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Review article

NANOTHERANOSTICS FOR CANCER THERAPY AND DETECTION: STRATEGIES, PROMISES AND IMPEDIMENTS

VARSHA JACQULYN, S. LAKSHMI PRIYA, R. THIRUCHELVI*, K. RAJAKUMARI

Department of Bioengineering, B. Tech Biotechnology, Vels Institute of Science, Technology and Advanced Studies (VISTAS), 600 117 Chennai, India
E-mail: *thiruchelvir13@gmail.com*

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* For correspondence.

ABSTRACT

Cancer is responsible for a significant portion of disease-related death worldwide. In pathological words, cancer is described as the uncontrolled rapid multiplication of aberrant cells that can subsequently infiltrate into new locations. Malignant tumors with metastatic potential are the most common cause of cancer-related morbidity and so attract the most interest from scientists and researchers around the world. While new treatment and diagnostic procedures have significantly increased the survival rate of cancer patients, a complete cure remains improbable. Theranostic (combination of therapy and diagnostics) has developed as a cutting-edge strategy for cancer management, offering a two-pronged advantage. Nanoparticle can be tailored to develop theranostic capabilities resulting in nanotheranostics agents. Nanotheranostics hold enormous potential since they combine non-invasive disease detection and treatment with the exciting possibility of monitoring medication release and distribution in real time, anticipating and evaluating the therapy effectiveness. The clinical application of nanotheranostics would allow for earlier disease detection and treatment, as well as earlier response assessment, allowing for the screening of individuals who might respond to therapy and have a better chance of a positive outcome. This article discusses various nanotheranostics and their most recent developments in the fight against cancer.

Keywords: malignant tumor, cancer treatment, theranostics, diagnostic procedures, response assessment.

AIMS AND BACKGROUND

On a global scale, one of the most frightening health issues is cancer[1]. The understanding of cancer biology has greatly improved over the past few decades, but the mortality rates for many malignancies have little altered[2]. Cancer continues to place a significant socioeconomic burden on society and is now second only to heart disease in terms of causes of death and suffering globally. Clinical research is essential to the fight against cancer, and at an unprecedented rate, new findings are being applied to patients[3]. The use of nanotechnology in the pharmaceutical sector, often known as nanomedicine, has recently garnered a great deal of attention as a flexible method for targeted drug delivery and diagnostic procedures. Theranostic nanomedicines, which combine therapeutic and imaging capabilities on a single platform, have become the focus of scientists' attention due to the monofunctional nanomedicines' already encouraging outcomes. Nanotheranostics show enormous promise because they combine the exciting potential to track drug release and distribution in real time, predicting and proving the efficacy of the therapy, with the simultaneous non-invasive diagnosis

and treatment of diseases. These characteristics make nanotheranostics very alluring for improving therapeutic outcomes in cancer and other serious disorders[4–7]. Most complex nano formulations with theranostic properties have made great strides in recent years, improving diagnostic precision and therapeutic efficacy and displaying shining potential in future biomedical applications[8–10]. Numerous nanomedicines have in fact been successfully advanced to clinical trials at various stages, and some of them have received FDA (Food and Drug Administration) approval for clinical usage and show excellent performances. But there are still several challenges standing in the way of their clinical translations. For instance, nanotheranostics' sensitivity, specificity, and detection limit, which are advantageous for early-stage diagnosis, need to be further enhanced. Optimising the pharmacokinetic and pharmacodynamic features of nanotheranostics might further improve the therapeutic results by modifying the manufacture and characteristics of nanocarriers and the resulting nano formulations. Furthermore, during clinical trials, side effects, whether they can be short-term immunotoxicity or long-term toxicity, are the primary reason why nanotheranostics fails, which encourages researchers to create novel materials and methods to get around these fatal constraints[11]. There are several molecular imaging techniques employed, including ultrasound, computed tomography, X-ray scatter imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), optical imaging (OI), and single-photon emission computed tomography (SPECT). There are benefits and drawbacks to each of these methods that must be considered. Radiation treatment (RT), photothermal therapy (PTT), and photodynamic therapy are therefore commonly prescribed approaches for the treatment of tumors (PDT). Small molecules, proteins, oligonucleotides, polymeric nanoparticles, high-molecular-weight antibody, and their combinations with different kinds of nanoparticles have all recently been developed as various sorts of nanotheranostics contrast agents[12].

