environment, thus preventing unwanted aggregation due to secondary interactions between nanoparticles. In addition, changing the surface of nanoparticles with hydrophilic polymers would minimize the recognition by proteins and cells in the body, which allows to nanomedicine circulate in the blood stream for a longer period of time, hence increasing the odds to reach the target site.

Polymers also bring an option to develop drug delivery systems, used as therapeutics in cancer treatments, holding the anticancer drug in the blood and then allowing a burst or continuous drug release at the cancer tissue, consequently reducing the dosage of the medicine and the collateral toxicity of the treatment. The drug is typically either dispersed within the polymeric nanoparticle, where the encapsulated drugs are gradually released from the polymer matrix by diffusion, or conjugated to the polymeric backbone, where degradation of the polymer matrix can play a primary role in drug release, and various techniques may be used to adjust the release rate.

In addition to simple conjugates based on linear or branched polymers, intricate polymeric conjugates have recently been produced using multivalent polymers, graft polymers, dendrimers, dendronized polymers, block copolymers and star-shaped polymers [53]. Conjugated polymers have also been used to form polymeric micelles for delivery of poorly soluble drugs [54-56].

Polymer Nanoencapsulation

Nanoencapsulation of drugs involves forming drug-loaded particles with diameters ranging from 1 to 1000 nm. Nanocapsules are vesicular systems in which the drug is confined to a core surrounded by a polymeric membrane [57]. The submicron size of nanoparticles offers a number of distinct advantages over microparticles, including a higher intracellular uptake [58].

The nanoencapsulation can be achieved either using monomers to perform a polymerization reaction, or may be achieved directly from a macromolecule or preformed polymer [57].

Emulsion polymerization

Emulsion polymerization is one of the fastest methods for nanoparticle preparation and is readily scalable [59]. The method is classified into two categories, based on the use of an organic or aqueous continuous phase. The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse microemulsion, or into a material in which the monomer is not soluble (non solvent). As one of the first methods for production of nanoparticles, surfactants or protective soluble polymers were used to prevent aggregation in the early stages of polymerization [60]. This procedure requires toxic organic solvents, surfactants, monomers and initiators, which are subsequently eliminated from the formed particles. In the aqueous continuous phase, the monomer is dissolved in a continuous phase that is usually an aqueous solution, and the surfactants or emulsifiers are not needed. The polymerization process can be initiated when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical. Alternatively, the monomer molecule can be transformed into an initiating radical by high-energy radiation, including γ -radiation, or ultraviolet or strong visible light. Chain growth starts when initiated monomer ions or monomer radicals collide with other monomer molecules according to an anionic polymerization mechanism [61].

Emulsification/solvent evaporation

An organic phase containing the dissolved drug and polymer is dispersed into nanodroplets, using a dispersing agent and high-energy homogenization [62] in a non solvent or suspension medium such as chloroform or ethyl acetate. The polymer precipitates in the form of nanospheres in which the drug is finely dispersed in the polymer matrix network. The solvent is subsequently evaporated by increasing the temperature under pressure or by continuous stirring. This method can only be applied to lipid soluble drugs, and limitations are imposed by the scale-up of the high-energy requirements in homogenization [63].

Solvent displacement and interfacial deposition

The polymer is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant. The fast diffusion of the solvent provokes deposition of the polymer on the interface between the water and the organic solvent, leading to the instantaneous formation of a colloidal suspension [64]. The usefulness of this simple technique is limited to water-miscible solvents, where the diffusion rate is enough to produce spontaneous emulsification. This method, as well as the emulsification/solvent evaporation method, is applicable to lipophilic drugs [65].

Emulsification/solvent diffusion

In this method the encapsulated polymer is dissolved in a partially water soluble solvent, such as propylene carbonate, and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is

emulsified in an aqueous solution containing the stabilizer, leading to solvent diffusion to the external phase and the formation of either nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration. As well as the other techniques that use a preformed polymer for encapsulation, this method is efficient encapsulating lipophilic drugs [64].

