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Review Article;

Nanoparticles Technology in Medicine, As A Diagnostic Tool, and Therapeutic Applications for Many Chronic and Genetic Diseases

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Abstract

Nanoparticle is an artificial cell-like particle (antigen-presenting artificial cell that can be tuned to target a specific disease or infections). The outer surface of each particle is covered with universal adaptor molecules having attachment points for antigens, specific molecules on specific cells, and fight off the targeted disease.
Inside of each particle, there is either cytokines, cytotoxic drugs, antimicrobial drugs, genetic material, iron, gold, herbs, and others; each for different curative purpose, yet all of them act locally with high specificity to avoid devastating side effects of the contents if given systemically or to target certain tissue for curing diseases due to genetic deletions, or as a vaccine. Different nanoparticles differ in size, shape, contents, material of the outer shell, and purpose (i.e. for diagnosis of cancer, fighting that cancer, dealing locally with autoimmune diseases, treating a disease with genetic deletion mutations, fighting an infection, monitoring, and control of biological systems.

Keywords Nanoparticles, diagnostic tool, therapeutic applications

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Introduction

Nanoparticles (NPs) are the most commonly used nanotechnology structures, consisting of two or more dimensions on the nanometer scale, according to the American Society for Testing and Materials (ASTM). Compared to their corresponding bulk materials, they have different enhanced chemical and physical properties, such as a high surface area-to-volume ratio and a specific quantum size effect due to their unique electronic structures [(1)]. The properties of NPs, in addition to their composition, depend on their size and shape [(2)]. To reduce aggregation and obtain monodispersed NPs, it is necessary to control their size and shape by facilitating their cell internalization [(3)].

Types of nanoparticles

NPs are classified into three main groups according to their chemical compounds: organic nanoparticles (liposomes, polymers), nonorganic nanoparticles (metals, metal oxides, ceramics, and quantity dots), and carbon-based nanoparticles [(4)]; different types' shapes shown in figure (1).

Liposome Nanoparticles

These are spherical vesicles containing an aqueous material with an outer lipid bilayer. The materials used to prepare these vesicles are amphiphilic, close to biological membranes,

in order to improve the efficacy and safety of different drugs [5]. Liposomes are used primarily for the delivery of chemotherapeutic drugs in cancer treatment [6].

Polymeric Nanoparticles

Most are considered to be biodegradable and biocompatible, and are the most frequently used NPs in drug delivery systems [7-9]. These are either made from natural polymers like chitosan or synthetic polymers like poly-lactides (PLA), poly-methyl methacrylate (PMMA), or poly-ethylene glycol (PEG) [7]. To improve the efficiency of drug loading and prolong the release of drugs, consideration must be given to the existence of polymer-drug interactions, the form of polymer and its physical-chemical properties [10].

Metallic Nanoparticles

They are either valuable metals (gold, silver) or magnetic metals (doped ferrites of iron oxide, cobalt and manganese). Metallic nanoparticles such as gold (Au) have unique electronic and optical characteristics and are non-toxic and biocompatible with other biomolecules due to their negative charges [11-12]. A surface of gold has the ability to conjugate ligands such as proteins, oligo nucleotides, and antibodies with functional groups such as phosphins, thiols, mercaptans, and amines [13]. Gold nano-conjugates coupled with strongly enhanced localized surfaces (gold plasmon resonance nanoparticles) can be used for the treatment of various diseases in imaging techniques [14].

Metal Oxide Nanoparticles

They have catalytic, antioxidant, chemical, optical, and biocompatibility activities that make them suitable for many biomedical applications. The most widely used types are ironoxide (Fe_3O_4), Titania (TiO_2), Zirconia (ZrO_2), and later Ceria (CeO_2) [15]. Titania nanoparticles, like a biosensor [16], are assembled into restorative inserts and used in critical applications. Ceria nanoparticles are able to switch between oxidation states, especially cerium (IV) and cerium (III) oxidation states, due to the proximity of multiple surrenders on their surface, enhancing their application in oxidation-related stress-related diseases [17]. Porous silica (SiO_2) has unique properties, including large surface area, pore volume, controllable particle-size, and good bio-compatibility make them very useful in the delivery of drugs [18].

Ceramic Nanoparticles

These are non-organic compounds used as drug carriers with porous properties. They can carry molecules like proteins, enzymes, or drugs without compromising swelling or porosity due to pH or temperature effects [19]. Silica and aluminum are the most commonly used materials of ceramic nanoparticles. But it is also possible to use a mixture of metallic and non-metallic materials [20]. For example, CeO_2-capped mesoporous silica nanoparticles, "MSN," were established as carriers for the delivery of therapy by releasing β-cyclo-dextrin into lung cancer cells [21].

Most types of ceramic materials are available with multiple applications, such as clay minerals, cement, and glass. Bio-ceramics, which have good biocompatibility, hydrophilicity, osteoconductivity, biodegradability and reabsorbability, are primarily used for bone, teeth and other medical applications, Calcium phosphate (CaP), calcium sulphate and carbonate, tri-calcium phosphate (TCP), hydroxyl-apatite (HAP), TCP + HAP, bio-active glasses, bio-active glass ceramics, titanium-based ceramics, alumina ceramics, zirconia ceramics, and ceramic polymer composites are the most commonly used ceramic nano-bio-materials. In addition to other bio-medical uses in the human body, most of them were used in nano-medicine, orthopedics, bone regeneration, dentistry, and tissue development [22].