IMAGING

Techniques for molecular imaging rely on *in vivo* molecular mechanisms (Fig. 1). This imaging method includes the molecular and cellular level observation, characterisation, and quantification of biological processes in individuals and other living systems. Nuclear medicine, optical imaging, ultrasound, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography-computed tomography (PET-CT) are some of the methods employed[13].

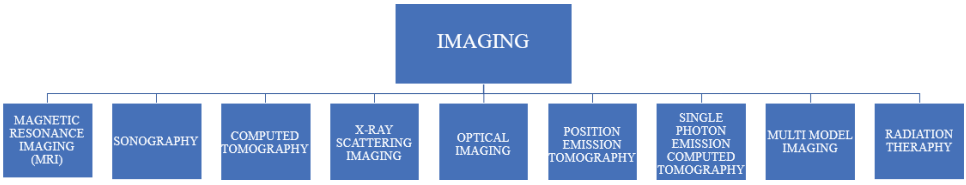

Fig. 1. Types of molecular imaging techniques[13]

MAGNETIC RESONANCE IMAGING (MRI)

The imaging technology known as magnetic resonance imaging, or more often known as MRI, is primarily employed in medical contexts to provide high-quality images of the inside of a human body. Nuclear magnetic resonance (NMR), a spectroscopic method used by scientists to gather microscopic chemical and physical information about molecules, provides the theoretical foundation of the mechanism behind MRI (Ref. 14). A huge, round magnet surrounds a tube in an MRI scanner. The patient is positioned on a mobile bed that is introduced into the magnet for normal MRI testing. A powerful magnetic field produced by the magnet aligns the protons of hydrogen atoms so that they can be struck by a radio wave beam. This causes the body's protons to spin, creating a weak signal that the MRI scanner's receiver section may pick up. A computer processes the information from the receiver, and after that, an image is created. Although MRI is effective for soft tissue and has excellent spatial and temporal resolution, it is noteworthy that it has limited sensitivity and a lengthy imaging time. As a result, adding contrast agents can improve the signal[15]. Ferromagnetic (negative agents) and paramagnetic materials are employed for this (positive agents). The main contrast agent for MR imaging was super paramagnetic iron oxide nanoparticles (SPIONs) (Ref. 16). Figure 2 depicts SPIONs with a total radius of the core with a shell and a water coat of 20 to 150 nm and a core radius of 5 to 15 nm.

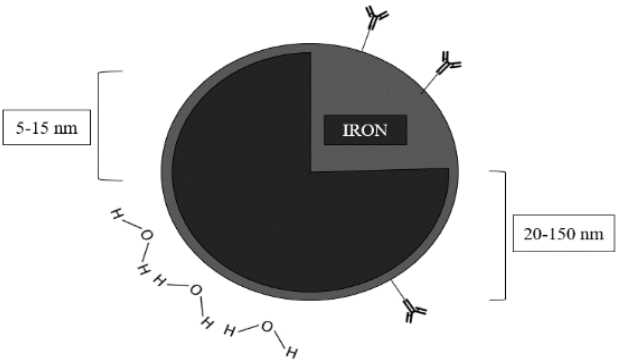

Fig. 2. SPIONs are depicted in a schematic diagram[16]

Ferumoxytol decreases T1 and T2* relaxation times because it belongs to the family of ultra-small SPIONs (USPIONs) (Ref. 17). Ferumoxytol has a therapeutic anti-cancer action, and intravenous treatment prevents liver metastases[18]. Additionally, SPIONs in breast cancer can prevent neovascularisation and cause endothelial progenitor cells to undergo autophagy[19]. The cytoskeleton can be harmed by high dosages of SPIONs, which also slow down cell proliferation[20]. According to some reports, Fe_3O_4, Al_2O_3, and TiO_2 have no detectable harmful effects at concentrations lower than 200 g/ml (Ref. 21). Gold nanoparticles can be employed for MR, photo acoustic, fluorescence, and X-ray scattering imaging since they lack this cytotoxic-