In this context, Jie *et al.* synthesized amphiphilic *N*-(2-hydroxy)-propyl-3-trimethylammonium-chitosan-cholic acid polymers by unification of cholic acid and glycidyltrimethylammonium chloride onto chitosan and self-assembled into nanoparticles in phosphate-buffered saline. Doxorubicin could be encapsulated into these nanoparticles and then could easily be taken up by breast cancer (MCF-7) cells and released into the cytoplasm [66]. Another interesting example was developed by Shengtang *et al.*, synthesize folic acid-conjugated chitosan-polylactide copolymers to build a drug carrier with active targeting of paclitaxel. Targeting characteristic was confirmed using folic acid receptor-expressed MCF-7 breast cancer cells [67]. Also, Park *et al.*, reported that glycol chitosan-based nanoparticles of adriamycin are useful for sustained and specific delivery of adriamycin, thus showing lower cytotoxicity than adriamycin alone [68].

Liposomes

Liposomes are spherical vesicles that have at least one lipid bilayer, as opposed to the micelles, which are composed of monolayers. A liposome encapsulates an aqueous solution inside a hydrophobic membrane and dissolved hydrophilic solutes cannot readily pass through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules. The diameter of these spheres goes from 50 nm to 1000 nm, making them a convenient delivery vehicle for biologically active compounds [69]. Liposomes are manufactured in majority using various procedures in which the water soluble (hydrophilic) materials are entrapped by using aqueous solution of these materials as hydrating fluid or by the addition of drug/drug solution at some stage during manufacturing of the liposomes. The lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid and then evaporated to a dry drug containing lipid film followed by its hydration. These methods involve the loading of the entrapped agents before or during the manufacturing procedure (passive loading). Certain type of compounds with ionizable groups, as well as those, which display both lipid and water solubility, can be introduced into the liposomes after the formation of intact vesicles (remote loading). Liposomes have the advantages of biological degradability and relative toxicological and immunological safety, and have diagnostic and therapeutic applications. For diagnosis, aqueous contrast-enhancing agents entrapped in liposomal carriers can be targeted to the liver and spleen, and distinctions can be made between normal and tumorous tissue using computed tomography [70,71], and gas filled liposomes are used for diagnostic ultrasound and magnetic resonance imaging due to their differing magnetic susceptibility and ability to reflect sound well [72,73]. Therapeutics liposomes have been used to deliver anticancer agents in order to reduce the toxic effects of the drugs when given alone or to increase the circulation time and effectiveness of the drugs as show by Uziely *et al.*, they utilized a formulation of doxorubicin encapsulated in polyethylene glycol coated which improved the pharmacokinetics of free doxorubicin [74]. Northfelt *et al.*, treated fifty-three patients with advanced Kaposi's sarcoma refractory to standard therapy, with Doxil®. One patient (2%) had a complete response whereas a partial response was observed in 19 patients (36%) [75]. Stage IV breast cancer patients also benefited from the treatment with liposomal doxorubicin according to a study by Ranson *et al.* complete and partial responses were obtained in 6% and 25% respectively [76]. Muggia *et al.*, found that liposomal doxorubicin had substantial activity against refractory

ovarian cancer [77]. Wolf *et al.* [58], have studied the delivery of a liposome-encapsulated DNA repair enzyme, T4 endonuclease V, in pH-sensitive liposomes composed of phosphatidylcholine, phosphatidylethanolamine, oleic acid and cholestryl hemisuccinate (2:2:1:5 molar ratio). Liposome encapsulation enhanced the delivery of T4 endonuclease across mouse skin *in vivo* leading to increased protection against UV radiation. This reduced the incidence of skin cancer in a UV-induced mouse model and prevented systemic immunosuppression of contact and delayed type of hypersensitivity.