Quantum Dots

Quantum dots (QDs) are made of a semi-conductor core (such as cadmium-selenium

(CdSe), cadmium-tellurium (CdTe), indium-phosphate (InP), or indium-arsenate (InAs)), over-coated with an outer layer (such as zinc-sulfide (ZnS)) to improve optical and physical properties and to prevent leakage of toxic heavy metals [23]. To be used in bio-imaging and bio-sensing strategies, they need to be combined with biomolecules such as proteins, peptides, or oligo-nucleotides that enable them to bind to specific sites [24].

Carbon-Based Nanoparticles

They are considered of interest in biomedical applications because of their high electrical conductivity and excellent mechanical power, but they are not bio-degradable and require surface modifications as they have a strong tendency to form large aggregates [25-27]. Either they are fullerenes or nanotubes. Fullerenes are novel allotropes of carbon with a polygonal structure consisting solely of 60-carbon atoms [28]. Carbon nanotubes are generally made from the deposition of chemical vapor graphite. There are two types of carbon nanotubes: single-walled (SWCNT) and multi-walled (MWCNT), the latter with strong anti-microbial properties [29]. Carbon nanotubes (CNTs) have amazing optical properties, which is why they are used as agents for labeling and imaging [28]. In fact, CNTs have optical transitions (transition of their electrons from orbit to another lead to transmission of energy in form of light in the near infrared (NIR) region), making them useful in biological tissue and cells, since NIR has lower excitation scattering and greater depth of penetration [30].

Therefore, in the NIR field, fluorescence shows much lower auto-fluorescence than ultraviolet or visible ranges. Therefore, for NIR fluorescence microscopy and optical coherence tomography, CNTs are efficient imaging agents with higher resolution and high tissue depth. That's why Cherukuri et al. controlled CNTs successfully in phagocytic cells and mice (intravenously administered) using NIR fluorescence [31].

Medical application of nanoparticles

Generation of oxidative stress

An increase in the levels of reactive oxygen and nitrogen species (RONS) derived from physiological cellular oxidation is characterized by oxidative stress. The antioxidant system fights the excess in RONS under normal conditions in order to maintain the organism's equilibrium. The imbalance that promotes oxidative stress is usually associated with several artery dysfunction-related pathological conditions such as hypertension, atherosclerosis, diabetes mellitus, or acute coronary syndrome [32]. NADPH-oxidase (Nox) [33], uncoupled endothelial enzyme NO-synthase (eNOS) [34], xanthine-oxidase (XO) [35] and enzymes in the respiratory chain [36]. Sources of reactive oxygen species (ROS) within the vascular wall are known. Under physiological conditions, Nox overwhelms, as Nox is associated with an increase in xanthine-oxidase activity, eNOS uncoupling and mitochondrial ROS production [36]. It should be noted that angiotensin II (AT II) is associated with vascular ROS production by increasing the expression of Nox [37] and XO [38] and reducing thioredoxin (antioxidant system) [39]. Blood flow exerts a frictional force on endothelial vascular cells, namely hemodynamic shear stress, which ultimately leads to ROS release [40]. Shear stress is released by eNOS from L-arginine by endothelial nitric oxide (NO). NO is a strong vasodilator [41] that prevents platelet adhesion and aggregation, leukocyte chemotaxis [42], vascular smooth muscle proliferation [43], anti-atherogenic effects [44], and increases the growth factor of the endothelial vascular system. Also included in the vascular wall are anti-oxidant processes such as superoxide dismutase (SOD), catalase, glutathione peroxidases, thioredoxin system, and peroxideroxins.

