



Nanoparticles in Cancer Treatment: A Narrative Review

Taimoor Hassan^{1,2*}, Xiaojia Huang¹, Chao Zhou¹, Muhammad Sikander Ghayas Khan²,
and Sana Saeed^{2,3}

¹School of Pharmacy & School of Medicine, Changzhou University, 1 Gehu Middle Rd,
Wujin District, Changzhou, Jiangsu, China

²Department of Health Professional Technologies, The University of Lahore,
Lahore, Pakistan

³Department of Pharmaceutical Sciences, Tianjin University, Tianjin, China

Abstract: Nanoparticles have revolutionized the world with their enormous blessings specifically in cancer treatment. In past, conventional chemotherapy was the primary choice of treatment for patients. However, chemotherapeutics also had several pharmaceutical limitations such as stability, drug-drug interaction, drug resistance, and aqueous solubility. Reciprocally, dose curbing toxicity is significant with non-specific toxicity to healthy cells, loss of appetite, hair loss, peripheral neuropathy, vomiting, muscular fatigue, and diarrhea being the typical adverse effects. The introduction of multi-drug resistance (MDR) also posed a great threat for successful cancer treatment, whereby the tumor cells became resistant to many of the chemotherapeutic agents used. Nanotechnology-based novel chemotherapy opened a new horizon for the treatment of cancer. Particularly, nanoparticle-related medication is a highly potential newcomer for curtailing systemic toxicity via producing functionalized particles for specific treatment. It is also an alternative to circumvent multidrug resistance for possessing an ability to bypass the efflux mechanism correlated with this phenotype. Besides having various advantages in treatment, nanoparticles are also playing a key role in diagnostic entities. This paper aims to specifically outline the role of nanotechnology which it is playing in today's era in the diagnosis and treatment of cancer with contemporary knowledge. To assess the role of nanoparticles in cancer treatment, this review analyzed all articles published from 2002 to 2021 in both Local and foreign journals. The article's inclusion criteria were based on the article which contained relevant data regarding applications of nanoparticles in cancer treatment. Articles with copyright, irrelevant information, and lacking the full text were excluded. This paper will highlight the breakthrough, impediments, and prospects of nanoparticles in cancer treatment with an updated review.

Keywords: Cancer therapy, Cancer treatment, Multidrug resistance, Nanoparticles, Nanotechnology, Nanocarriers, Nanomedicine.

1. INTRODUCTION

Cancer is a lethal disease resulting from uncontrolled cellular proliferation. American Cancer Society opines that men have a 41 % probability of developing cancer while in women this percentage is 38% [1]. The existing therapeutic approaches to treat cancer are chemotherapy, immunotherapy, radiation therapy, hormone therapy, and surgery [2]. The aforementioned therapeutic approaches have dynamically improved patients' survival and treatment outcomes. But still, we have a lot of confusion, limitations regarding the use of

these therapies today [3]. Drug targeting and drug delivery is the most challenging limitation because of non-selective tissue intoxication, the presence of organized barriers (Physiological, Physical, Enzymatic) which hinders the drug partitioning and drug distribution to its targeted site [4]. Remarkable advancements in drug targeting and drug delivery talk of the town among research pantheons in recent years [11]. Nano-based drugs delivery system enables the delivery of macromolecules and micromolecules in a targeted or localized manner [5]. Precisely, the development of therapeutic agents in biocompatible nanocomposites like

drug conjugates, micellar systems, nano-capsules, nanoparticles have gained more focus [6]. Nanotechnology gained the spotlight since the 1980s through the emergence of cluster science, the development of carbon nanotubes and fullerenes, the invention of tunneling microscopes [7]. The development of semiconductor particles widely known as Quantum dots, semiconductor nanocrystals are the edicts of nanotechnology [14]. Nanoparticles are nano-sized colloidal particles, and the therapeutic agent incorporated within the particle-matrix, with the size <100 nm, is partly absorbed through systematic or functional modifications which improve drug efficacy and drug stability [8]. The dimensional resemblance of nano-particles with biomolecules: volume ratio, high-surface, capacity for surface engineering have made them powerful candidates for diagnosis and treatments [9]. Having the advantage of being micro-sized particles, they can deeply penetrate tissues, easily cross epithelial surfaces, easily be taken up by the targeted cells, improves the bioavailability of therapeutic moieties. By manipulating the polymer characteristics, the rate of moiety release can be well-optimized. Bio-specific drug-ligand joint-ventures increase cell targeting and tissue-specific drug delivery [10,11]. Figure 1 is showing the timeline which is representing key moments in the history of biomaterials.

1.1 Nano-Bio Interactions of Nanomedicines

Because of the excellent physicochemical properties, engineered nanomaterials (ENMs)

have been created for drug delivery, diagnostics, imaging, and clinical treatment applications. However, the function and final effectiveness of nanomedicines remain inadequate for clinical use, owing to a lack of knowledge of nanomaterial/nanomedicine–biology (nano-bio) interactions. The biological milieu's nonequibrated, dynamic, and diverse character invariably impacts the dynamic bio identity of nanoformulations at each site of nano-bio interactions (i.e., the interfaces at various biological fluids (biofluids), surroundings, or biological structures). The constant interaction between biological chemicals and nanomedicine and structures in biological settings, for example, might influence cellular absorption or entirely alter the nanomedicine's planned function. As a result, the weak and strong driving forces at the nano-bio interface may cause structural reconfiguration, reduce bioactivity, and promote nanomaterial malfunction and/or redox interactions with biological molecules, all of which may result in undesired and unanticipated biological consequences. These driving factors, on the other hand, may be adjusted to reduce the toxicity of ENMs or increase their targeting abilities [112, 113].

1.2 Advantages of Nanoparticles in Drug-Delivery

The polymeric nanoparticles are the most favorable structures because of their peculiar property of surface modification and can be designed for active and passive drug-targeting [12]. This very

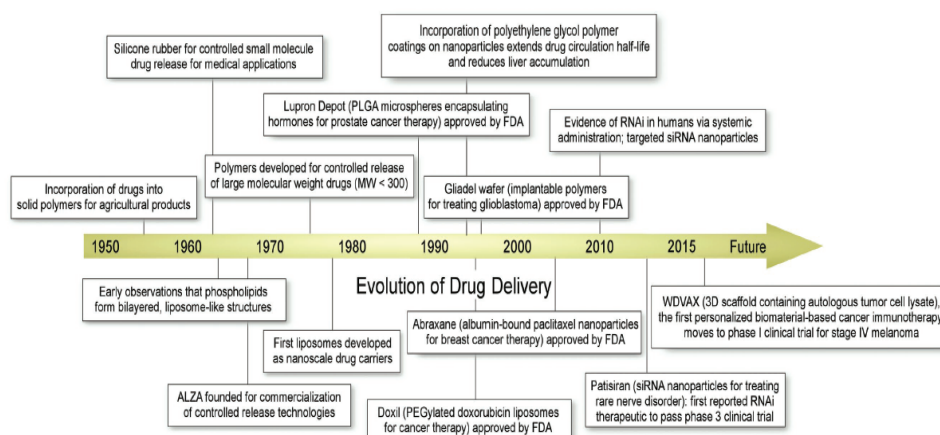


Fig. 1. This figure shows a timeline which is representing key moments in the history of biomaterials [7].

characteristic allows them to be used widely in vivo and *in vitro* sensors targeted therapy and imaging [9]. The steady relation between the nanoparticles and drug equips them for subsequent clearance of the drug, altered organ distribution, and stimulus-triggered site-specific drug release for 'on demand' treatment [13, 14].

These carriers also enhance the stability of the drug by impeding the breakdown of the encapsulated carrier. However, a large number of drugs can be added directly irrespective of chemical reaction, which plays a vital role in drug preserving activity [15]. The development of dry solid dosage forms of drugs is considered a fruitful strategy to optimize the drug's chemical stability [16]. These are considered to be more stable than nano-liquid products [17]. The ionic stabilizers (Sodium dodecyl sulfate, Sodium lauryl sulphate, docusate sodium, and lecithin) or Non-ionic stabilizers (Polyvinylpyrrolidone, Polyethylene glycol, Polyvinyl alcohol, Tween 80) are also used to provide molecular stability to nanoparticles [18]. The production of porous nanoparticles also enhances their stability [19].

Tumors elicit peculiar pathophysiological traits which are different from healthy tissues such as defective vasculature, full-partially impaired lymphatic system, extensive angiogenesis. Nanoparticles vigilantly identify those defected anatomical regions and extensively release the drugs into tumor sites [20, 21]. Because of compromised venous return into tumors, poor lymphatic drainage, nanoparticles are retained in the targeted tumor site for a long time [17]. This process or mechanism is called enhanced permeability and retention [22]. Likewise, the target-specific delivery can be maintained by targeting the tissue which is adjacent to the tumor such as targeting Kupffer cells in the liver [23].

The administration of nanoparticles can be done via several routes like; Oral, parenteral, nasal, instar-ocular, etc [21]. Nanoparticles have a relatively higher surface-to-volume ratio and intracellular uptake as compared to microparticles [23]. Through experiments, it is reported that nanoparticles are more effective for drug delivery than their microparticles sized ($>1 \mu\text{m}$) counterparts. These characteristics equip them to release the drug in a controlled manner in malignant tissues [24, 25].

1.3 Limitations of Nanoparticles in Drug-Delivery System

While inking on the advantages of nanoparticles in drug delivery, they possess several limitations too which cannot be overlooked. Studies demonstrated that nanoparticles get unstable over a prolonged period [26]. The manufacturing conditions like high pressures, high temperatures, change the crystallinity of drugs. During prolonged storage, crystal growth, sedimentation, and particle agglomeration also destabilize the products [7]. The development of nanoparticles is a quite delicate, challenging process as compared to conventional drug formulations [27]. Precise control of particle size, and surface functionality are uncompromised factors that are required for the successful production of nanoparticles [13].