ity[22]. Additionally, they generate heat when subjected to NIR laser light, making them appropriate for photo thermal treatment (PTT) of cancer[23]. So, as an MR imaging nanoprobe, various investigations have reported employing AuNPs ultra-small, and nanoclusters covered with natural tripeptide glutathione (GSH) (Ref. 24). As a result, 2 nm-sized ultra-small GSH-coated AuNPs (AuGSH) are not stable in biological fluids. By substituting the negatively charged GSH (GSH has a net charge of 1) ligand for its zwitterionic derivative, glutathione monoethyl ester, a novel ultra-small AuNPs was created to get around size-dependent stability. The novel AuGSHzwt is more resistant to interactions with serum proteins and has better colloidal stability. It was determined that zwitterionic glutathione (AuGSHzwt) monoethyl ester surface-coated ultra-small AuNPs have greater aggregation resistance. Indeed, due to their small size and resistance to interactions with serum proteins, they are efficiently eliminated from the circulatory system[25]. The results showed that improving the density of ultra-small AuNPs ligands on their surfaces is crucial to improving their performance in imaging, especially for cancer therapy.

Gadolinium is the most often used commercial contrast material in MRI, but due to its low molecular weight, it only lasts a brief time in the bloodstream[26]. Low molecular weight contrast compounds can be coupled to macromolecules like Gd-DTPA-pullulan[27], synthetic polymers, and synthetic particles to alleviate this issue. But gadolinium can cause an uncommon but serious condition called nephrogenic fibrosis[28]. Mn^{2+} and manganese oxide nanoparticles are two categories of manganese-based contrast agents (MnONs). Mn^{2+} is a subpar contrast agent for MR imaging due to its short blood circulation time and toxicity at large doses[29]. MnONs have a low level of toxicity, which can reduce hypoxia and enhance therapy. In contrast to the gadolinium molecule, MnONs are now used in treatment and diagnosis more frequently[30]. In general, several T1/T2-weighted contrast agents based on gadolinium (Gd), manganese (Mn), and iron oxide nanoparticles (Fe_3O_4 NPs) have been developed to improve image sensitivity in MRI. Gd has seen low blood flow rates and in vivo toxicity, both of which have the potential to lead to nephrogenic systemic fibrosis. Due to their inherent dark signals and susceptibility artefacts in MRI, SPIONs, particularly Fe_3O_4 NPs, have sadly been somewhat restricted in their clinical applicability. As a result, it is challenging to distinguish between small early-stage tumors and hypo intense regions. Mn-based compounds are therefore regarded as the best alternatives because to their strong signals and outstanding biocompatibility[31]. In addition to MnO, the scientists reported using *trans* esterified oleic acid with TETT silane (N-(trimethoxysilylpropyl) ethylenediamine triacetic acid)[32]. Polyvinylpyrrolidone (PVP) has been coated on MnO nanoparticles (MnO@PVP NPs) by Hu et al.[33] such that they can cross the blood-brain barrier (BBB) and gradually metabolise in other regions where blood is flowing. In 2020, the researchers used the ENO1 antibody to analyse Enolase 1 (ENO1)-targeted SPIONs to assess pancreatic ductal adenocarcinomas (PDACs), the most lethal cancer with a 5-year survival rate of 5% for all stages[34].

Their findings show that this nanoparticle improves the effectiveness of PDACs early diagnosis MR imaging both *in-vitro* and *in-vivo*[35].

SONOGRAPHY

Ultrasound is used in sonography, a real-time, non-invasive technique that produces sharp images of soft tissues. Non-microbubble contrast agents, such as echogenic liposomes, perfluorocarbon nanodroplets, solid nanoparticles, and gas-filled microbubbles (with a gaseous core made of air, nitrogen, perfluorocarbon, and sulphur hexafluoride and a shell made of albumin, lipids, synthetic polymer, or galactose with a diameter of 2–1 m), are used in this modality. High sensitivity and specificity can be found in microbubble. The fact that B-mode ultrasound imaging has a low specificity for malignant lesions despite being extremely sensitive is noteworthy[36].