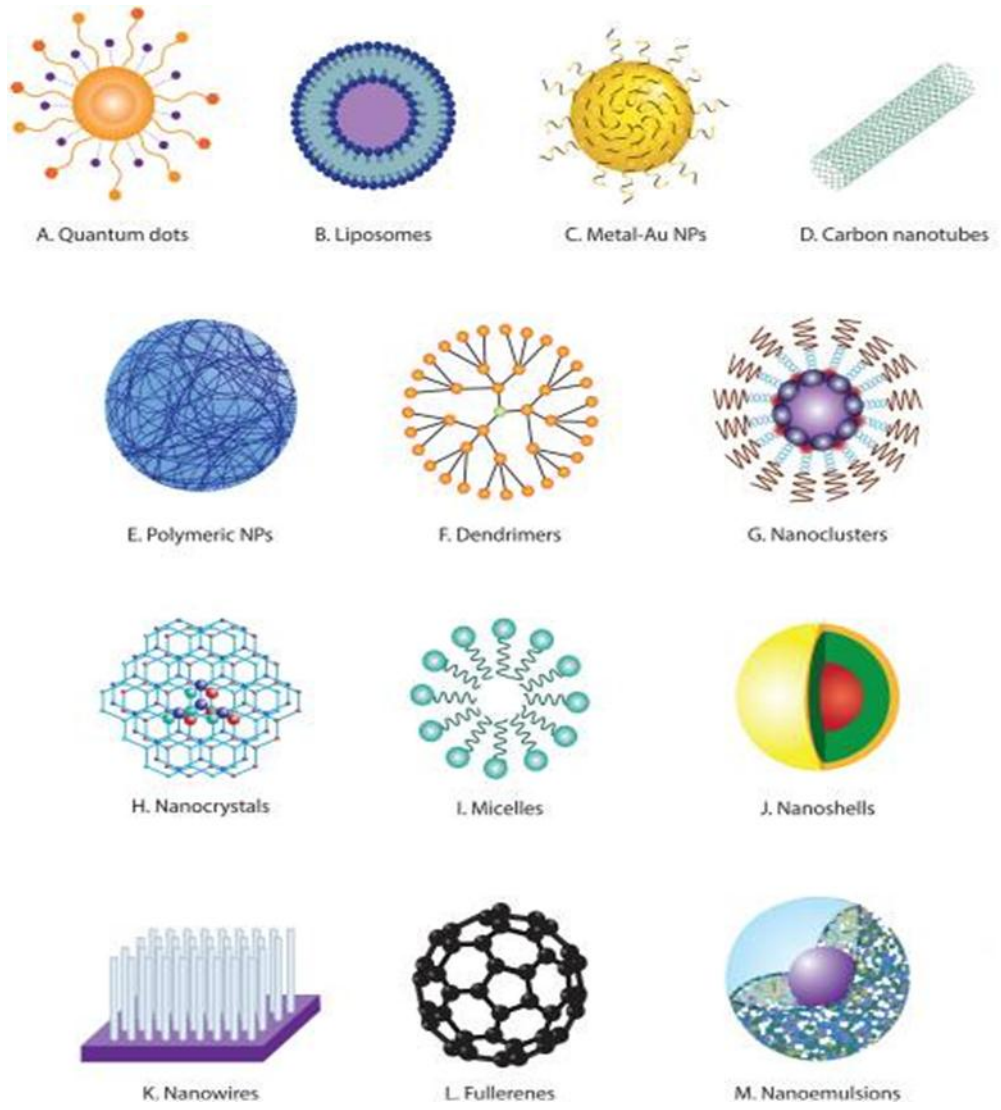

Figure 1. Shapes of different types of nanoparticle. From Bench to Bedside [45].

Nanoparticles for targeting vascular oxidative stress

Uncoupled endothelial NO (eNO) nanoparticles

An interesting recent study [46] developed a hybrid molecule consisting of a copolymer (poly lactic-co-glycolic acid) (PLGA) nanoparticle containing SA-2 and having functionalities both anti-oxidant and NO donor and supplying a sufficiently therapeutic level of NO to cure peripheral arterial disease.

Angiotensin II converting enzyme (ACE) inhibitor nanoparticle

Both Ile-Pro-Pro (IPP) or Val-Pro-Pro (VPP) are the best anti-hypertensive peptides obtained (inhibiting angiotensin-converting enzyme (ACE)). Nevertheless, due to their gastrointestinal deterioration, they are impaired by their poor oral bio-availability. The use of nanoparticles to encapsulate these peptides could therefore prevent their proteolysis and increase their systemic absorption. A study by Yu et al. [47] PLGA nanoparticles (PLGANPs) tested in a model of essential hypertensive rats as an oral delivery system for anti-hypertensive small peptides.

The final conclusion was that PLGANP was a hypertension treatment that was potentially effective.

Nanoparticle with natural anti-oxidants mimetic activity

Ceria (CeO_2) nanoparticles are likely to restore vasodilatation depending on the endothelial. Minarchick et al. studied the impact of nanoceria on vascular reactivity in hypertensive rats and concluded that the microvascular dysfunction and oxidative stress associated with hypertension were reduced by these nanoceria [(48)]. Nano-ceria contain a high O_2 vacancy density in their structure, allowing them to store O_2 during the lean process and return O_2 to metal particles during the oxygen-rich phase. This capacity is referred to as ceria's O2 storage capacity [(17)]. Several experiments have shown that nanoceria is in vitro SOD mimetic [(49)] and has antioxidant and anti-inflammatory activity in the myocardium murine [(50)]. CeO2NPs can therefore have cardiovascular-protective effects that make them endothelial inflammatory controllers. Hence, beneficial effects on oxidative stress in cardiovascular diseases can be achieved by inducing nanoparticles to overproduce H_2O_2. Poly-oxalate has been shown to have anti-oxidative and anti-inflammatory properties-producing nanoparticles, since they have been able to limit the impact of H_2O_2 on ischemia / reperfusion injury [(51)]. Researchers have developed nanoparticles carrying SOD1 that have been shown to enhance cardiac function after myocardial infarction [(52-53)]. Some nano-materials, such as nano-ceria, have mimetic multi-enzyme activities because they can imitate SOD, catalase, oxidase, phosphatase, and peroxidase. For this reason, nano-ceria can scavenge radicals of hydroxyl and nitric oxide [(54)]. In this sense, cerium nanoparticles have great potential to cure oxidative stress-related diseases, since most nano-materials only scavenge one form of RONS.

Early detection of cancer utilizing nanotechnology

Because tumor cells grow faster than the normal ones, so neovascularization occurs to fulfill their requirements for nourishment and oxygen, those new blood vessels are yet abnormal, i.e. are leaky, and lacking effective drainage as shown in figure (2). Therefore, scientists could make use of this phenomenon to settle these nanoparticles in cancerous cells, in addition to that, nanoparticles can reach cancerous cells even if they have metastasized - or spread to other organs in the body.

In the fight against cancer, half of the battle is won based on its early detection. Nanotechnology provides new molecular contrast agents and materials to enable earlier and more accurate initial diagnosis.