Nanotechnology is very expensive and costs a lot. Product processing, difficulty in handling molecular structures, high labor costs are the contributing factors for their increased cost [28]. It is quite difficult to develop a formulation in a reproducible manner using nanotechnology [29]. While comparing the costs of drugs containing nanoparticles are described, in 2009, the cost per dose of Paclitaxel was between \$90 - \$454 as compared to \$5,054 for Abraxane (Paclitaxel containing nanoparticles formulations) [34]. Similarly, the cost per dose of pure Doxorubicin was between \$62 - \$162 as compared to \$ 5,595 for Doxil® (Doxorubicin containing nanoparticles formulations) [30].

The next limitation is that the physiological response of nano-carriers is yet not very well understood. For example, studies showed that the crystalline silver nanoparticles might cause cytotoxicity in the human fibroblasts, keratinocytes, lesioned skin [31]. Liposomal vesicles can be arrested by the immune system [32]. Various publications have reported the post-treatment accumulation of nanoparticles in the skin. Granite and Dolomite nanoparticles are revealed to be more toxic for lung epithelial cells [29].

2. ADME OF NANOPARTICLES

Several barriers prevent extraneous substances, such as bacteria, viruses from entering the body. These same barriers, which include the pulmonary

system, the gastrointestinal tract, and the skin, regulate nanoparticle access. Previously, only tiny lipophilic compounds (600 Da) and metallic ions (such as cobalt and nickel) could pass through the skin barrier. However, due to their tiny size, nanoparticles may be easily absorbed through the dermis of the skin, as well as the pulmonary and gastrointestinal mucosa, positioning these substances for distribution through the vascular circulation to all tissues in the body. The vascular endothelium, with an average pore size of 5 nm in mammals, provides another possible barrier to nanoparticle absorption and distribution, although nanoparticles smaller than this limit pass readily from the blood over the endothelium and into tissue. Furthermore, because the discontinuous endothelium of these organs includes holes of 50-100 nm in diameter, nanoparticles may be able to translocate efficiently from the blood into the liver, spleen, and bone marrow. As a result, techniques for determining the quantity of total external exposure, absorption effectiveness, and tissue biodistribution of nanoparticles are required. However, the excretion of nanoparticles is majorly done by two ways; from renal filtration through urine and hepatobiliary processing. Choi *et al.* demonstrated that quantum dots are excreted through renal filtration as urine. Another study demonstrated that gold nanoparticles were excreted through hepatobiliary processing [112, 114].

3. IMPEDIMENTS IN CANCER CHEMOTHERAPY

To ensure the success of chemotherapy, a handsome amount of parent drugs should reach the targeted site [33]. At the tumor location, the unpredictable blood flow, abnormal vasculature, are the key factors that prevent the drug penetration into the malignant tissue [29, 33].

A crucial limitation to systematic chemotherapy is peripheral neuropathy, systematic toxicity, loss of appetite, skin damage, hair loss, and diarrhea [34]. Chemotherapy can successively lead towards neutropenia which further instigates infections [65]. These side-effects depend upon several factors like; the duration of treatment, patient-specific characteristics, the prescribed dosage of drugs for treatment [35].

Chemoresistance is a critical phenotype that helps the cancer cells to evade the cytotoxic effects of chemotherapeutic agents [31]. This phenotype results from several mechanisms including decreased apoptosis, increased DNA repair, intracellular sequestration, increased drug detoxification, decreased drug influx, and increased drug efflux [36]. Chemoresistance can either be acquired or intrinsic. Acquisition of an idiosyncratic type of resistance named multi-drug resistance (MDR) is a challenging phenotype in cancer treatments [29]. MDR can appear after exposure to a single anti-cancer agent which results in cross-resistance to a wide array of chemotherapeutic drugs [37].

MDR is strongly associated with overexpression of ATP-dependent multidrug efflux membrane transporters which belong to the ATP-binding cassettes superfamily of which P-glycoprotein is a prototypical relative [31]. The over-expression of the aforementioned transporters helps cellular evasion of cytotoxicity by properly maintaining the sublethal intracellular concentrations of chemotherapeutic drugs. This act leads to the failure of treatment [38].

The genetic accretion of multi-drug resistance has been well studied and recently the spread of MDR through Non-genetic mechanisms like tunneling nanotubes, cell-to-cell contact has been well explained [35]. The spread of MDR in the non-presence of any cellular contact has been discovered, Whereas, the extracellular vesicles (Microparticles (MP's)) facilitate the broad-range and short-range movement of resistance phenotype to hitherto drug-sensitive cells [39, 40].

The microparticles are membrane-derived vesicles whose size ranges 0.1 – 1 μm and shed from many cell types following the calcium-dependent loss of phospholipid asymmetry, cleavage of filaments which attaches cytoskeleton to plasma membranes, and budding of cellular membranes [36]. MP's plays a vital role in extracellular signaling and enhance the dissemination of cellular products via the transfer of vesicle cargo [41].

Including cancer, in many diseases, MP shedding is highly reported and it contributed to the direct progressions of disease [26]. Microparticles

shed from multi-drug resistant cells and have been shown that the MDR phenotype confers to the hitherto drug-sensitive cells *in vivo* and *in vitro* [42]. The transfer of these vesicles from MDR allows the proteomic re-templating and transcription of the recipient cells [38]. Taken together the microparticles play a crucial role in the maintenance of cancer characteristics [43].

4. OVERCOMING THE IMPEDIMENTS IN TUMOR TARGETING

The prime goal of drug delivery is to transport the desired amount of drug into a targeted site for the optimal period [44]. This positive upshot will be achieved with the improved and advanced interactions between the biological barriers and drug carriers. Biological barriers restrict the entry of drugs into tumors [39]. The injectable drug administration route provides minimum barriers so that the drug can reach its target site safely [40]. The small vesicles diffuse along with the biological barriers, hence facilitating the absorption of administered drug [45].

The surface properties of nanoparticles depend upon the nature of the surface component [41]. While talking about the particles which contain amphiphilic copolymers, their hydrophilic part is embedded onto the particle surface because of the hydrophobic moiety of the copolymer [46]. For example; nanoparticles' surface grafted with thiomers have reported well-improved interactions with the intestinal mucosa. Because of their small particle size, nanoparticles mask their recognition by the macrophages and reside in systemic circulation for a longer period [41]. Cyclodextrins and Biotins are widely used surface ligands to optimize nanoparticle-tumor cell interactions [42].

Not long ago, pantheons are giving attention to the delivery of nucleic acids and antibodies for treating cancers in humans [47, 48]. Nucleic acid drugs such as small interfering RNA (siRNA), anti-sense DNA/RNA, aptamers have shown tremendous results in cancer therapy [43]. However, their effectiveness is limited by opsonization and clearance by macrophages, serum nucleases, and lastly by the renal system [28]. These above-mentioned limitations can be overcome using nano-carrier-based drug delivery systems [50]. Nanocarriers have the affinity to be strongly

attached to specific cells and other targeting agents like ligands [21].

5. NANOPARTICLES TO OVERCOME THE PROBLEMS CAUSED BY MDR IN CANCER THERAPY

Nanoparticles are receiving attention specifically in cancer treatment because of their ability to co-encapsulate multiple therapeutic agents in targeted specific drug delivery systems [51]. The researchers have reported the co-delivery of Pyrrolidine dithiocarbamate and Doxorubicin using multifunctional Chitosan-folate micellar nanoparticles to gain pH-responsive specific target release of drug to overthrow Doxorubicin MDR [44]. The slow release of these drugs at neutral or alkaline pH, rapid release of both drugs in a weakly acidic medium, and pH-sensitive folate receptor-mediated endocytosis have a high potential to overcome MDR in liver cancers [52].

A group of researchers described a Paclitaxel encapsulated nanocrystal formulation by using D- α -tocopheryl polyethylene glycol 1000 succinate for circumvention of MDR. D- α -tocopheryl polyethylene glycol 1000 succinate works as a surfactant to balance the nanocrystals and meantime it also acts as a P-gp (Pharmacological inhibitor) [45]. These nanocrystals reported controlled release kinetics, and good therapeutic effect in Taxol (A clinical formulation of Paclitaxel formulation – resistant cancer cells. Similarly, intranuclear localization of TAT peptide conjugated doxorubicin encapsulated mesoporous silica nanoparticles have been reported as a strategy to evade cancer MDR [53]. The covered drug is directly released into the nucleus. Advanced nuclear delivery is a favorable strategy to cope-up MDR [46].

The co-delivery of P-gp siRNA along with Doxorubicin has been reported employing mesoporous silica nanoparticles. This dual delivery in KB-V1 cells was proficient in enhancing intranuclear and intracellular drug amounts to levels exceeding that of the free drug [47, 48].

6. MECHANISMS OF CELLULAR TARGETING

For cancer therapy to be more effective, the chosen delivery system should be selective to target cells

without affecting healthy cells [49]. For successful cancer therapy, the anticancer drug reaches the tumor site via two targeting means; either it is active or passive targeting mean [54].

6.1 Passive Targeting of Nanoparticles

The passive tumor targeting highly depends upon certain factors like tumor microenvironment, punctured tumor vasculature, and the direct local application [50]. It is important to note that the presence of tight junctions between the non-malignant tissues, results in resistance to the passage of nanoparticles. Specifically in cancer, the neovasculature is leaky and disorganized [49]. This whole scenario allows the extravasation of nanocarriers in the endothelium of the tumor vessels due to the presence of fenestrations (Figure 2) [51].