Micelles

A micelle is an aggregate of molecules having both polar and non-polar regions (amphiphilic molecules) dispersed in an aqueous solution. In a typical micelle the polar or hydrophilic heads form an outer shell in contact with water, while non polar or hydrophobic tails are sequestered in the interior. Micelles are widely used in industrial and biological fields for their ability to dissolve and move non polar substances through an aqueous medium, or to carry drugs which are, often, scarcely soluble in water.

In an aqueous solution, micelles with core-shell structures are formed through the segregation of insoluble hydrophobic blocks into the core, which is surrounded by a shell composed of hydrophilic blocks. In general, there are three major methods for loading drugs into polymer micelle cores: chemical conjugation, physical entrapment or solubilization, and finally, polyionic complexation.

Chemical conjugation

For this method a drug is chemically conjugated to the core-forming block of the copolymer via a carefully designed pH- or enzyme-sensitive linker that can be cleaved to release a drug in its active form within a cell. The polymer-drug conjugate then acts as a polymer prodrug, which self assembles into a core-shell structure [53,78]. Bae *et al.* [79], prepared targeted anti-cancer micelles by conjugating folate to the distal end of poly (ethilen glycol)-*b*-poly(aspartate) block copolymer, or PEG-PAsp, aimed at increasing tumor accumulation. The folate-conjugated polymeric micelle loaded with Dox showed significantly increased cellular uptake. Cytotoxicity analysis *in vitro* indicated that the cell growth-inhibitory activity of the folate-conjugated micelle was enhanced, suggesting that this could be an effective approach for ligand-mediated uptake for cancer treatment [79].

Physical entrapment

This method is preferred for hydrophobic drug molecules. A variety of drugs can be physically incorporated into the core of the micelles by engineering the structure of the core-forming segment. Different loading methods can be used for physical entrapment of the drug into the micelles, such as dialysis [80], oil in water emulsification [81], direct dissolution [82], or solvent evaporation techniques [83].

Tumor-specific targeting of polymer micelles to molecular markers expressed at the surface of the cancer cells has been also explored to eradicate tumor cells. Mixed micelles of poly (ethylene oxide) (PEO)-*b*-poly (L-histidine) and PEO-*b*-poly(L-lactic acid) block copolymers with solubilized doxorubicin or micelles of PEO-*b*-poly(DL-lactic-co-glycolic acid) block copolymer with covalently attached doxorubicin each were surface modified by conjugating folate molecules to the free PEO ends [84,85]. In both cases *in vitro* and *in vivo* studies demonstrated increased antitumor activity of the micelle incorporated drug resulting from such modification.

Polyionic complexation

Charged therapeutic agents can be incorporated into block copolymer micelles through electrostatic interactions with an oppositely charged ionic segment of block copolymer. This approach is now widely used for the incorporation of various polynucleic acids

into block ionomer complexes for developing non-viral gene delivery systems.

As an example, the metal-complex formation of ionic block copolymer, PEO-*b*-poly(L-aspartic acid), was explored by Yokoyama *et al.* to prepare polymer micelles incorporating *cis*-dichlorodiamminoplatinum (II) (CDDP) [86], a potent chemotherapeutic agent widely used in the treatment of a variety of solid tumors, particularly, testicular, ovarian, head and neck, and lung tumors [87,88]. The CDDP-loaded micelles had a size of approximately 20 nm. These micelles showed remarkable stability upon dilution in distilled water, while in physiological saline they displayed sustained release of the regenerated Pt complex over 50 h due to inverse ligand exchange from carboxylate to chloride. The release rate was inversely correlated with the chain length of poly (L aspartic acid) segments in the block copolymer. The stability of CDDP loaded micelle against salt was shown to be improved by the addition of homopolymer, poly (L-aspartic acid), in the micelles. Recently, Nishiyama *et al.* prepared CDDP-loaded micelles using another block copolymer, PEO-*b*-poly(glutamic acid) to improve and optimize the micellar stability, as well as the drug release profile [89]. The drug loading in the micelles was as high as 39% (w/w), and these micelles released the platinum in physiological saline at 37° C in sustained manner for over 150 h without initial burst of the drug [90].