For cancer, nanodevices are being investigated for the capture of blood borne biomarkers, including cancer-associated proteins circulating tumor cells, circulating tumor DNA, and tumor-shed exosomes. Nano-enabled sensors are capable of high sensitivity, specificity and multiplexed measurements. Next generation devices couple capture with genetic analysis to further elucidate a patient's cancer and potential treatments and disease course.

Nanotechnology based imaging contrast agents being developed and translated today, offer the ability to specifically target and greatly enhance detection of tumor in vivo by way of conventional scanning devices, such as magnetic resonance imaging (MRI), positron Emission tomography (PET), and computed tomography (CT). Moreover, current nanoscale imaging platforms are enabling novel imaging modalities not traditional utilized for clinical cancer treatment and diagnosis, for example photoacoustic tomography (PAT), Raman spectroscopic imaging and multimodal imaging (i.e., contrast agents specific to several imaging modalities simultaneously). Nanotechnology enables all of these platforms by way of its ability to carry multiple components simultaneously (e.g., cancer cell-specific targeting agents or traditional imaging contrast

agents) and nanoscale materials that are themselves the contrast agents of which enable greatly enhanced signal [55].

Researchers at Stanford University and Memorial Sloan Kettering Cancer Center developed multimodal nanoparticles capable of delineating the margins of brain tumors both preoperatively and intra-operatively. These MRI-PAT-Raman nanoparticles are able to be used both to track tumor growth and surgical staging, by way of MRI, but also in the same particle be used during surgical resection of brain tumor to give the surgeon 'eyes' down to the single cancer cell level, increasing the potential tumor specific tissue removal [56].

For metastatic melanoma, researchers at Memorial Sloan Kettering Cancer Center (MSKCC) and Cornell University have developed silica-hybrid (SiO_2) nanoparticles ('C-dots') that deliver both PET and optical imaging contrast in the same platform. These nanoparticles are actively targeted to the cancer with fouropore, cyanine 5.5 (Cy5.5) and surrounded by polyethylene glycol (PEG) chains attached to cyclo-(Arg-Gly-Asp-Tyr) cRGDY peptides that target this specific tumor type and have already made it successfully through initial clinical trials [56].

Similarly, gold nanoparticles are being used to enhance light scattering for endoscopic techniques that can be used during colonoscopies. One really powerful potential that has always been envisioned for nanotechnology in cancer has been the potential to simultaneously image and deliver therapy in vivo and several groups have been pushing forward these 'theranostic' nanoscale platforms. One group at Emory University has been developing one of these for pancreatic cancers, which are traditionally harder to deliver therapeutics to. Their platform for pancreatic cancer can break through the fibrotic stromal tissue of which these tumors are protected by in the pancreas. After traversing through this barrier, they are composed of magnetic iron cores which allow MRI contrast for diagnosis and deliver small-molecule drugs directly to cancer cells to treat [55].

Finally, nanotechnology is enabling the visualization of molecular markers that identify specific stages and cancer cell death induced by therapy, allowing doctors to see cells and molecules undetectable through conventional imaging. A group at Stanford has developed the Target-Enabled in Situ Ligand Assembly (TESLA) nanoparticle system. This is based off nanoparticles which form directly in the body after IV-injection of molecular precursors. The precursors contain specific sequences of atoms, which can only form larger nanoparticles after being cleaved by enzymes produced by cancer cells during apoptosis (i.e., cell death) and carry various image contrast agents to monitor (PET, MRI, etc.) local tumor response to therapies. Being able to track cancer cell death in vivo and at the molecular level is extremely important for delivering effective dosing regimens and/or precisely administering novel therapies or combinations [55] as shown in figure (3).

Nanotechnology for treatment of cancer

Magnetic nanoparticles (MNPs) for treatment of cancer

These are able to convert electromagnetic energy into heat [57]. Therefore, the most popular application for MNPs is most likely the destruction of tumor cells by heating them to their apoptosis threshold [58]. A study illustrated the successful use of spin-vortex, disk-shaped permalloy magnetic particles in a low-frequency, rotating magnetic field for the in vitro and in vivo glioma destruction [59].

Nanoparticles as photosensitizing drugs treatment (PDT) for cancer

Is an externally-active and minimally invasive technique for treatment of cancer. The process of PDT involves the systemic or local use of photo-sensitizing drugs, called photo-sensitizers (PSs), then a photo-excitation of the PSs in the tissue using light of the appropriate wave-length and power [60]. In oxygen presence, the PS is excited from the ground

state to the excited state after activation with light of an appropriate wave-length, and an electron is transferred to nearby tissue oxygen, producing oxygen free radicals or excited singlet oxygen i.e. ROS [61-63], leading to cell damage, and eventually to cancer tissue damage. To enhance the effect of PSs, building a targeted drug delivery system with MNPs has become of interest. For instance, a study by Park et al. [64] synthesized multifunctional cobalt ferrite ($CoFe_2O_4$) NPs ($CoFe_2O_4$-hematoporphyrins (HPs)-FAs) functionalized by coating them with HP for introducing photo-functionality and by conjugating with FA for targeting cancer cells. Pyropheophorbide-a (PPA) as a novel chlorin PS was prepared for PDT. PPA-coated multifunctional magneto-fluorescent NPs, Fe_3O_4, SiO_2, CS, PPA (MFCSPPA) were designed. The experiments demonstrated that MFCSPPA had strong photodynamic therapy activity and low dark toxicity [65].