The passive drug targeting also depends upon the accumulation of drug at the targeted site and the half-life of the drug carrier. The therapeutic potential of nanoparticles depends upon the surface charge, solubility, biodegradability, and morphology [55]. A hydrophilic biomaterial's (Polyethylene glycol) covering or coating is used to defend nano-formulation against the attack of macrophages and to enhance the circulation time of nano-formulations. In the passive targeting, the nanoparticles conglomerate in the affected tissues because of their retention and permeability effect [52]. The trafficking of nanoparticles over the neoplastic tissues highly depends upon the surface charge, tumor microvasculature, size, and shape

[56].

6.2 Active Targeting of Nanoparticles

The active targeting mode of nanoparticles depends upon the utilization of certain ligands like folate and transferrin, which bind to the proteins that are over-expressed or somewhat expressed on the target cellular sites [57]. This instigates the inbound folding of membranes and incorporates the nanoparticles into the cells through a phenomenon named receptor-mediated endocytosis (Figure 3). Under the non-alkaline conditions of the endosome, the encapsulated drug is released from the nanoparticles and sets foot in the cytoplasm after that it acts on the cellular target [58]. The strategies of tumor-targeting are classified into three classes. i) Angiogenesis-associated targeting through the growth factor receptors of vascular endothelial, matrix metalloproteinase receptors, vascular cell adhesion molecule-1 and $\alpha v \beta 3$ integrins. ii) Tumor cell targeting for targeting colorectal cancer, for targeting lungs cancer, for targeting breast cancer, for targeting prostate cancer, etc., and iii) the targeting of uncontrolled cellular proliferation through human folate receptors, endothelial receptors, and transferring receptors [56]. Scientists have reported the active targeting of tumor cells by using the multi-functional dendritic nanodevice attached with folic acid which contained Methotrexate as a chemotherapeutic agent. In addition, the Rapamycin-loaded epithelial growth factor antibody-conjugated nanoparticles reported increased efficacy in MCF 7 breast cancer cells

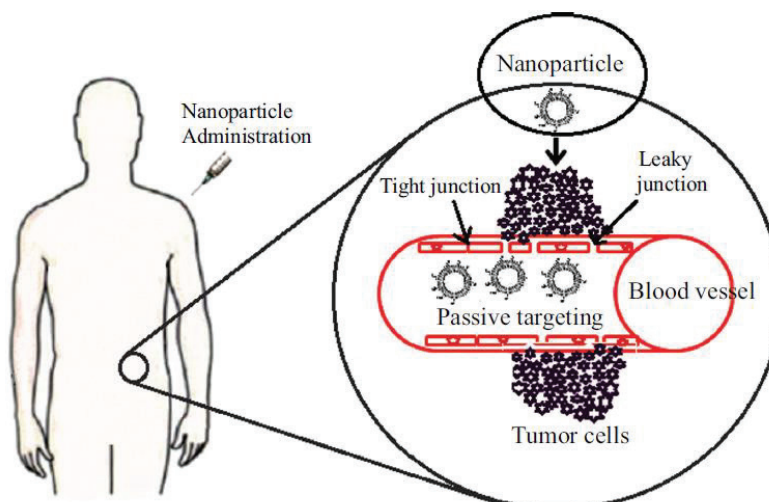


Fig. 2. The figure shows the phenomena of passive tumor targeting by the nanoparticles. The targeting process depends upon the infiltration of nanoparticles of ideal size, shape, and surface charge across a leaky neovasculature [53].

[58, 45].

7. NANOPARTICLES IN THE TREATMENT OF CANCER THERAPY

A plethora of nanotechnology-based products have widely been used as drug delivery agents in cancer therapy, [60] these products include liposomes, dendrimers, carbon nanotubes, polymeric micelles, magnetic nanoparticles, Solid Lipid Nanoparticles, Quantum dots, etc (Figure 4) [61, 62].

7.1 Dendrimer-based Nanoparticles

Dendrimers having nano-size (<5 nm diameter) are spherical polymeric particles. They possess a larger area for the incorporation of therapeutic agents [63]. The conceptualization of dendrimers destroys the morphology and characteristics of malignant tumors like; rapid proliferation, specific cell surface antigen expression, and leaky vasculature [61]. The synthesis of dendrimers initiates with an ammonia core which reacts with acrylic acid and fabricates tri-acid molecules [57]. The newly produced tri-

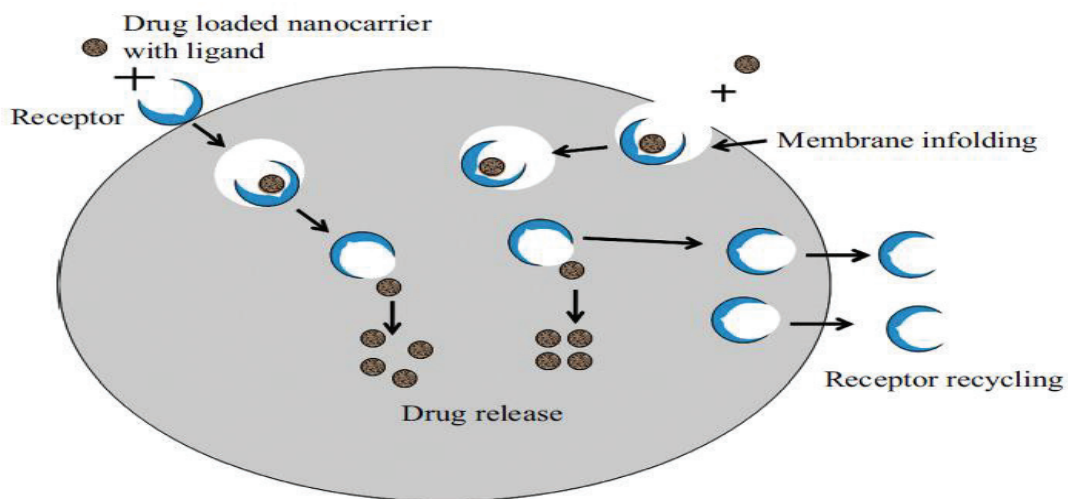


Fig. 3. The process of active tumor targeting by nanoparticles via receptor-mediated endocytosis process. Attaching of nanoparticle surface ligands to the tumor cells leads to membrane inbound folding and incorporation of nanoparticles via receptor-mediated endocytosis. Under the acidic conditions of the endosome, the drug is release from the nanoparticles to the cytoplasm [59].

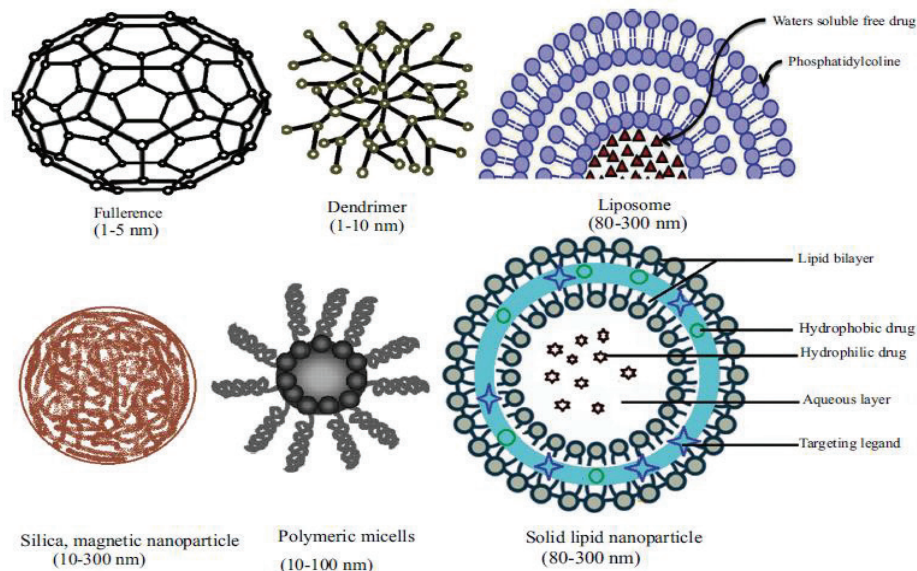


Fig. 4. Different nanoparticles possessing peculiar characteristics, different sizes are being used in cancer therapy [59].

acid molecule then reacts with Ethylenediamine to make a tri-amine molecule generally known as (G0) generation 0 product. This generation 0 product then reacts with acrylic acid to form a Hexa-acid. This Hexa-acid product further reacts with ethylenediamine to form Hexa-amine (G1) the process goes on. Changes in reactions with ethylenediamine and acrylic acid continue until the desired result is not achieved. Polyamidoamine shortly known as PAMAM-based dendrimers is the most investigated and widely accepted for therapeutic applications [64]. The DNA-based polyamidoamine dendrimers for cancer-cell-specific targeting are well described by Choi et al., Folic acid and Fluorescein coupled dendrimers are developed by a mechanism named Acetylation to lessen the drug toxicity [55, 79].

The *in vitro* studies showed specific binding to KB cells expressing the folate receptor [92]. A group of scientists explained the use of paclitaxel-packed multi-functional dendrimers coupled with folic acid and fluorescein isothiocyanate to hit the cancer cells which over-expresses the folate receptors [64]. Multifaceted dendrimers were synthesized from ethylenediamine core whose primary amino acid group has neutralized via partial acetylation [74]. The dendrimer couple investigated the cytotoxic effect on the KB folate receptor. Furthermore, another group of scientists prepared methotrexate-loaded dendrimers for intravenous administration to hit the folate receptors which lie on the surface of cancer cells, these prepared dendrimers tremendously inhibit the growth of epithelial cancer [65].