By adding concentrated microbubbles to it, one can make it more particular. According to ultrasound research, cavitation can increase the formation of nanoparticles and the distribution of medications in tumors. For instance, under US advice, PEG-PDLA (polyethylene glycol-poly (D-lactide) nanoparticles) are employed to get over paclitaxel's water solubility hurdles[37].

COMPUTED TOMOGRAPHY (CT)

CT imaging is a different modality that offers benefits like high resolution, quick data gathering, deep tissue penetration, and simplicity in three-dimensional tissue reconstruction. However, it is limited in its ability to differentiate between soft tissues of the same density and has a low signal-to-noise ratio (SNR)[38]. As a result, CT contrast media are used to improve the contrast of soft tissues. As contrast media in CT, atoms like iodine, tungsten, and barium are frequently utilised. As CT contrast media, gold nanoparticles (AuNPs) with a high X-ray absorption coefficient and nanoscale metal organic frameworks (NMOFs) with a high Z element content are now frequently utilised[39]. When NPs are employed, expected dosages of CT contrast moieties can be reduced. Due to this, NPs have lower number density, viscosity, and osmolality when compared to molecular contrast agents of the same concentration. Therefore, it is anticipated that administering nanoparticles CT contrast will reduce imaging duration and kidney damage[40].

X-RAY SCATTER IMAGING

The difference in X-ray penetration intensity is the foundation of X-ray scatter imaging. This imaging technique has drawn a lot of attention because of the variations in X-ray penetration intensity brought on by variations in tissue thickness and density[41]. According to the findings of AuNPS investigations, these particles are the best contrast medium for X-ray scatter imaging because they have a larger atomic number than iodine nanoparticles and are less hazardous. In order to create contrast

when imaging hepatocellular carcinoma (HCC) cell pellets using X-ray scattering[42]. Rand et al. employed AuNPs coated with polyelectrolyte. They demonstrated that ultra-small AuNPs are more sensitive as a contrast medium in X-ray scatter imaging and are more effective than conventional X-rays diffraction in the diagnosis of small clusters of HCC. They evaluated 10 and 50 nm AuNPs (Ref. 43).

OPTICAL IMAGING

Using various colours of light, optical imaging is a non-invasive technique that enables visualisation and measurement of various organ properties. This modality has a shallow penetration depth. Utilising near-infrared (NIR) light with a wavelength range of 650–900 nm is one way to solve this problem. Endoscopy, optical coherence tomography (OCT), photoacoustic imaging (PAI), Raman spectroscopy, diffuse optical tomography (DOT), and super-resolution microscopy are new optical imaging as molecular imaging modalities. In this modality, utilising NPs has recently been taken into consideration. In a 2013 study, silica/poly (4-vinyl benzyl chloride-co-pyrene-1-ylmethyl acrylate) core-shell particles had pyrene conjugated on the shell. The findings showed that the presence of pyrene in the polymer shell caused the high fluorescence intensity[44]. According to a recent study, UiO-66 (Universiteteti Oslo) is a metal organic framework formed of $[Zr_6O_4(OH)_4]$ with 1,4-benzodicarboxylic acid within 1,2-dioleoyl-sn-glycero-3-phosphate (DOPA) lipid bilayer (DOPA-LB) (UiO-66@DOPA-LB), which has improved stability, outstanding blood circulation Additionally, UiO-66@DOPA-LB labeled with the NIR dye IRDye 800 nm CW enabled the imaging of breast cancer tumors and the early detection of tumors[45]. Monoclonal anti-EGFR antibodies have been joined by Sokolov et al. to gold nanoparticles with diameters of 5 and 40 nm. Their findings demonstrated that gold nanoparticles as small as 5 nm exhibit high infrared absorption, and their photoacoustic signal is comparable to that of particles as small as 40 nm. Furthermore, they demonstrated that despite their small size, particles as small as 5 nm have good *in vivo* penetration and clearance[46].

POSITRON EMISSION TOMOGRAPHY (PET)

Even while PET imaging is highly sensitive and has no depth penetration restrictions, it lacks the anatomical data necessary to identify molecular events. To get around this constraint, however, imaging techniques like CT and MRI are paired with PET. Multimodality imaging techniques like PET/CT and PET/MRI can be used to find lesions and tumors from both anatomical and functional perspectives. In 2019, scientists discovered a coated SPIONs with S-2-(4-isothiocyanato benzyl)-1,4,7,10-tetraazacyclododecane tetra acetic acid (DOTA) as chelators, N,N,N-trimethyl chitosan (TMC) and bombesin (BN) as targeted ligands. According to their findings, the nanoparticles were appropriate for PET/MRI prostate, breast, and lung cancer diagnosis[47].