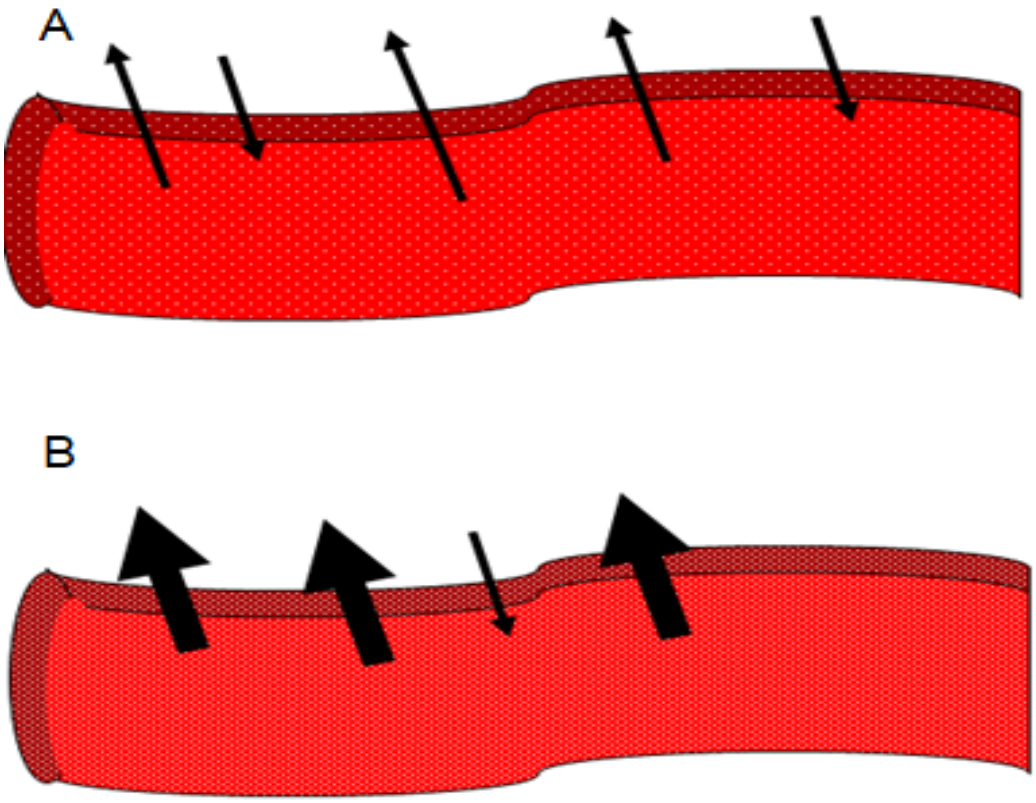

Figure 2. A) Normal blood vessels have selective capacity for passage of molecules, and with effective drainage, (thickness of the arrows is indicative to the size of molecules getting in or out of the vessel, while number of the arrows is indicative to the number of molecules getting in or out of the vessel). B) Blood vessels of cancerous tissues, don't have selective capacity for molecular passage in or out of the vessel, and are leaky, with defective draining capacity, so larger molecules can pass out of them to cancerous tissues, and reside there as they can't drain them back effectively. Credit: National Cancer Institute [54]