Ceramic based carriers

The use of nanoparticles as carriers is a very promising approach because these nanomaterials can be used as photosensitizing agents in cancer treatment as Photodynamic therapy (PDT). PDT involves the uptake of a photosensitizer by cancer tissue followed by photoirradiation. PDT has been used as a clinical treatment of cancer and particularly for the treatment of superficial tumors [91]. The properties of an ideal photosensitizer are: stable composition, easily synthesized or readily available, minimal self-aggregation tendency, not highly hydrophobic or encapsulated inside appropriate carriers, non-toxic in the absence of light exposure, photostable, absorbance in the red region of spectrum with high extinction molar coefficient, target specificity, and has to be quickly cleared from the body. Recent advances have been made in the use of this nanoparticles in terms of stability, photocytotoxic efficiency, biodistribution and therapeutic efficiency. The possibility of using ceramic nanoparticles for Photodynamic therapy (PDT) was shown by Prasad *et al.* [92], it was encapsulated HPPH, a photosensitizer that is currently undergoing phase I and II clinical trials for esophageal cancer [93], by controlled hydrolysis of triethylvinylsilane in micellar media. *In vitro* experiments showed significant levels of cell death for both HPPH-tween-80 micelles and HPPH-nanoparticles in which the photosensitizer were covalently attached to the silica matrix [94], and they were able to show that $^1\text{O}_2$ was deactivated mainly outside the nanoparticles [95].

Dendrimers

Fritz and coworkers first introduced the term dendrimer in 1978 [96]. The dendrimer architecture permits control over properties such as shape, size, polarity, reactivity, density and solubility. Dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy. A treatment of cancer mainly focused on the targeting the active drug molecule at the site without affecting the neighbor cells and dendrimers have this property, which is useful in diagnosis and treatment purpose. For instance, Liposomal locked-in dendrimers (LLDs), the combination of liposomes and dendrimers in one formulation, represents a relatively new term in the drug carrier technology. Konstantinos *et al.* synthesized 1 and 2-hydroxy-terminated dendrimers and were then locked in liposomes consisting of DOPC/DPPG. The anticancer drug doxorubicin (DOX) was loaded into pure liposomes or LLDs and the final products were

subjected to lyophilization. The loading of DOX as well as its *in vitro* release rate from all systems was determined and the interaction of liposomes with dendrimers was assessed by thermal analysis and fluoresce spectroscopy. The results were very promising in terms of drug encapsulation and release rate, factors that can alter the therapeutic profile of a drug with low therapeutic index such as DOX. Physicochemical methods revealed a strong, generation dependent, interaction between liposomes and dendrimers that probably is the basis for the higher loading and lower drug release from the LLDs comparing to pure liposomes [97]. Hsueh-Chen *et al.* studied the changes in global gene-expression profiles in human cervical cancer HeLa cells exposed to non activates and activates poly(amiidoamine) (PAMAM) dendrimers, alone or in complexes with plasmid DNA (dendriplexes). Real-time quantitative reverse transcriptase-polimerase chain reaction was used to confirm four regulated genes (PHF5A, ARNTL2, CHD4, and P2RX7) affected by activated dendrimers and dendriplexes alike induced multiple gene expression changes, some of which overlapped with their dendriplexes. Dendrimers and dendriplexes principally affect genes with the molecular functions of nucleic acid binding and transcription activity, metal-ion binding, enzyme activity, receptor activity, and protein binding. These findings provide a deeper insight into the changes in gene expression patterns caused by the molecular structure of PAMAM dendrimers for gene-based cancer therapy [98].