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT imaging relies on a less sensitive and precise method of detecting gamma rays than PET. According to reports, the preclinical investigation used micro-SPECT, which has a greater spatial resolution than PET. 99mTc imaging is the most helpful for this in this modality. Zhao et al. added 199Au to Au nanoparticles and used SPECT to analyse the results. They discovered that 199Au-doped Au nanoparticles might function as a C-C chemokine receptor 5 (CCR5)-targeted nanoprobe for the sensitive and accurate detection of both triple-negative breast cancer (TNBC) and its metastases[48].

MULTI-MODEL IMAGING

As previously mentioned, multi-modal imaging has recently drawn a lot of interest due to the shortcomings of each imaging modality. Wei et al. tested the effectiveness of $NaGdF_4$, $CaCO_3$-PEG core-shell nanoparticles in the diagnosis of prostate tumors in 2017 using this method. Their findings show that the progressive dissolution of $CaCO_3$ under the acidic conditions of the tumor environment enhances the collision of $NaGdF_4$ with the surrounding aqueous media. The comfort of the water proton and the MRI signal are improved by this approach[49]. Additionally, it generates CO_2 bubbles from the breakdown of $CaCO_3$, which produces powerful echoes for ultrasound imaging. Another study used the core-shell Up conversion nanoparticles (UCNP) coated with Porphyrin-phospholipid (PoP) to map lymph nodes. The findings showed that six methods, i.e. near-infrared (NIR), fluorescence (FL), NIR-to-NIR up conversion luminescence (UC), photoacoustic (PA), Cerenkov luminescence (CL), CT, and PET could be used to compute PoP-UCNPs (Ref. 50). Renal cell cancer was investigated[51] using AS1411-Manganese-Molybdenum disulphide quantum dots (Mn-MoS_2 QDs). According to their findings, AS1411-Mn-MoS_2 QDs offers a novel nanoprobe for MRI and fluorescence imaging and outperform Gd-DTPA as an MR contrast agent for renal cell cancer.

RADIATION THERAPY

Nanoparticles can be applied to both diagnostic and therapeutic purposes. The inability of existing cancer medicines to destroy healthy tissues selectively is a crucial issue. Therefore, research efforts have concentrated on developing new targeted agents to reduce injury to healthy tissue. They can, for instance, encapsulate drugs like doxorubicin (DOX) and release them at specific locations, reducing systemic toxicity and enhancing pharmacokinetic profile[52]. In fact, nanoparticles enable the delivery of therapeutic medicines to certain tumor areas, reducing the toxicity of many treatments when administered off-target. Chemotherapy, which has major side effects, exhibits this[53]. In 2016, an injectable nanoparticles generator was loaded with polymeric doxorubicin (pDOX) (iNPG). The outcomes showed that iNPG-pDOX was superior to DOX alone in treating breast metastatic tumors[54]. It was discovered that

poly (d,l-lactide-co-glycolide) (PLGA) nanoparticles coated with chitosan might be employed as an oral drug delivery strategy for diosmin in 2019 (Ref. 55). Diosmin has anti-inflammatory, free radical-scavenging, and anti-ulcer effects[56]. However, this medication is poorly soluble and requires large oral doses[57]. The findings show that chitosan coated PLGA can lengthen the duration the drug spends at the delivery site, improve bioavailability, lower the dosage and frequency of administration, and lessen side effects[58].

BIOLOGICAL EFFECTS OF NANOPARTICLES ON CANCER CELLS

The interactions between the nanoparticles and various cell types determine the in vivo deposition of nanomaterials in targeted and off-target tissues. It could be able to utilise the accumulation of treatments at target organs and minimise off-target exposure by controlling these interactions. Because it can lessen the toxicity that occurs from drug interactions with off-target organs, more accurate targeting can increase the therapeutic index of chemotherapy treatments. Once nanoparticles enter cancer cells, their effects can be seen.