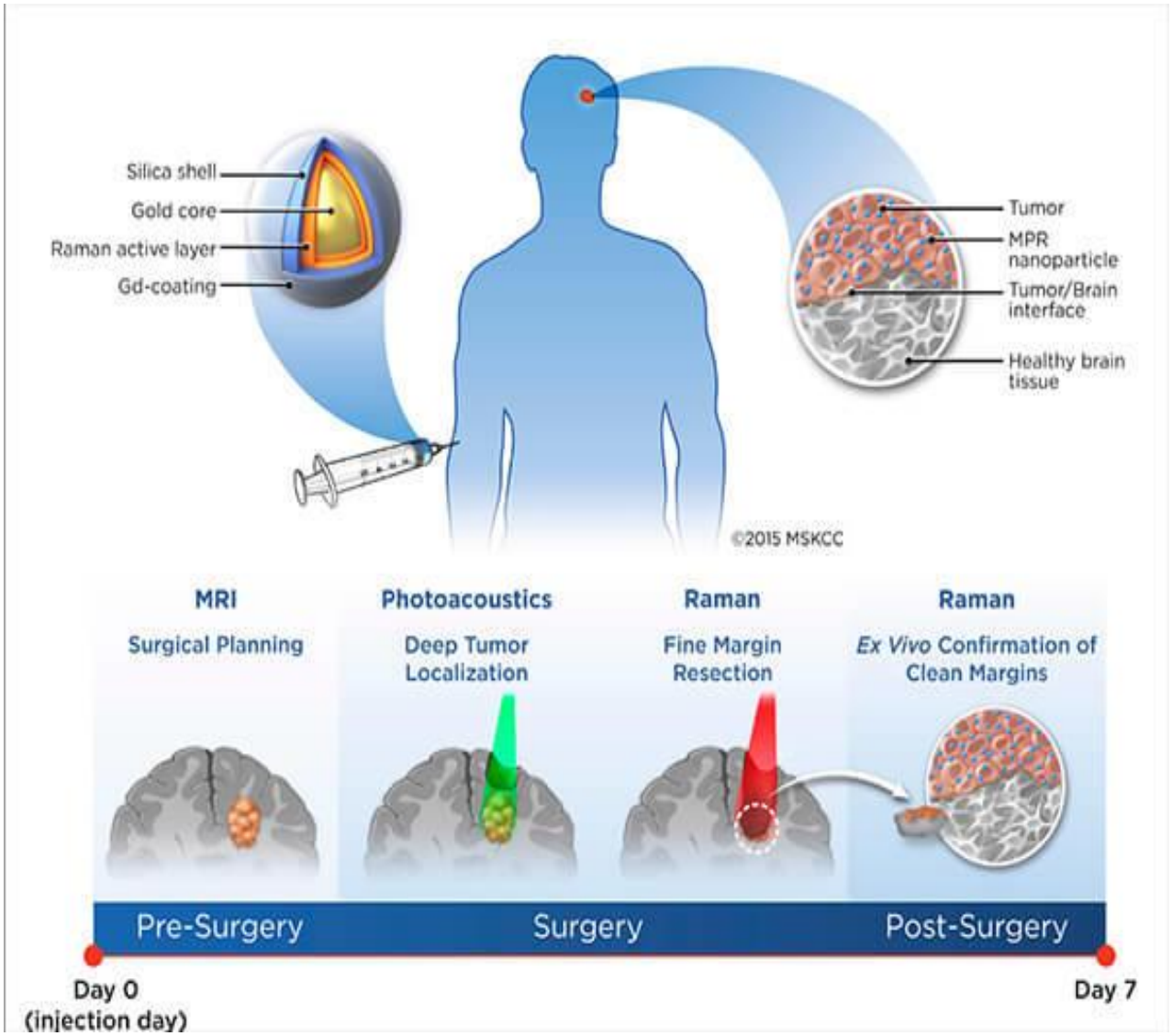

Figure 3. Principle of a triple-modality MRI-photoacoustic-Raman nanoparticle for clinical use. The nanoparticle is injected intravenously. In contrast to small molecule contrast agents that wash out of the tumor quickly, the nanoparticles are stably internalized within the brain tumor cells, allowing the whole spectrum from preoperative MRI for surgical planning to intraoperative imaging to be performed with a single injection. T1-weighted MRI depicts the outline of the tumor due to the T1-shortening effect of the gadolinium. During the surgery, photoacoustic imaging with its greater depth penetration and 3D imaging capabilities can be used to guide the gross resection steps, while Raman imaging can guide the resection of the microscopic tumor at the resection margins. Raman would be used for rapid conformation of clean margins in the operating room instead of the time-consuming analysis of frozen sections

Nanoparticle as photo-thermal treatment (PTT) for cancer

Despite that near infra-red (NIR) is with low toxicity on skin and deep tissue penetration, yet it may directly kill cancer cells by PTT, which has become a controlled treatment strategy [66]. PTT using photo-thermal agents in combination with NIR has also gained increasing attention for cancer treatment [67]. An example of this is engineering phosphopeptide-decorated MNPs as efficient photo-thermal factor for solid tumor treatment [68]. Compared with individual magnetic Fe_3O_4 NPs, clustered Fe_3O_4 NPs may result in a marked increase in NIR absorption [69]. Upon NIR irradiation at 808 nm, clustered Fe_3O_4 NPs

inducing higher temperatures were more cytotoxic against A549 cells [69]. In the majority of cases, PTT and MRI are carried out in combination [70,71]. However, a study indicated that, compared with their large counterparts, small Fe_3O_4 NPs exhibited greater cellular internalization, thus enabling a higher PTA efficacy in vitro [72]. In addition, 120 nm may be the optimal diameter of Fe_3O_4 NPs for MRI and PAT in vitro [72]. Therefore, the size of MNPs may be an important factor for PTT.

Nanoparticles as carrier for lethal therapies for cancer

Anti-cancer drugs (chemotherapy, hormone and biological therapy) are the choice for metastatic cancers that are currently used. Chemotherapy works by separating rapidly growing cells, a characteristic of cancer cells, but it also affects normal cells with rapid proliferation rates, sadly, like hair follicle cells, bone marrow and gastrointestinal tract cells, this leads to common chemotherapy side effects. Because of these side effects as well as the development of multidrug resistance, there has been a need to find new effective targeted therapies based on changes in tumor cells' molecular biology. Targeted cancer drugs approved by the Food and Drug Administration (FDA) in recent years, block biological transduction pathways and/or specific tumor proteins to induce cancer cells apoptosis in addition to immune system stimulation, or specifically deliver chemotherapeutic drugs to cancer cells, reducing unwanted side effects. Targeted therapies can be performed directly by modifying specific cell signals by using monoclonal antibodies or small molecular inhibitors to over-expressed receptors on the surface of tumor cells [73].

Nanoparticles as carriers for chemotherapeutic drugs

To deliver the anti-cancer drugs directly to bone tissue, nanoparticles were developed attracted to calcium, which concentrates in high levels in bones. This done by covering the surface of the nanoparticles with a substance known as alendronate, which binds to calcium. Then these spheres engineered to carry an anti-cancer drug called bortezomib. When these tiny particles were tested in mice with myeloma, it was found that they could find and target the cancer cells present in the bone. The treatment slowed the growth of tumors while also strengthening the bone in these mice. There by these engineered targeted therapies manipulate the tumor cells in the bone and surrounding microenvironment to effectively prevent cancer from spreading in bone [74].