Nanoshells

Nanoshell-based complexes have recently been expanded to include two diagnostic capabilities, MRI and near-infrared fluorescence imaging [99], in addition to photothermal therapy which use the ability of nanoshells to convert absorbed light to heat [100,101]. For instance, Jianlin *et al.* used uniform Au NRs-capped magnetic core/mesoporous silica shell nanoellipsoids (Au NRs-MMSNEs) prepared by coating a uniform layer of Au NRs on the outer surface of a magnetic core/mesoporous silica shell nanostructure. This multifunctional nanocomposite integrate simultaneous chemotherapy, photo-thermotherapy, *in vivo* MR-, IR thermal and optical imaging into one single system. The obtained multifunctional nanoellipsoids showed very low cytotoxicity, and the cancer cell uptake and intracellular location of the nanoellipsoids were observed by confocal laser scanning microscopy and bio-TEM. It was shown the synergistic effect of combined chemo- and photo-thermotherapy [102]. Another interesting example was developed by Maoquan *et al.* gold (Au) nanoshells with solid silica cores have great potential for cancer photothermal therapy. The silica shells were synthesized using nanoliposome templates, and the Au nanoshells were grown on the outer surface of the silica shells. After doxorubicin (DOX) was incorporated into liposome/SiO₂/Au, the DOX-loaded Au nanoshells killed cancer with high therapeutic efficacy when irradiated with near-IR light, suggesting that the Au nanoshells delivered both DOX chemotherapy and photothermal therapy with a synergistic effect [102].

Carbon nanotubes

Carbon nanotubes as unique and novel class of nanomaterials have shown considerable promise in cancer therapy and diagnosis among the countless of nanocarriers. The presence of a large surface area enables the engineering of the surface of nanotubes, thus making them biocompatible, and large benefits can be harnessed from them. Together with their ability to encapsulate small molecules, stacking interactions and conjugation, nanotubes have improved the profile of anticancer agents. The propensity to absorb the body transparent NIR radiation also envisages photothermal and photoacoustic therapy using nanotubes [1,103]. For instance, Ojima *et al.* effectively employed carbon nanotubes-polymer hybrid nanomaterials to deliver biologically active therapeutic agents into the tumor site for the purposes of cancer diagnosis and therapy [104].

Li *et al.* use functionalized -CNTs in gene therapy because they are easily able to cross cell membranes and deliver genes into cells. In many reports, DNA and RNA have been covalently [105,106] and noncovalently [107] attached to functionalized CNTs. It has been found that not only DNA molecules can be linked to the tips and walls of CNTs, but also can be encapsulated inside the structure [108]. Release of DNA molecules from CNTs-based delivery systems using thermal properties of CNTs has been investigated and it has been found that DNAs can be released from functionalized-CNTs transported to the nucleus after the laser pulses [109].

While scientist focus on the development of safer and more efficient techniques for rapid diagnosis and smart drug delivery in cancer therapy also the toxicity and immunogenicity of carbon nanotubes (CNTs) in both *in vitro* and *in vivo* studies has been studied and attributed to various factors such as number of walls, length and aspect ratio, surface area, degree of aggregation, extent of oxidation, hydrophobicity, surface topology, methods of administration, dispersibility, type and degree of functionalization, and method of manufacture. Although toxicity of CNTs is also dependent on their concentration, dose, duration and method that cells or organism are exposed to them and even the utilized dispersant to solubilize the nanotubes [1].

Tumor environment and basis of tumor targeting mechanism

There are two main ways in which nanoparticles can be delivered into the tumor tissue: by either passive or active targeting.

Passive targeting takes advantage of the inherent size of nanoparticles and the unique properties of tumor vasculature, such as the enhanced permeability and retention (EPR) effect and the tumor microenvironment [110-113].