BOTH CANCEROUS CELLS AND EXPERT PHAGOCYTES ABSORB NANOPARTICLES VIA MULTIPLE METHODS

The features of the nanoparticles themselves, such as the availability of ligand that attach and activate certain receptors on the cell surface, impact the endocytosis methods used by cells. Since most macromolecules and nanomaterials cannot pass through the cell membrane, both nutrition and nanoparticles are primarily delivered by energy-dependent methods of absorption[59].

BLOOD/SERUM INTERACTION

Immediately after being exposed to biological conditions, nanoparticles quickly bind proteins to their surfaces. The protein corona is the name given to this layer, which has the power to alter the dimensions, structure, surface properties, aggregation state, and ensuing biological behaviours of the nanoparticles. *In vivo* nanoparticle destiny is influenced by this binding and activation[60]. Nanoparticle size and the surface chemistry both influence how quickly cells exocytose. The researchers found that in HeLa cells, nanoparticle exocytosis was 40% for transferrin-coated gold nanoparticles of 14 nm diameter, but only 10% for particles of the same size with identical chemical nature.

PROPERTIES OF NANOMATERIALS IMPACT ENDOCYTOSIS

Nanoparticles are prone to two conflicting processes after they reach the bloodstream and engage with serum proteins: removal via renal or phagocytic routes and retention into the tumor environment. The total bioavailability and pharmacokinetics seen for

nanomaterials rely on the relative rates at which these processes occur. Particularly, the size of nanoparticles has a significant impact on how quickly they enter cells.

DELIVERING CARGO TO PARTICULAR CELLULAR COMPARTMENTS USING NANOPARTICLES IS LIMITED BY ENDOSOMAL ESCAPE

Numerous nanoparticles have been seen to collect in endosomal compartments, where they may be broken down before they may have their intended therapeutic effect. The nanoparticles or its contents must enter additional cellular compartments in order to have a therapeutic potential. The influenza virus is one disease that is affected by this issue. In response, it has developed particular peptides that rupture or merge well with endosomal membrane and allow its cargo into the cell cytoplasm. To increase the transfection effectiveness of liposomes containing siRNA, the researchers used a synthetic peptide termed as "GALA" owing to the protein sequence's repeating unit. This peptide performs a structural shift at pH 5.0 (the normal acidity in late lysosomes) to create an amphiphilic alpha helix which destroys phospholipid bilayer and induces endosomes to leak, similarly to the influenza peptide previously stated. They consequently noticed that after altering their liposomal constructs with GALA, the transfection effectiveness of those constructs was 100 times greater (objectively measured in this case as the production of luciferase). Substantial improvements in their effectiveness may also be achievable if comparable methods are used for other sorts of nanoparticles[61].

RATES OF ACCUMULATION ARE DETERMINED BY EXOCYTOSIS OF NANOPARTICLES

Nanoparticles can release their cargo to have a therapeutic effect after being endocytosed by cancer cells or phagocytes. The intensity of this action, however, partly depends on how rapidly the nanoparticles accumulate inside cells and how long they stay there. A different method for enhancing the medicinal effect of nanoparticles is to manipulate the rate of exocytosis. The concentration of nanoparticle inside cells at a particular period varies depending on the relative levels of endocytosis and exocytosis. Nanoparticle size and the surface chemistry both influence how quickly cells exocytose. The researchers found that in HeLa cells, nanoparticle exocytosis was 40% for transferrin-coated gold nanoparticles of 14 nm diameter, but only 10% for particles of the same size with identical chemical nature[62]. The researchers demonstrated that exocytosis of nanoparticles with just an aroma existing role at the end of a cation PEG modification was larger than that of nanoparticles with a hydrocarbon surface functionality[63].