7.2 Magnetic Nanoparticles

Magnetic nanoparticle-transfection methods follow a principle developed by a group of scientists named Widder and others in the past 1970s for targeting the drug delivery magnetically [74]. The first therapeutic use of these magnetic nanoparticles for transfection was reported in C12S cells in mice by Mah and coworkers [101]. Recombinant single-chain FV antibody fragment-mediated superparamagnetic iron oxide nanoparticles are investigated to be a potential candidate for cancer-specific medical resonance imaging [44]. Superparamagnetic iron oxide nanoparticles conjugated with Luteinizing hormone are shown

to be effective for targeting and imaging breast cancers. Roughly, nine or ten magnetic nanoparticle products have been introduced into the market for clinical trials purposes which include Feridex (AMAG pharmaceuticals, Inc) for imaging of liver cancer, Resovist® (Bayer Schering Pharma AG) for imaging of colon cancer and liver metastasis, Ferumoxytol (AMAG pharmaceuticals, Inc) for imaging the Central Nervous System (CNS) cancers [66, 67].

7.3 Calcium Phosphate Nanoparticles

Calcium phosphate nanoparticles alone or in conjugation with non-viral and viral vectors reported tremendous outcomes as drug delivery agents in cellular gene transfer [104]. Calcium phosphate nanoparticles are more advantageous over others because of their low production costs, biocompatibility, reduced microbial degradation, and storage stability. Moreover, it is biodegradable, hence it does not cause any severe damage or side effects at the injection site. It is used as a vehicle to deliver medications like contraceptives, growth factors, antibiotics, and insulin. Their precipitation is used for the delivery of Plasmid DNA and oligonucleotides [49]. A group of researchers investigated that liposomal Nanolipoplex, formulation of glycerol and calcium has decreased cytotoxicity and improved transfection properties of cells [70].

7.4 Polymeric Nanoparticles

Polymeric nanoparticles are the most promising drug delivery agents, despite having many challenges with production, these are the most investigated in nanotechnology for the targeted delivery of anticancer drugs [29]. Polymeric nanoparticles are mainly composed of polylactic acid, polyglycolic acid, acrylates [71]. Scientists find out that nanoparticles that contain anti-human epidermal growth factor receptor 2 and doxorubicin reported nuclear localization of anticancer drug in the human epidermal growth factor 2-overexpressing breast cancer SKBR-3 cells. Another research reported that indomethacin encapsulated nanocapsules shown a significant decrease in the size of the tumor and also reported the increased survival in a xenograft glioma model among rats [72]. Abraxane is an example of polymeric nanoparticle

which is a formulation of Paclitaxel, conjugated to albumin has been approved for metastatic breast cancer treatment [73]. It is another emerging field in medical sciences with more than ten polymeric nanoparticles containing anticancer drugs are currently under clinical trials which includes Paclitaxel poliglumex (Xyotax), PEG-camptothecin (Prothecan), HPMA copolymer-DACH-platinatate (AP5346), HPMA copolymerplatinatate (AP 5280), HPMA copolymer-doxorubicinalgalactosamine (PK2), N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-camptothecin (MAG-CPT), Modified dextran-camptothecin (DE 310), etc. [73, 74].

7.5 Quantum Dots

Quantum dots are semi-conduction nanoparticles. They elicit some unique characteristics like broad absorption spectrum, higher photostability, broad ultraviolet excitations, narrow emission bands, and brighter fluorescence [75]. The narrow emission bands and wider absorption spectrum grant only one wavelength of light to instigate a cluster of quantum dots of many sizes which reciprocally discharge multiplex imaging at different wavelengths [23]. To cope-up with limitations regarding imaging in the visible spectral region, quantum dots that fluoresce in the near-infrared spectral region (700-1000 nm) have been reported [110]. The near-infrared region quantum dots have been experimented with for lymphatic mapping in various animal studies. In 2004, Gao et al. reported that the quantum dots can be effective against cancer targeting in animal models [115]. Another group of scientists Bagalkot et al. investigated quantum dots aptamer – doxorubicin couple for targeting the prostate cancer cells. The prepared nanoparticle couple demonstrated the sensitivity and specificity for cancer therapy and imaging [76]. In the near past, Liu et al. reported a biological activity of conjugated molecules of alyl isothiocyanate and silicon quantum dots, the scientists find out that this conjugation showed identical anticancer properties like alyl isothiocyanate at higher doses by avoiding the lower dose stimulation effect of alyl isothiocyanate on DNA damage and cell migration. Alyl-isothiocyanate coupled silicon quantum dots outlined biphasic anticancer properties in human hepatoma HepG2 cells [77].

7.6 Liposomes

Liposomes are made up of natural phospholipids. Thus, they are biologically inert, elicit low intrinsic toxicity and weak immunogenicity [78]. They are spherical-shaped nanoparticles consisting of the lipid bilayer to encase therapeutic drugs [79]. The presence of lipid bilayer made them prodigious candidates to deliver hydrophilic and hydrophobic drugs. Myocet®, Doxil®, DuanoXomer® are globally approved liposome-based nanoparticles which contain Duanorobucin as an anticancer drug for metastatic breast cancer treatment. MCC-465 (PEG-immunoliposome-doxorubicin) is going through clinical trials for the treatment of stomach cancer, similarly, SPI-077 (Liposomal cisplatin) is also undergoing clinical trials for the treatment of various cancers, OSI-211 (liposomal lurtotecan), Aroplati, (liposomal oxaliplatin), OSI-7904L (liposomal thymidylate synthase inhibitor), LEP ETU (liposomal paclitaxel), LE-SN38 (liposomal SN38 or liposomal irinotecan metabolite) are the products for liposomal-based nanoparticles which are going through clinical trials phase 2 for the treatment of various cancers [91]. A group of scientists has reported the production of the first C60 based slow-release liposomal aerosol to deliver paclitaxel for treating lungs cancer and this product marked a big achievement with promising outcomes [80, 81].

7.7 Gold Nanoparticles

Gold nanoparticles are the intracellular drug delivery agents and possess unique properties, like; their size can be controlled very easily, their surface properties can be modified accordingly, their visible light extinction behavior makes them feasible to encounter nanoparticle trajectories in the cells [82]. To target HER2 positive breast carcinoma, Anti-HER2 functionalized gold-on-silica nano-shells have been prepared, to wipe out the problem of the presence of salt in gold Sodium bromohydride is used [61]. However, sodium bromohydride is unsuitable for target-specific peptides because it lessens the chemical composition of peptides [71]. Hydrazine, dimethyl formamide, sodium bromohydride are the limitations in the therapeutic use of gold nanoparticles [83, 84].

7.8 Silica Nanoparticles

Silica is a prominent component of natural materials such as glass, sand, etc. It has been widely used for thousands of years. Recently, its biomedicine use has been identified [23]. Silica-nanoparticles such as N-(6-aminohexyl) – 3 – aminopropyltrimethoxysilance can effectively result in the transfection of Cos-1 cells with very lower toxicity [85]. A group of scientists Gary-Bobo et al. reported that the anticancer drug camptothecin loaded on mesoporous silica nanoparticles is very effective against colorectal cancer cells [86, 87].

7.9 Carbon Nanotubes

Carbon nanotubes were prepared in the late 1980s [103]. While mentioning their properties they are single and multi-walled tubes and are being used for thermal ablation therapy and used as DNA delivery vectors [88]. Heister et al. investigated that the monoclonal antibody and oxidized single-walled nanotubes which contained fluorescent marker targeted delivery of doxorubicin is effective against the treatment of colon cancer cells [45]. It is also reported that multi-walled carbon nanotube chitosan nanoparticle hybrids are prepared by an inotropic gelatin process has drastically decreased cellular toxicity, improved protein immobilization efficiency as compared to carboxylated multi-walled carbon nanotubes [89].

7.10 Solid Lipid Nanoparticles

These are the colloidal nanocarriers which are composed of phospholipid monolayer coating a solid hydrophobic core and encasing a drug in a high melting point like waxes or glycerides [90]. Anticancer drug mitoxantrone encased in SLN has reported improved bioavailability, drug safety, reduced toxicity. Increased efficacy of doxorubicin and idarubicin being incorporated in SLN's demonstrated better results to treat leukemia cells and murine leukemia in mice models [91, 111].

7.11 Fullerenes

They are big carbon-caged molecules typically known as Buckyballs. They are the most promising anticancer carriers because of their unique physical, electrical, structural (hollow sphere), and chemical

properties [92]. Their stability makes them a very choice candidate for effective and safe drug delivery to the tumor cells. Similarly, the existence of π -conjugation, they can absorb light, high triplet yield, and can generate reactive oxygen species upon illumination. These photo properties make them suitable for photodynamic therapy of cancer [93]. Krishna et al. reported the photoacoustic and photothermal properties of polyhydroxy fullerenes for cancer therapy and imaging [94].

7.12 Microbes-mediated nanoparticles

In recent years, there has been a paradigm change toward environmentally friendly, green, and biological production of metal nanoparticles (MNPs) for various nanomedicine applications, including cancer nanotheranostics. Aside from the well-known green synthesis methods of plant materials, the microbial world's (bacteria, fungus, alga, etc.) potential in biofabrication is also realized. Biomolecules and enzymes found in microbial cells can catalyze the biosynthesis process. These microbially generated inorganic nanoparticles have been extensively studied as possible agents in cancer treatments, with promising findings. These microbial-derived nanoparticles have the ability to destroy cancer cells via cellular and molecular mechanisms. Given recent advances in the anticancer uses of microbially generated inorganic MNPs, there is a pressing need to conduct clinical studies [112].

8. APPROVED NANOPARTICLES FOR ONCOLOGICAL APPLICATIONS

In the past few decades, the use of nanoparticles has gained the spotlight. Here are several nanoparticles which are used commercially.

- Doxil® is the first nanoparticle approved by the FDA in 1995 for the treatment of metastatic breast cancer, ovarian cancer, HIV related Kaposi's sarcoma [95].
- DaunoXome® was approved by FDA in 1994 for the treatment of HIV-related Kaposi sarcoma.
- Abraxane® was also approved by FDA in 2005 for the treatment of metastatic breast cancer. Abraxane alone with gemcitabine is effective against pancreatic cancer.