In the EPR effect, the angiogenic blood vessels in tumor tissues (unlike those in normal tissues) have gaps as large as 600 to 800 nm between adjacent endothelial cells [114]. Defective vascular architecture coupled with poor lymphatic drainage induces the EPR effect [115], which allows nanoparticles to extravasate through these gaps into extravascular spaces and accumulate inside tumors tissues. The tumor drug accumulation can be achieved when a drug is delivered by a nanoparticle rather than as a free drug [116]. In general, the accumulation of nanoparticles in tumors depends on factors including the size, surface characteristic, and circulation half-life of the nanoparticle and the degree of angiogenesis of the tumor. Usually, less nanoparticle accumulation is seen in pre angiogenic or necrotic tumors.

Regarding to the Active targeting, the polymeric nanoparticles that have been tested clinically so far have mostly lacked a targeting moiety and instead rely mainly on the EPR effect of tumors, the tumor microenvironment, and tumor angiogenesis to promote some tumor selective delivery of nanoparticles to tumor tissues. An alternative strategy to overcome these limitations is to conjugate a targeting ligand or an antibody to nanoparticles. By incorporating a targeting molecule that specifically binds an antigen or receptor that is either uniquely expressed or overexpressed on the tumor cell surface, the ligand-targeted approach is expected to selectively deliver drugs to tumor tissues with greater efficiency. Indeed, several targeted polymeric nanoparticles are currently undergoing preclinical studies [117].

Nano-formulated drugs

As described previously drug delivery to solid tumors is one of the seminal challenges to developing more effective cancer therapies and it has exponentially increased in the last decades. Nanoparticles come in an almost infinite variety of sizes, shapes, and compositions, as a matter of fact it can be designed with multiple functionalities to aid in cancer therapies [118]. Nonetheless, the body possesses numerous defense mechanisms to protect itself against foreign substances including viruses, bacteria, protein toxins, and other chemicals [119]. Nanoparticles are no exception and are actively cleared by the body [120]. These defense mechanisms are in place at every level of organization, systemic, organ, tissue, cellular, and intracellular. On the other hand, most chemotherapeutic drugs are cytotoxic agents, which have specific targets for action inside a cancerous cell [121] and most of the time the drug administered to the patient becomes at best ineffective, and at worst toxic to the patient [122]. Nanotechnology might have a deep impact in solving many of the problems associated with conventional anti cancer drugs because nano-formulated drugs can be made as relatively safe, injectable formulations. Doxil and Abraxane are the two major nano-formulated drugs currently available on the market and already they have made an impact in cancer treatment worldwide. Doxil, which is doxorubicin formulated in nano-liposome [123], has shown significant improvements over its counterpart, free doxorubicin. Abraxane® (Abraxis), with a size around 100 nm, is an albumin-bound nanoparticle formulation of paclitaxel [124-126] and is widely used for treatment of metastatic breast cancer. The major advantage of Abraxane® is that it evades the hypersensitivity reaction associated with Cremophor EL, the solvent used in conventional paclitaxel therapy. Thus, Abraxane clearly demonstrates the ability to convert insoluble or poorly soluble drugs, avoiding the need for toxic organic solvents. A list of the

Table 1: Nano-formulations commercial- and currently available.

Product	Company	Drug	Formulation/ROA	Application	Status
Abraxane	Abrasix Bioscience, AstraZeneca	Paclitaxel	Albumin-bound nanoparticles-iv	Metastatic breast cancer	Marketed
Caelyx	Schering-Plough	Doxorubicin	Pegylated liposome-im	Metastatic breast and ovarian cancer; Kaposi sarcoma	Marketed
Myocet	ZeneusPharma Ltd	Doxorubicin	Liposoma/iv	Metastatic breast cancer	Marketed
Doxil	Sequus Pharmaceutical	Doxorubicin	Liposome/iv	Kaposi sarcoma	Marketed
L-Annamycin	Callisto Pharmaceuticals	Annamycin	Liposome/iv	Children and young adults with refractory or relapsed ALL or AML	Phase I/II
Genexol-PM	Samyang Pharmaceuticals	Paclitaxel	Methoxy PEG-PLA/iv	Breast and lung cancer	Phase II
CALAA-01	Calando Pharmaceuticals	Anti-R2 SiRNA	Cyclodestrin-containing polymer (CAL 101) and targeting agent (AD-PEG-Tf)/iv	Solid tumors that are refractory to standard-of-care	Phase I
Rexin-G	Epeius Biotechnologies	Dominant negative cyclin G1 construct	Pathotropic nanoparticles/iv	Recurrent or metastatic breast cancer	Phase I/II
BikDD Nanoparticle	MD Anderson Cancer Center/NCI	Pro-apoptotic Bik gene (BikDD)	Liposome/iv	Pancreatic Cancer	Phase I
Docetaxel-PNP	Samyang	Docetaxel	Polymeric nanoparticles/iv	Advanced solid malignancies	Phase I