TYPES OF METALLIC NANOPARTICLES

Many nanoparticles are employed (Fig. 3). The following are a few of the most typical nanoparticles employed here:

– Gold nanoparticles
– Silver nanoparticles
– Zinc nanoparticles
– Iron nanoparticles

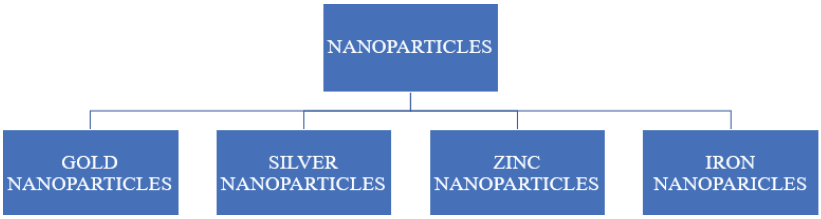

Fig. 3. Different types of metallic nanoparticles used for cancer theranostics

IRON AND IRON OXIDE NANOPARTICLES

Iron(III) oxide, usually called as Fe_2O_3, represents one of the three primary oxides of iron, another two including FeO and Fe_3O_4. It is a reddish-brown, inorganic material with a paramagnetic characteristic. Superparamagnetic in natural, Fe_3O_4 also occurs in nature as the mineral's magnetite. Superparamagnetic iron oxide nanoparticles (SPION) are now attractive candidates for a wide range of biomedical purposes due to their nano size, saturation magnetisation, and bio-compatibility. These applications include targeted drug administration and image analysis, heat exhaustion, genetic manipulation, cell therapy monitoring, single – molecule monitoring, magnetic separation techniques (like rapid DNA sequencing), early recognition of acute inflammation, cancer, and diabetes, and more[64]. For any of these biomedical applications providing high-resolution MR imaging, the nanomaterials must have high magnetism values. Superparamagnetic nanoparticles are typically decent imaging sensors that can be employed as contrast agents for MRI because they greatly alter the MR sensitivity for detecting while maintaining its *in vivo* stability[65]. In the subjected to a magnetic field, SPIONs assist external biofluid protons in calming more rapidly, which leads to a non-homogeneous magnetic force. These substances are employed as contrast media for imaging purposes in MRI because of their feature[66]. The impact strength that SPIONs undergo because of Neel relaxation that results in hyperthermia is thought to be the cause of their therapeutic effects. Apoptosis, the induction of immune function, a spike in tumor blood circulation and oxygen, and other subcellular events can contribute to hyperthermia, which itself is defined as a rise in the environment of a tissue's temperatures to 40–45°C. Cell death is the outcome of these activities[67]. The effectiveness of the IONPs was assessed in *in-vivo* and *in-vitro* by MRI after the

researchers created them and coupled them with the therapeutic drug methotrexate and the targeted ligand chlorotoxin. Their research showed greater cytotoxicity in cancerous cells, indicating the potential for these multifunctional nanoparticles to be used in the diagnosis and therapy of cancer[68]. For diagnosing pancreatic cancer, the researchers created imaging contrast agents employing SPION that has a bovine serum albumin cap. Their deployment of these SPIONs as T2-weighted MRI contrast agents was ensured by the 13.3:1 r2:r1 ratio. The capability combined near-infrared (NIR) fluorescent dye as well as mAbs for the targeted bi-modal imaging of pancreatic cancer has been improved through further conjugation[69].

GOLD NANOPARTICLES

A dispersion (or colloid) of gold nanoparticles is referred to as Au nanoparticles, also referred to as gold nanoparticles. These colloidal solutions have a long tradition, going back to the ancient era where they were employed to decorate glass with stains. However, Michael Faraday's study from the 1850s, in which he noted that now the colloid gold solution has characteristics that are distinct from the mass gold, began the process of the scientific analysis of colloidal gold. These gold nanoparticles' intriguing visual characteristics are the result of a special contact they have with light. The excited electrons of the metallic nanoparticles oscillate in relation to the metallic structure in the availability of the light's fluctuating electrical waves. Plasmons are aggregate vibrations of free electrons that are quantisation, and surface plasmons are collectively vibrations of electron that are present at the surface. Surface plasmon resonance is a phenomenon in which these plasmons combine with visible region. Every one of the features of Au that are radioactive such as scattering and absorption and nonradioactive (such as the transformation of light that is absorbed to temperature) is enhanced by SPR because it creates strong electromagnetic energy on the particle surface[70]. By specifically delivering AuNPs to the nucleus of cancer cells, it has been demonstrated[71,72] the utilisation of metal nanoparticles for medical diagnostics. They attached an arginine-glycine-aspartic acid peptides (RGD) as well as a nuclear localised signaling peptide (NLS) to something like a 30-nm AuNPs through PEG in effort to specifically convey that AuNPs into in the cancerous cell's nucleus. The absorbance of spherical gold nanoparticles has not proved satisfactory for *in vivo* applications. The maximum absorption coefficients have been restricted around 520 nm for 10 nm diameter, which explains this. The tissue scarcely warms up in the absence of a rod-shaped gold nanoparticles featuring IR absorption when laser beam in the IR region is aimed towards malignancies, but the nanorods transform light into heat, killing the cancer cell. The gold nanorods' prospective use distinguishes these from many other nanoprobes[73]. Small nanoparticles are preferable for PTT since light is predominantly absorbed by them and is effectively turned into heat, but large nanoparticle is chosen for imaging due to increased scattering efficacy[74]. The scientist created a nanocomposite including biopolymer chitosan and highly fluorescent Au nanoclusters, which could be easily reduced to nanoparticles to make a stable polyplex with the suicide gene