Table 1. Clinically approved drug-delivery systems [111].

S. No.	Type of Drug Delivery System	Clinically Approved Drugs
1	Nanoparticles	Doxil (Doxorubicin), Abraxane (Paclitarel), DaunoXome (Daunorubicin), Margibo (Vincristine), MEPACT (Mifamurtide), ADYNOVATE (antinemophilic factor (recombinant) PEGylated), Onivyde MM-398 (Irinotecan), Estrasorb (estradiol), Depocyte (cytarabine), AmBisome (amphotericin B), Visudyne (Verteporfin)
2	Microparticle-based depots	Decapeptyl/Trelstar (Triptorelin), Zmax (Azithromycin), Vivitrol (Naltrexone), Risperdal/Consta (Risperidone), Sand-ostatin LAR Depot (Octreotide), Arestin (Minocycline), Nutropin Depot (Somatropin), Lupron Depot (Leuprolide), DepoDur (Morphine), Bydureon (Exenatide), DepoCyt (Cytarabine), Somatuline LA (Lanreotide), Suprefact Depot (Buselerin), Zoladex (Goserelin), Signifor (Pasireotide)
3	Transdermal materials and devices	Nitro-Dur (Nitroglycerin), Transderm-Scop (Scopolamine), Catapres TTS (Clonidine), Estraderm (Estradiol), Duragesic (Fentanyl), Combipatch (Estradiol with norethindrone), Androderm (Testosterone), Lidoderm (Lidocaine), Climara Pro (Estradiol with levonorgestrel), Synera (Lidocaine and tetracaine), Daytrana (Methylphenidate), Oxytrol (Oxybutynin), Emsam (Selegiline), Neupro (Rotigotine), Exelon (Rivastigmine), Sancuso (Granisetron), Butrans (Buprenorphine), Ortho Evra (Estradiol and norelgestromin), Flector (Diclofenac epolamine), NicoDerm/Habitrol/ProStep (Nicotine), Qutenza (Capsaicin), Retin-A (Tretinoin), IONSYS (Fentanyl), SonoPrep (Lidocaine via ultra-sound), LidoSite (Lidocaine and epinephrine via iontophoresis), Iontocaine (Lidocaine and epinephrine via iontophoresis)
4	Oral	Ditropan XL (Oxybutynin), Concerta (Methylphenidate), Teczem (Enalapril Diltiazem), Dilacor XR (Diltiazem), Covera-HS (Verapamil), Minipress XL (Prazosin), Procardia XL (Nifedipine), DynaCire CR (Isradipine), Fortamet (Metformin), Altoprev (Lovastatin), Glucotrol XL (Glipizide), Tegretol-XL (Carbamazepine), Allegra D (Pseudoephedrine and Fexofenadine), Invega (Paliperidone), Efdac/24 (Pseudoephedrine and Brompheniramine or Chlorphenir-amine), Volmax (Albuterol), Orenitram (Treprostinil), Sudafed 24 h (Pseudoephedrine), Exalgo (Hydromorphone), Vesanoid (Tretinoin), Venclexta (venetoclax), Farydak (panobinostat), Syndros (Dronabinol), Renagel (Sevelamer)
5	Pulmonary	Proventil HFA (Albuterol), Tudorza/Pressair (Aclidinium), Ventolin HFA (Albuterol), ProAir HFA (Albuterol), Combivent Respimat (Albuterol and ipratropium), Brovana (Arformoterol), QVAR (Beclomethasone), DuoNeb (Albuterol and ipratropium), Pulmicort Flexhaler (Budesonide), Symbicort (Budesonide and Formoterol), Alvesco (Ciclesonide), Bro/Ellipta (Fluticasone and vilanterol), Flovent/Diskus (Fluticasone), Flovent HFA (Fluticasone), Foradil/Aerolizer (Formoterol), Perforomist (Formoterol), Arcapta Neohaler (Indacaterol), Atrovent HFA (Ipratropium), Xopenex HFA (Levalbuterol), Asmanex/Twisthaler (Mometasone), Dulera (Mometasone and Formoterol), ADVAIR Diskus (Salmeterol Fluticasone), Serevent/Diskus (Salmeterol), ADVAIR HFA (Salmeterol Fluticasone), Spiriva/Handihaler (Tiotropium), Cayston (Aztreonam), Ventavis (Iloprost), Tyvaso (Treprostinil), TOBI Podhaler (Tobramycin), Afrezza (human insulin).
6	Implants	Retisert (Fluocinolone), Vitrasert (Ganciclovir), Ozurdex (Dexamethasone), Gliadel (Prolifeprosan and Carmustine), Zoladex (Goserelin), Vantas/Supprelin LA (Histrelin), Viadur (Leuprolide), NuvaRing (Etonogestrel and ethinyl estradiol), Nexplanon (Etonogestrel), Mirena/Norplant (Levonorgestrel), Paragard (Copper).

- Myocet® was approved in Europe and Canada for the treatment of metastatic breast cancer [96].
- Depocyt® was approved in 1996 for treating Lymphomatous Meningitis
- Genexol PM® a South-Korean approved nanoparticle is used to treat metastatic cancer; it is under clinical phase 2 study for Pancreatic cancer treatment [97].
- Oncaspar® was approved by FDA in 2006 to treat Lymphoblastic Leukemia.

9. TOXICITIES OF NANOPARTICLES

The toxicity concerns about nanoparticles are a non-negligible act and this should be addressed too [98]. The particle size, particle shape, aggregation solubility, drug release, nanoparticle-drug interactions, surface area are the major concerns. The small size makes them more vulnerable to health hazards [99]. These nanoparticles are more prone to lung deposition and are responsible for rapid systemic translocation having several cytotoxic, oxidative, inflammatory effects as compared to larger particles [100]. Hussain et al. conducted a study on the toxicity of metal-based nanoparticles and investigated that silver was highly toxic for human lungs, whereas, molybdenum, iron oxide, aluminum, manganese oxide, and tungsten were reported less toxicity. However, it is still unclear that how nanoparticles induce toxicity, it might be because of oxidative stress [101]. Lam et al. investigated that rats and mice showed a higher degree of pulmonary toxicity being treated with carbon nanotubes as compared to the treatment with carbonyl ion particles and carbon black. It is also investigated that surface modification in quantum dots with N-acetylcysteine lowers the issues of toxicity [102]. Therefore, it is recommended that the screening of nanoparticles should be made while considering their chemical, physical, properties, cellular, and tissue interactions in animal testing [103].

10. CONCLUSION AND FUTURE PROSPECTS

It is worth mentioning that nanotechnology has given us tremendous outcomes for cancer diagnosis, detection, therapy, and circumventing multi-drug resistance [104]. They provide a wide range of

opportunities to improve therapeutic outcomes. While forecasting the prospects of nanomedicines and drug delivery systems, there is no ambiguity in saying that this emerging field has revolutionized the world with its contemporary research dynamics [104,105]. The science of nanomedicine is right now among the top-notch research areas. Much of the research in this domain has been conducted in the past two decades, thousands of patents have been completed and hundreds of clinical trials have been conducted [106]. Tumor cells therapy is still the point of discussion among scientists, there is a lot more is still to be done. It is also a point of focus that nanoparticle development is challenging due to the lack of suitable in vitro models which are masking accurately the in vivo state. Contemporary therapeutic applications of the nano-formulations are prepared on in vitro evaluation while using cell lines which fails to capture the peculiarity and complexity of nanoparticle-cell interactions in vivo [107,108]. But still, there is no ambiguity in saying that it is an emerging area and it remained very helpful in treating cancers [109]. For a logical nanotechnology outline, we need an enhanced understanding of cellular, pharmaceutical, physiological constituents regulating nanotechnology-based drug delivery [110, 111].

11. ACKNOWLEDGMENTS

The authors would like to acknowledge Prof. Deng Linhong and Prof. Chen Xn for their worthy guidance and support.

12. CONFLICT OF INTEREST

The authors declared no conflict of interest.

13. REFERENCES

1. K. Sztandera, M. Gorzkiewicz, and B. Klajnert-Maculewicz. Gold nanoparticles in cancer treatment. *Molecular Pharmaceutics* 16: 1-23 (2018).
2. S. Rezvantlab, N.I. Drude, M.K. Moraveji, N. Güvener, E.K. Koons, Y. Shi, T. Lammers, and F. Kiessling. PLGA-based nanoparticles in cancer treatment. *Frontiers in Pharmacology* 29: 1260-72 (2018).
3. H. Khan, H. Ullah, M. Martorell, S.E. Valdes, T. Belwal, S. Tejada, A. Sureda, and M.A. Kamal. Flavonoids nanoparticles in cancer: Treatment,