ROA: Route of administration, iv: intravenous, im: intramuscular, ALL: Acute lymphocytic leukemia, AML: Acute myelogenous leukemia, PEG-PLA: Poly[ethylene glycol]-poly[lactide], Tf: Human transferringprotein, HCC: Hepatocellular carcinoma

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nanoformulations currently available on the market is the table 1 [127].

Nanotechnology not only has the potential to conjugate the required targeting moiety, but also has the ability to carry the moiety for site-specific delivery without compromising its activity. Various polymeric materials are often used to synthesize nanoparticles loaded with conventional chemotherapy drugs such as docetaxel or doxorubicin, and then coated with polyethylene glycol to evade the patient's immune system. Additionally, nanoparticles can be conjugated with a targeted moiety such as an aptamer bioconjugated that binds, for example, to prostate-specific membrane antigens present on prostate cancer cells [128]. This type of active-targeted delivery to the tumor by using a tumor-specific moiety can be achieved by exploring various natural interactions like lectin-carbohydrate, ligand-receptor, and antibody-antigen interactions within the tumor cell [129], resulting in preferential accumulation within the cancer-bearing organ or cancerous tumor cells. Active targeting has the potential to change current cancer treatments scenarios.

Some nanoparticles have the ability to accumulate in tumor vasculature, known as enhanced permeability and retention (EPR) [130-132], thus increasing accumulation of the payload to the tumor site. Passive targeting in this case takes advantage of the rapid vascularization of hyper-permeable cells. This results in leaky, defective vessels and impaired lymphatic drainage. Nanoparticles sized at 10 to 100 nm have the ability to accumulate within tumors because of their ineffective lymphatic drainage. Thus, consideration of the size and surface properties of nanoparticles is vital, particularly for passive targeting. Particles must be less than 100 nm to avoid uptake by the reticulo-endothelial system and their surface should be hydrophilic to avoid rapid clearance by macrophages [133]. Furthermore, both active and passive targeting can be exploited simultaneously to obtain maximum efficacy.

Future perspective

Nanotechnology has already made an impact on medicine. The rapid intrusion of this cutting-edge technology in the current state-of-the-art has bring new avenues in the detection, treatment and therapy of cancer and due to this technologies are in preclinical stages there is still plenty of work to be done and some very promising new nanotechnology treatment methods are in the works. For instance, Singh *et al.* have recently developed Metal oxide nanoparticles (MO-NPs), which are multidisciplinary nano-scaled molecules used in the diagnosis and treatment of cancer. The MO-NPs in combination with other chemotherapeutic anticancer agents not only increase their bioavailability but also lower down the requirement of active dosages [134]. In this context, there is a tremendous potential for nanotechnology to enable cancer detection in its early stages. Most interesting is the potential to replace highly invasive conventional cancer detection and treatment, which often includes biopsies, irradiation, and painful therapies. As we become better able to engineer more sophisticated nanodevices and to equip them with effective targeting techniques for biomolecules, we will gain the ability to treat various kinds of cancer more and more effectively, there is no doubt that a bright future lies ahead for this discipline.

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