Bisphosphonates (BPs) are commonly used to treat bone disease due to their high bone tissue affinity. Makes BPs useful for bone tissue delivery of NPs. BPs' traditional applications are promoting the prevention of fracture, healing, or osteoporosis, and Paget's bone disorder disease. The emerging evidence, however, indicate that BPs also have anti-tumor activity and can be used for treatment with cancer bone metastases. Preclinical studies have shown that second-generation BPs (zoledronic acid) can inhibit angiogenesis, invasion and adherence of malignant cells, and overall progression of cancer, indicating their ability to block bone metastasis growth. Serum levels of the vascular endothelial growth factor (VEGF), a critical factor for angiogenesis, have been significantly reduced in patients receiving zoledronic acid in clinical studies, indicating that zoledronic acid may be capable of inhibiting angiogenesis. BPs of the third generation (risedronate (RIS)) have recently been available and are assumed to be more effective with less toxicity [74].

Nanoparticles as carriers for lethal gene therapy for cancer treatment

1. (Rexin-G)

Rexin-G is a nanoparticle designed to deliver a fatal gene directly into tumor cells, this trial, designed to test the safety of the drug primarily, the agent was well-tolerated, without treatment-related side effects. There were only 9 patients enrolled in this study, but what the authors found interesting was that all 9 patients had either stable disease or partial response (more responses with the higher dose tested) of their tumors. Rexin-G is now being evaluated in larger phase II studies in pancreatic cancers, and sarcomas [75].

2. The "Trojan Horse" therapy

In this trial a package of RNA is delivered into cancer cells, this RNA signal is called a "silencing RNA", or siRNA. This siRNA signals a cancer cell to stop production of proteins that cause chemotherapy resistance. A second mini-cell is then injected which delivers chemotherapy drugs into the cancer cells. So far, this Trojan Horse approach has the potential to treat a large number of different types of cancer, and particularly some of those with very poor survival rates like pancreatic cancers [76].

Nanotechnology for diagnosis, treatment of autoimmune diseases

Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens. The diagnosis of ADs depends on the identification of disease-associated clinical signs and symptoms as well as the detection of autoantibodies.

A. Diagnostic techniques

ADs can be organ specific e.g., type I diabetes mellitus (T1DM) or systemic (e.g., systemic lupus erythematosus (SLE)). Therefore, an important group of targets are disease-related membrane antigens. These antigens can act as biomarkers and could help define the phenotype of the disease and sometimes identify therapeutic targets.

Gold NPs, one of the NPs used in this respect, have the potential biocompatibility, relatively low short-term toxicity, high absorption coefficient and physical density compared with other metal NPs [77]. Other important NPs are iron NPs, which have been used for more than two decades as contrast agents for MRI. These particles can be organized according to their hydrodynamic diameter into several categories: standard superparamagnetic iron oxide particles (SPIOs) (50 to 180 nm), ultrasmall superparamagnetic iron oxide particles (USPIOs) (10 to 50 nm), and very small superparamagnetic iron oxide particles (VSPIOs) (< 10 nm) [78]. Tourdias et al. reported that combination of gadolinium and USPIO in patients with multiple sclerosis (MS) can help identify additional active lesions compared with the current standard, the gadolinium-only approach, even in progressive forms of MS [79].

This method uses iron-oxide NPs that are targeted to sites of complement activation with a recombinant protein that contains the C3d-binding region of complement receptor 2. Iron-oxide NPs darken (negatively enhance) images obtained by T2-weighted MRI [80]. Due to its unique ability to directly image myocardial necrosis, fibrosis and edema, cardiac magnetic resonance (CMR) is now considered the primary tool for noninvasive assessment of patients with suspected myocarditis. Moon et al. has described a CMR imaging with magneto-fluorescent NP that allows visualization of myocardial inflammation cellular infiltrates and distinction of the extent of the inflammation compared with conventional CMR in a preclinical model of experimental autoimmune myocarditis in rats [81].

Recently, Gaglia et al. [82] developed a noninvasive method to visualize T1DM at the target organ (pancreas) in patients with active insulinitis; using magnetic resonance imaging of magnetic NPs. The authors visualized islet inflammation, manifested by microvascular changes and monocyte/macrophage recruitment and activation. PET, single-photon emission computed tomography (SPECT) technologies in combination with radiolabeled immunoglobulin derived targeting probes could be used for tracking inflammatory cells in vivo. Dearling et al. [83] described the use of radio-labeling of an anti-β7 integrin antibody with the positron-emitting radionuclide ^{64}Cu in detecting acute colitis in experimental murine model with the aid of micro-PET. It was found that higher uptake of the radio-labeled antibody in the intestine of mice with acute colitis compared with controls observed by using both micro-PET imaging and ex-vivo tissue assay, suggesting that the β7 integrin monomer could be used as the target for colitis imaging, and that the radio-labeled antibody targeting a subset of lymphocytes, can serve as a specific imaging tool.

Nanobodies are the smallest antigen-binding antibody-fragments, that shows fast and

specific targeting in vivo and have low immunogenicity due to their large sequence identity with human VH genes of the VH III family [84]. Recently, Put et al. [85] reported the use of SPECT/micro-CT imaging with 99mTc-labeled Nanobodies directed against the macrophage mannose receptor for monitoring and quantifying joint inflammation in collagen-induced arthritis, a mouse model for rheumatoid arthritis (RA). The authors showed that macrophage mannose receptor is expressed on macrophages in vitro and in vivo in synovial fluid of inflamed paws, whereas expression is relatively low in other tissues.