- prevention and clinical prospects. In: *Seminars in Cancer Biology*, Vol 69. Elsevier Academic Press, USA, p. 200-211 (2021).
4. R. Awasthi, A. Roseblade, P.M. Hansbro, M.J. Rathbone, K. Dua, and M. Bebawy. Nanoparticles in cancer treatment: opportunities and obstacles. *Current Drug Targets* 19: 1696-709 (2018).
 5. A. Aghebati-Maleki, S. Dolati, M. Ahmadi, A. Baghbanzadeh, M. Asadi, A. Fotouhi, M. Yousefi, and L. Aghebati-Maleki. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *Journal of Cellular Physiology* 235: 1962-72 (2020).
 6. A. Mahapatro, and D.K. Singh. Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines. *Journal of Nanobiotechnology* 9: 1001-21 (2011).
 7. M. Singh, S. Singh, S. Prasad, and I.S. Gambhir. Nanotechnology in medicine and antibacterial effect of silver nanoparticles. *Digest Journal of Nanomaterials and Biostructures* 3: 115-22 (2008).
 8. M. Wu, and S. Huang. Magnetic nanoparticles in cancer diagnosis, drug delivery and treatment. *Molecular and Clinical Oncology* 7: 738-46 (2017).
 9. J. Peng, X. Liang. Progress in research on gold nanoparticles in cancer management. *Medicine* 98: 234-39 (2019).
 10. N.A. Nasab, H.H. Kumleh, M. Beygzadeh, S. Teimourian, and M. Kazemzad. Delivery of curcumin by a pH-responsive chitosan mesoporous silica nanoparticles for cancer treatment. *Artificial Cells, Nanomedicine, and Biotechnology* 46: 75-81 (2018).
 11. M. Fan, Y. Han, S. Gao, H. Yan, L. Cao, Z. Li, X.J. Liang, and J. Zhang. Ultrasmall gold nanoparticles in cancer diagnosis and therapy. *Theranostics* 10: 4944- (2020).
 12. H. Zhang, X.L. Liu, Y.F. Zhang, F. Gao, G.L. Li, Y. He, M.L. Peng, and H.M. Fan. Magnetic nanoparticles based cancer therapy: current status and applications. *Science China Life Sciences* 61: 400-14 (2018).
 13. Y. Cai, W. Si, W. Huang, P. Chen, J. Shao, and X. Dong. Organic dye based nanoparticles for cancer phototheranostics. *Small* 14: 1704247 (2018).
 14. A. Sharma, A.K. Goyal, and G. Rath. Recent advances in metal nanoparticles in cancer therapy. *Journal of Drug Targeting* 26: 617-32 (2018).
 15. S. Kang, W. Shin, K. Kang, M.H. Choi, Y.J. Kim, Y.K. Kim, D.H. Min, and H. Jang. Revisiting of Pd nanoparticles in cancer treatment: all-round excellence of porous Pd nanoplates in gene-thermo combinational therapy. *ACS Applied Materials & Interfaces* 10: 13819-28 (2018).
 16. S. Goodall, M.L. Jones, and S. Mahler. Monoclonal antibody-targeted polymeric nanoparticles for cancer therapy—future prospects. *Journal of Chemical Technology & Biotechnology* 90: 1169-76 (2015).
 17. E.R. Evans, P. Bugga, V. Asthana, and R. Drezek. Metallic nanoparticles for cancer immunotherapy. *Materials Today* 21: 673-85 (2018).
 18. H. Wang, X. Li, B.W. Tse, H. Yang, C.A. Thorling, Y. Liu, M. Touraud, J.B. Chouane, X. Liu, M.S. Roberts, and X. Liang. Indocyanine green-incorporating nanoparticles for cancer theranostics. *Theranostics* 8: 1227- (2018).
 19. Z. Zhou, J. Song, R. Tian, Z. Yang, G. Yu, L. Lin, G. Zhang, W. Fan, F. Zhang, G. Niu, and L. Nie. Activatable singlet oxygen generation from lipid hydroperoxide nanoparticles for cancer therapy. *Angewandte Chemie* 129: 6592-6 (2017).
 20. M. Saeed, W. Ren, and A. Wu. Therapeutic applications of iron oxide based nanoparticles in cancer: basic concepts and recent advances. *Biomaterials science* 6: 708-25 (2018).
 21. H. Dong, L. Pang, H. Cong, Y. Shen, and B. Yu. Application and design of esterase-responsive nanoparticles for cancer therapy. *Drug Delivery* 26: 416-32 (2019).
 22. Z.Q. Zuo, K.G. Chen, X.Y. Yu, G. Zhao, S. Shen, Z.T. Cao, Y.L. Luo, and J. Wang. Promoting tumor penetration of nanoparticles for cancer stem cell therapy by TGF- β signaling pathway inhibition. *Biomaterials* 82: 48-59 (2016).
 23. S. Bayda, M. Hadla, S. Palazzolo, P. Riello, G. Corona, G. Toffoli, and F. Rizzolio. Inorganic nanoparticles for cancer therapy: a transition from lab to clinic. *Current Medicinal Chemistry* 25: 4269-303 (2018).
 24. V.S. Madamsetty, A. Mukherjee, and S. Mukherjee. Recent trends of the bio-inspired nanoparticles in cancer theranostics. *Frontiers in Pharmacology* 10: 1264- (2019).
 25. J.H. Ryu, H.Y. Yoon, I.C. Sun, I.C. Kwon, and K. Kim. Tumor-Targeting Glycol Chitosan Nanoparticles for Cancer Heterogeneity. *Advanced Materials* 32: 2002197 (2020).
 26. R. Meir, K. Shamalov, T. Sadan, M. Motiei, G. Yaari, C.J. Cohen, and R. Popovtzer. Fast image-guided stratification using anti-programmed death ligand 1 gold nanoparticles for cancer immunotherapy. *ACS*

- Nano* 11: 11127-34 (2017).
27. M. Hematyar, M. Soleimani, A. Es-Haghi, and A.R. Mokarram. Synergistic co-delivery of doxorubicin and melittin using functionalized magnetic nanoparticles for cancer treatment: loading and in vitro release study by LC-MS/MS. *Artificial Cells, Nanomedicine, and Biotechnology* 46: S1226-35 (2018).
 28. G. Yu, T.Y. Cen, Z. He, S.P. Wang, Z. Wang, X.W. Ying, S. Li, O. Jacobson, S. Wang, L. Wang, and L.S. Lin. Porphyrin Nanocage-Embedded: Single-Molecular Nanoparticles for Cancer Nanotheranostics. *Angewandte Chemie International Edition* 58: 8799-803 (2019).
 29. S. Sau, H.O. Alsaab, K. Bhise, R. Alzhrani, G. Nabil, and A.K. Iyer. Multifunctional nanoparticles for cancer immunotherapy: A groundbreaking approach for reprogramming malfunctioned tumor environment. *Journal of Controlled Release* 27: 24-34 (2018).
 30. S. Uthaman, K.M. Huh, and I.K. Park. Tumor microenvironment-responsive nanoparticles for cancer theragnostic applications. *Biomaterials research* 22: 101-10 (2018).
 31. O. Sahin, A. Meiyazhagan, P.M. Ajayan, and S. Krishnan. Immunogenicity of externally activated nanoparticles for cancer therapy. *Cancers* 12: 3559- (2020).
 32. K. Li, H. Nejadnik, and H.E. Daldrup-Link. Next-generation superparamagnetic iron oxide nanoparticles for cancer theranostics. *Drug Discovery Today* 22: 1421-9 (2017).
 33. B. García-Pinel, C. Porras-Alcalá, A. Ortega-Rodríguez, F. Sarabia, J. Prados, C. Melguizo, and J.M. López-Romero. Lipid-based nanoparticles: application and recent advances in cancer treatment. *Nanomaterials* 9: 638 (2019).
 34. X. Zhen, P. Cheng, and K. Pu. Recent advances in cell membrane-camouflaged nanoparticles for cancer phototherapy. *Small* 15: 1804105 (2019).
 35. M.E. Vance, T. Kuiken, E.P. Vejerano, S.P. McGinnis, M.F. Hochella, D. Rejeski, and M.S. Hull. Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory. *Beilstein journal of nanotechnology* 6: 1769-80 (2015).
 36. K. Dua, S.D. Shukla, D.J. Andreoli T. Pinto, and P.M. Hansbro. Nanotechnology: Advancing the translational respiratory research. *Interventional Medicine and Applied Science* 9: 39-41 (2017).
 37. N. Sanvicens, and M.P. Marco. Multifunctional nanoparticles—properties and prospects for their use in human medicine. *Trends in biotechnology* 26: 425-33 (2008).
 38. A. Prokop, and J.M. Davidson. Nanovehicular intracellular delivery systems. *Journal of pharmaceutical sciences* 97: 3518-90 (2008).
 39. J. Panyam, and V. Labhasetwar. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Advanced drug delivery reviews* 55: 329-47 (2003).
 40. R. Singh, and J.W. Lillard. Nanoparticle-based targeted drug delivery. *Experimental Molecular Pathology* 86: 215-23 (2009).
 41. J. Jose, R. Kumar, S. Harilal, G.E. Mathew, A. Prabhu, M.S. Uddin, L. Aleya, H. Kim, and B. Mathew. Magnetic nanoparticles for hyperthermia in cancer treatment: an emerging tool. *Environmental Science and Pollution Research* 27: 19214-25 (2020).
 42. J. Key, and K. Park. Multicomponent, tumor-homing chitosan nanoparticles for cancer imaging and therapy. *International journal of molecular sciences* 18: 594 (2017).
 43. J. Kolosnjaj-Tabi, and C. Wilhelm. Magnetic nanoparticles in cancer therapy: how can thermal approaches help?. *International journal of molecular sciences* 21: 967-75 (2020).
 44. H. Chugh, D. Sood, I. Chandra, V. Tomar, G. Dhawan, and R. Chandra. Role of gold and silver nanoparticles in cancer nano-medicine. *Artificial cells, nanomedicine, and biotechnology* 46: 1210-20 (2018).
 45. Y. Zhai, J. Su, W. Ran, P. Zhang, Q. Yin, Z. Zhang, H. Yu, and Y. Li. Preparation and application of cell membrane-camouflaged nanoparticles for cancer therapy. *Theranostics* 7: 2575 (2017).
 46. M. Neek, T.I. Kim, and S.W. Wang. Protein-based nanoparticles in cancer vaccine development. *Nanomedicine: Nanotechnology, Biology and Medicine* 15: 164-74 (2019).
 47. M.O. Ansari, M.F. Ahmad, G.G. Shadab, and H.R. Siddique. Superparamagnetic iron oxide nanoparticles based cancer theranostics: A double edge sword to fight against cancer. *Journal of Drug Delivery Science and Technology* 45: 177-83 (2018).
 48. S.K. Sharma, N. Shrivastava, F. Rossi, and N.T. Thanh. Nanoparticles-based magnetic and photo induced hyperthermia for cancer treatment. *Nano Today* 29: 100795 (2019).
 49. Y. Wang, S. Song, S. Zhang, and H. Zhang. Stimuli-responsive nanotheranostics based on lanthanide-