B. Therapeutic techniques

Current therapeutic strategies against ADs may be divided into three main classes: (1) sign and symptom amelioration therapies, i.e., non-steroidal anti-inflammatory drugs (NSAIDs); (2) medications to change the normal nature of the illness, including disease-modifying anti-rheumatic drugs (DMARDs) for biological and non-biological diseases; and (3) therapies directed to the complications resulting from the disease-associated organ damage [86].

Steenblock et al. [87] mimicked physiological antigen presentation by engineering NPs, which influence the particle-phagocyte interaction as has been demonstrated by Mitragotri and colleagues [88], who invented microcapsules mimicked live mouse red blood cells. They demonstrated three preliminary examples: surface-absorbed hemoglobin for oxygen delivering, encapsulated iron oxide nanocrystals as imaging contrast agents, and encapsulated heparin as an anticoagulant. New strategies to deliver anti-inflammatory drugs to innate immune cells selectively and inflamed tissues and reverse their pathological phenotypes are of great interest as a therapeutic tool for ADs. Nano-delivery systems are capable of reducing drug dose and administration frequency by extending half-life and increasing the metabolic stability of small molecules. Nano-carriers can preferentially accumulate in arthritic joints due to enhanced vascular permeability at inflammation sites where they are subsequently phagocytozed by recruited monocytes/macrophages, to activate them and eventually inducing their apoptosis [89].

Yuan et al. [90] developed a novel pH-sensitive drug delivery system of dexamethasone (Dex) specifically accumulates in inflamed joints in an animal model of arthritis [91]. Several therapeutic strategies reported about NPs to improve T1DM are mainly based on insulin delivery systems, gene therapy and islet cell-targeting molecular therapeutics. Niu et al. [92], have shown that the human insulin gene can be transfected successfully by chitosan NPs in-vivo and in-vitro. Au-NPs-DNA functionalized conjugates used as an islet-targeting gene therapy have shown to be an effective and non-toxic transfection vehicle for islet cells by both in vitro and in vivo studies [93,94]. Jeong et al. [95], demonstrated surface camouflage of pancreatic islets using combination of cyclosporine and anti-CD4 monoclonal antibody (OX-38) along with PEGylation showed a highly improved synergistic effects on the inhibition of sensitized host immune reactions occurring against graft tissues. A study by Bhol et al. [96], silver nanocrystals were administered intracolonically at a dose as low as 4 mg/kg, and were effective to decrease the signs of colitis in a rat model of UC and was as effective as 100 mg/kg sulfasalazine.

Nanotechnology to correct deletion mutation (like thalassemia)

With the combined efforts of three Yale laboratories, researchers conducted the first demonstration of site-specific gene editing in a fetus, correcting a mutation that causes a severe form of anemia. The technique, which is developed in 2018, involves an intravenous injection of nanoparticles carrying a combination of donor DNA and synthetic molecules known as peptide nucleic acids (PNAs). The PNAs, which mimic DNA, bind to the target gene and form a triple helix — an aberration that triggers the cells' repair mechanisms. As part of this process, the healthy donor DNA, paired with the PNA in a nanoparticle, is used to fix the mutation. The researchers, made the nanoparticles with a degradable polymer and designed them small enough, 200 to 300 nanometers, to readily

accumulate in the liver of the fetus, where the stem cells are located before migrating to the bone marrow.

For the study, this gene-editing package was injected into the fetuses of mice as shown in figure (4). At four months after birth, the mice had been cured of thalassemia, an inherited defect in oxygen-carrying red blood cells. "The treated mice had normal blood counts, their spleens returned to normal size, and they lived a normal life span, whereas, the untreated ones died much earlier [97].

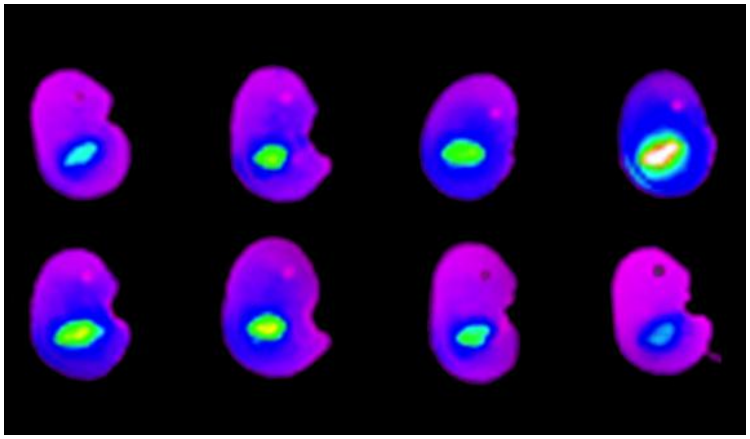

Figure 4. Distribution of nanoparticles in a litter of fetal mice after intravenous nanoparticle treatment. The intense green, yellow, and red areas show higher concentrations. The highest accumulation of nanoparticles in each mouse is in the fetal liver

Conclusion

Nanotechnology is a vast science, with a lot of advantages and some disadvantages that can be overcome by multiple, continuous and keen trials, until the best results gained.

In field of medicine, this technology opened new hopes to treat a lot of diseases that the traditional managements are not curative, so in other words, it reduced mortality for fatal diseases and improved life style for chronic morbid conditions.

The present review aimed is to illustrate nanoparticles types, and their clinical applications whether diagnostic or therapeutic, taking in consideration shape, size and consistency of the cover and core for each nanoparticle, as each type of them has its specific applications.

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