- doped upconversion nanoparticles for cancer imaging and therapy: current advances and future challenges. *Nano Today* 25: 38-67 (2019).
50. P. Singh, S. Pandit, V.R. Mokkalapati, A. Garg, V. Ravikumar, and I. Mijakovic. Gold nanoparticles in diagnostics and therapeutics for human cancer. *International Journal of Molecular Sciences* 19: 1979- (2018).
 51. B. Shrestha, L. Tang, and G. Romero. Nanoparticles-mediated combination therapies for cancer treatment. *Advanced Therapeutics* 2: 1900076 (2019).
 52. M. Cordani, and A. Somoza. Targeting autophagy using metallic nanoparticles: a promising strategy for cancer treatment. *Cellular and Molecular Life Sciences* 76: 1215-42 (2019).
 53. D. Zhi, T. Yang, J. Yang, S. Fu, and S. Zhang. Targeting strategies for superparamagnetic iron oxide nanoparticles in cancer therapy. *Acta Biomaterialia* 10: 13-34 (2020).
 54. C.G. Liu, Y.H. Han, R.K. Kankala, S.B. Wang, and A.Z. Chen. Subcellular performance of nanoparticles in cancer therapy. *International Journal of Nanomedicine* 15: 675 (2020).
 55. T.T. Tran, P.H. Tran, T.J. Yoon, and B.J. Lee. Fattigation-platform theranostic nanoparticles for cancer therapy. *Materials Science and Engineering* 75: 1161-7 (2017).
 56. H. Zhou, J. Ge, Q. Miao, R. Zhu, L. Wen, J. Zeng, and M. Gao. Biodegradable inorganic nanoparticles for cancer theranostics: Insights into the degradation behavior. *Bioconjugate chemistry* 31: 315-31 (2019).
 57. W. Hong, F. Guo, N. Yu, S. Ying, B. Lou, J. Wu, Y. Gao, X. Ji, H. Wang, A. Li, and G. Wang. A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β -Cyclodextrin Nanoparticles for Cancer Treatment. *Drug Design, Development and Therapy* 15: 2843 (2021).
 58. A. Nikkhoo, N. Rostami, S. Farhadi, M. Esmaily, S.M. Ardebili, F. Atyabi, M. Baghaei, N. Haghnava, M. Yousefi, M.R. Aliparasti, and G. Ghalamfarsa. Codelivery of STAT3 siRNA and BV6 by carboxymethyl dextran trimethyl chitosan nanoparticles suppresses cancer cell progression. *International journal of pharmaceuticals* 58: 119236 (2020).
 59. Y. Zhao, X. Zhao, Y. Cheng, X. Guo, and W. Yuan. Iron oxide nanoparticles-based vaccine delivery for cancer treatment. *Molecular Pharmaceutics* 15: 1791-9 (2018).
 60. P. Aiello, S. Consalvi, G. Poce, A. Raguzzini, E. Toti, M. Palmery, M. Biava, M. Bernardi, M.A. Kamal, G. Perry, and I. Peluso. Dietary flavonoids: Nano delivery and nanoparticles for cancer therapy. In: *Seminars in Cancer Biology*, Vol. 69. Elsevier Academic Press, USA, p. 150-71 (2021).
 61. R. Nasr, H. Hasanzadeh, A. Khaleghian, A. Moshtaghian, A. Emadi, and S. Moshfegh. Induction of apoptosis and inhibition of invasion in gastric cancer cells by titanium dioxide nanoparticles. *Oman Medical Journal* 33: 111 (2018).
 62. T.T. Le, T.Q. Bui, T.M. Ha, M.H. Le, H.N. Pham, and P.T. Ha. Optimizing the alginate coating layer of doxorubicin-loaded iron oxide nanoparticles for cancer hyperthermia and chemotherapy. *Journal of Materials Science* 53: 13826-42 (2018).
 63. P.H. Tsai, M.L. Wang, J.H. Chang, A.A. Yarmishyn, P.N. Nguyen, W. Chen, Y. Chien, T.I. Huo, C.Y. Mou, and S.H. Chiou. Dual delivery of HNF4 α and cisplatin by mesoporous silica nanoparticles inhibits cancer pluripotency and tumorigenicity in hepatoma-derived CD133-expressing stem cells. *ACS Applied Materials & Interfaces* 11: 19808-18 (2019).
 64. R.A. Revia, Z.R. Stephen, and M. Zhang. Theranostic nanoparticles for RNA-based cancer treatment. *Accounts of Chemical research* 52: 1496-506 (2019).
 65. Y.G. Yuan, Q.L. Peng, and S. Gurunathan. Silver nanoparticles enhance the apoptotic potential of gemcitabine in human ovarian cancer cells: combination therapy for effective cancer treatment. *International Journal of Nanomedicine* 12: 6487 (2017).
 66. A. Rostami, and A. Sazgarnia. Gold nanoparticles as cancer theranostic agents. *Nanomedicine Journal* 6: 147-60 (2019).
 67. R. Mrówczyński, A. Jędrzak, K. Szutkowski, B.F. Grześkowiak, E. Coy, R. Markiewicz, T. Jesionowski, and S. Jurga. Cyclodextrin-based magnetic nanoparticles for cancer therapy. *Nanomaterials* 8: 170-79 (2018).
 68. Y. Yin, Q. Hu, C. Xu, Q. Qiao, X. Qin, Q. Song, Y. Peng, Y. Zhao, and Z. Zhang. Co-delivery of doxorubicin and interferon- γ by thermosensitive nanoparticles for cancer immunochemotherapy. *Molecular Pharmaceutics* 15: 4161-72 (2018).
 69. A. Pugazhendhi, T.N. Edison, I. Karuppusamy, and B. Kathirvel. Inorganic nanoparticles: a potential cancer therapy for human welfare. *International Journal of Pharmaceutics* 539: 104-11 (2018).
 70. F. Mottaghitlab, M. Farokhi, Y. Fatahi, F. Atyabi,

- R. Dinarvand. New insights into designing hybrid nanoparticles for lung cancer: Diagnosis and treatment. *Journal of Controlled Release* 295: 250-67 (2019).
71. H.G. Almaghadim, Z. Nourollahzadeh, N.S. Khademi, M.D. Tezerjani, F.Z. Sehrig, N. Estelami, M. Shirvaliloo, R. Sheervalilou, and S. Sargazi. Application of nanoparticles in cancer therapy with an emphasis on cell cycle. *Cell Biology International* 23: 3678-86 (2021).
 72. R. Iyer, T. Nguyen, D. Padanilam, C. Xu, D. Saha, K.T. Nguyen, and Y. Hong. Glutathione-responsive biodegradable polyurethane nanoparticles for lung cancer treatment. *Journal of Controlled Release* 321 :363-71 (2020).
 73. R. Khalifehzadeh, and H. Arami. Biodegradable calcium phosphate nanoparticles for cancer therapy. *Advances in Colloid and Interface Science* 279: 102157 (2020).
 74. M. Sun, D. Peng, H. Hao, J. Hu, D. Wang, K. Wang, J. Liu, X. Guo, Y. Wei, and W. Gao. Thermally triggered in situ assembly of gold nanoparticles for cancer multimodal imaging and photothermal therapy. *ACS Applied Materials & Interfaces* 9: 10453-60 (2017).
 75. V. Krishnan, and S. Mitragotri. Nanoparticles for topical drug delivery: Potential for skin cancer treatment. *Advanced Drug Delivery Reviews* 153: 87-108 (2020).
 76. S. Mondal, P. Manivasagan, S. Bharathiraja, M.M. Santha, V.T. Nguyen, H.H. Kim, S.Y. Nam, K.D. Lee, and J. Oh. Hydroxyapatite coated iron oxide nanoparticles: a promising nanomaterial for magnetic hyperthermia cancer treatment. *Nanomaterials* 7: 426 (2017).
 77. B. Zhou, Q. Wu, M. Wang, A. Hoover, X. Wang, F. Zhou, R.A. Towner, N. Smith, D. Saunders, J. Song, and J. Qu. Immunologically modified MnFe₂O₄ nanoparticles to synergize photothermal therapy and immunotherapy for cancer treatment. *Chemical Engineering Journal* 396: 125239 (2020).
 78. M.G. Le, A. Paquirissamy, D. Gargouri, G. Fadda, F. Testard, C. Aymes-Chodur, E. Jubeli, T. Pourcher, B. Cambien, S. Palacin, and J.P. Renault. Irradiation effects on polymer-grafted gold nanoparticles for cancer therapy. *ACS Applied Bio Materials* 2: 144-54 (2018).
 79. A.D. Pandya, E. Jäger, S.B. Fam, A. Höcherl, A. Jäger, V. Sincari, B. Nyström, P. Štěpánek, T. Skotland, K. Sandvig, and M. Hrubý. Paclitaxel-loaded biodegradable ROS-sensitive nanoparticles for cancer therapy. *International journal of nanomedicine* 14: 6269 (2019).
 80. B. Li, Q. Li, J. Mo, and H. Dai. Drug-loaded polymeric nanoparticles for cancer stem cell targeting. *Frontiers in Pharmacology* 84: 51-59 (2017).
 81. E. Darrigues, Z.A. Nima, W. Majeed, K.B. Vang-Dings, V. Dantuluri, A.R. Biris, V.P. Zharov, R.J. Griffin, and A.S. Biris. Raman spectroscopy using plasmonic and carbon-based nanoparticles for cancer detection, diagnosis, and treatment guidance. Part 1: diagnosis. *Drug Metabolism Reviews* 49: 212-52 (2017).
 82. J. He, C. Li, L. Ding, Y. Huang, X. Yin, J. Zhang, J. Zhang, C. Yao, M. Liang, R.P. Pirraco, and J. Chen. Tumor targeting strategies of smart fluorescent nanoparticles and their applications in cancer diagnosis and treatment. *Advanced Materials* 31: 1902409 (2019).
 83. S.R. Patade, D.D. Andhare, S.B. Somvanshi, S.A. Jadhav, M.V. Khedkar, and K.M. Jadhav. Self-heating evaluation of superparamagnetic MnFe₂O₄ nanoparticles for magnetic fluid hyperthermia application towards cancer treatment. *Ceramics International* 46: 25576-83 (2020).
 84. Z. Liu, L. Xiong, G. Ouyang, L. Ma, S. Sahi, K. Wang, L. Lin, H. Huang, X. Miao, W. Chen, and Y. Wen. Investigation of copper cysteamine nanoparticles as a new type of radiosensitizers for colorectal carcinoma treatment. *Scientific Reports* 7: 112-19 (2017).
 85. G. Kandasamy, A. Sudame, T. Luthra, K. Saini, and D. Mait. Functionalized hydrophilic superparamagnetic iron oxide nanoparticles for magnetic fluid hyperthermia application in liver cancer treatment. *ACS omega* 3: 3991-4005 (2018).
 86. R. Liu, C. Hu, Y. Yang, J. Zhang, H. Gao. Theranostic nanoparticles with tumor-specific enzyme-triggered size reduction and drug release to perform photothermal therapy for breast cancer treatment. *Acta Pharmaceutica Sinica B* 9: 410-20 (2019).
 87. R.D. Mokoena, P.B. George, and H. Abrahamse. Enhancing breast cancer treatment using a combination of cannabidiol and gold nanoparticles for photodynamic therapy. *International journal of molecular sciences* 20: 4771 (2019).
 88. N.K. Pandey, L. Chudal, J. Phan, L. Lin, O. Johnson, M. Xing, J.P. Liu, H. Li, X. Huang, Y. Shu, and W. Chen. A facile method for the synthesis of copper-cysteamine nanoparticles and study of

- ROS production for cancer treatment. *Journal of Materials Chemistry B* 7: 6630-42 (2019).
89. A.Y. Elmaboud, K.S. Mekheimer, and T.G. Emam. Numerical examination of gold nanoparticles as a drug carrier on peristaltic blood flow through physiological vessels: cancer therapy treatment. *BioNanoScience* 9: 952-65 (2019).
90. H. Abrahamse, C.A. Kruger, S. Kadanyo, and A. Mishra. Nanoparticles for advanced photodynamic therapy of cancer. *Photomedicine and laser surgery* 35: 581-8 (2017).
91. A. Ashkbar, F. Rezaei, F. Attari, and S. Ashkevarian. Treatment of breast cancer in vivo by dual photodynamic and photothermal approaches with the aid of curcumin photosensitizer and magnetic nanoparticles. *Scientific Reports* 10: 1-2 (2020).
92. S. Gulla, D. Lomada, V.V. Srikanth, M.V. Shankar, K.R. Reddy, S. Soni, and M.C. Reddy. Recent advances in nanoparticles-based strategies for cancer therapeutics and antibacterial applications. *Methods in Microbiology* 46 :255-93 (2019).
93. V. Ivošev, G.J. Sánchez, L. Stefancikova, A.D. Haidar, C.R. Vargas, X. Yang, R. Bazzi, E. Porcel, S. Roux, and S. Lacombe. Uptake and excretion dynamics of gold nanoparticles in cancer cells and fibroblasts. *Nanotechnology* 31: 135102 (2020).
94. R. Li, Y. He, S. Zhang, J. Qin, and J. Wang. Cell membrane-based nanoparticles: a new biomimetic platform for tumor diagnosis and treatment. *Acta Pharmaceutica Sinica B* 8: 14-22 (2018).
95. C. Xu, F. Haque, D.L. Jasinski, D.W. Binzel, D. Shu, and P. Guo. Favorable biodistribution, specific targeting and conditional endosomal escape of RNA nanoparticles in cancer therapy. *Cancer Letters* 41: 357-70 (2018).
96. N. Sahakyan, A. Haddad, S. Richardson, V. Forcha-Etieundem, L. Christopher, H. Alharbi, and R. Campbell. Personalized nanoparticles for cancer therapy: a call for greater precision. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents* 17(8):1033-9 (2017).
97. A. Jurj, C. Braicu, L.A. Pop, C. Tomuleasa, C.D. Gherman, and I. Berindan-Neagoe. The new era of nanotechnology, an alternative to change cancer treatment. *Drug Design, Development and Therapy* 11: 2871 (2017).
98. A. Gholami, S.M. Mousavi, S.A. Hashemi, Y. Ghasemi, W.H. Chiang, and N. Parvin. Current trends in chemical modifications of magnetic nanoparticles for targeted drug delivery in cancer chemotherapy. *Drug Metabolism Reviews* 52: 205-24 (2020).
99. E. Spyratou, M. Makropoulou, E.P. Efstathopoulos, A.G. Georgakilas, and L. Sihver. Recent advances in cancer therapy based on dual mode gold nanoparticles. *Cancers* 9: 173-79 (2017).
100. D. Maity, and G. Kandasamy. Superparamagnetic Nanoparticles for Cancer Hyperthermia Treatment. *In Nanotechnology Characterization Tools for Tissue Engineering and Medical. Springer, Berlin, Heidelberg, p. 299-332 (2019).*
101. T. Li, S. Shi, S. Goel, X. Shen, X. Xie, Z. Chen, H. Zhang, S. Li, X. Qin, H. Yang, and C. Wu. Recent advancements in mesoporous silica nanoparticles towards therapeutic applications for cancer. *Acta Biomaterialia* 89: 1-3 (2019).
102. M.J. Gorbet, and A. Ranjan. Cancer immunotherapy with immunoadjuvants, nanoparticles, and checkpoint inhibitors: Recent progress and challenges in treatment and tracking response to immunotherapy. *Pharmacology & Therapeutics* 207: 107456 (2020).
103. K. Zabielska-Koczywaś, and R. Lechowski. The use of liposomes and nanoparticles as drug delivery systems to improve cancer treatment in dogs and cats. *Molecules* 22: 2167 (2017).
104. A. Dadwal, A. Baldi, and R.K. Narang. Nanoparticles as carriers for drug delivery in cancer. *Artificial Cells, Nanomedicine, and Biotechnology* 46: 295-305 (2018).
105. B. Wu, S.T. Lu, L.J. Zhang, R.X. Zhuo, H.B. Xu, and S.W. Huang. Codelivery of doxorubicin and triptolide with reduction-sensitive lipid-polymer hybrid nanoparticles for in vitro and in vivo synergistic cancer treatment. *International Journal of Nanomedicine* 12: 1853 (2017).
106. Y. Liu, L. Qiao, S. Zhang, G. Wan, B. Chen, P. Zhou, N. Zhang, and Y. Wang. Dual pH-responsive multifunctional nanoparticles for targeted treatment of breast cancer by combining immunotherapy and chemotherapy. *Acta Biomaterialia* 6: 310-24 (2018).
107. G. Raja, Y.K. Jang, J.S. Suh, H.S. Kim, S.H. Ahn, and T.J. Kim. Microcellular environmental regulation of silver nanoparticles in cancer therapy: a critical review. *Cancers* 12: 664 (2020).
108. J. Guo, and L. Huang. Membrane-core nanoparticles for cancer nanomedicine. *Advanced Drug Delivery Reviews* 156: 23-39 (2020).
109. W. Yu, X. He, Z. Yang, X. Yang, W. Xiao, R. Liu, R. Xie, L. Qin, and H. Gao. Sequentially responsive biomimetic nanoparticles with optimal size in

- combination with checkpoint blockade for cascade synergetic treatment of breast cancer and lung metastasis. *Biomaterials* 217: 119309 (2019).
110. Y. Xia, G. Tang, M. Guo, T. Xu, H. Chen, Z. Lin, Y. Li, Y. Chen, B. Zhu, H. Liu, and J. Cao. Silencing KLK12 expression via RGDfC-decorated selenium nanoparticles for the treatment of colorectal cancer in vitro and in vivo. *Materials Science and Engineering: C* 110: 110594 (2020).
111. Z. Zhang, Q. Wang, Q. Liu, Y. Zheng, C. Zheng, K. Yi, Y. Zhao, Y. Gu, Y. Wang, and C. Wang, X. Zhao. Dual-Locking nanoparticles disrupt the PD-1/PD-L1 pathway for efficient cancer immunotherapy. *Advanced Materials* 31: 1905751 (2019).
112. A.T. Khalil, M. Ovais, J. Iqbal, A. Ali, M. Ayaz, M. Abbas, I. Ahmad, and H.P. Devkota. Microbes-mediated synthesis strategies of metal nanoparticles and their potential role in cancer therapeutics. *In Seminars in Cancer Biology*, Vol 69. Elsevier Academic Press, USA, p.145-59 (2021).
113. Y. Wang, R. Cai, and C. Chen. The nano-bio interactions of nanomedicines: Understanding the biochemical driving forces and redox reactions. *Accounts of Chemical Research* 52: 1507-18 (2019).
114. Y. Yoshioka, K. Higashisaka, S.I. Tsunoda, and Y. Tsutsumi. The absorption, distribution, metabolism, and excretion profile of nanoparticles. In: *Engineered Cell Manipulation for Biomedical Application*, Springer, Tokyo, p. 259-271 (2014).