for inducing apoptosis in cervical tumor cells. Despite the use of additional colours, synchronous red, green, and blues fluorescence from nanoclusters served as useful optic image and flows monitoring probes (Fig. 4)[75].

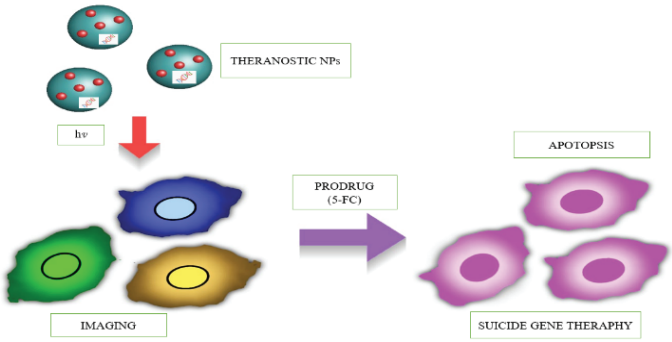

Fig. 4. Chitosan nanoparticles with concurrent RGB emission Au nanoclusters for cancer gene theranostics[75]

AuNP have also been investigated as effective radio sensitisers, where they make cancer cells more sensitive to radiation by changing their microenvironment. AuNP have all shown promise, but they also have disadvantages like a high cost and prolonged retention in the hepatic, spleen, or other tissues. Before AuNP may be applied clinically, these problems must be resolved[76].

SILVER NANOPARTICLES

Silver nanoparticles are tiny silver particles, ranging in size from 1 to 100 nm. Some materials, despite being widely referred to as "silver," include a significant amount of silver oxide because of the huge proportion of surfaces to mass silver atoms. Ionic silver seems to have a lengthy history and was first employed to yellow-stain glass, like gold nanoparticles. There is currently works being done to include nano particles into a variety of medical products, such as surgical masks, bone cement, and other items. Ionic silver has also been demonstrated to be effective in curing wounds when used in the proper dosages. These nanomaterials have gained a lot of attention in bioimaging utilising SERS due to their appealing physiochemical characteristics. The researchers showed that silver nanoparticles react to HIV-1 in a size-dependent manner, having particles confined to the 1–10 nm range adhering to the virus[77]. The scientists created biocompatible AgNPs using chitosan that was surface coupled with FA and tagged with such a *p*-amino thiophenol Raman detector molecule. It was demonstrated that the particles' SERS identity is strongly conserved inside cells. An effective therapeutic response was obtained by the targeted therapy of cancer cells using an NIR laser in resonant with their plasmonic band. These nanomaterials are a strong contender for application as individualised cancer therapeutics since they combine the benefits of multimodal optical imaging, SERS detection, and hyperthermia characteristics through

site specificity[78]. The researchers functionalised four Raman-active molecules, four antibodies specific to breast cancer indicators, a leukocyte-specific CD45 marker, and tunable Ag-Au nanorods with limited surface-enhanced Raman scattering (SERS) as well as excellent photothermal contrast. When compared to standard Ag nanorods, a SERS signal boost of further then 2 orders of magnitude could be seen employing these mixed nanostructures (Fig. 5)[79].

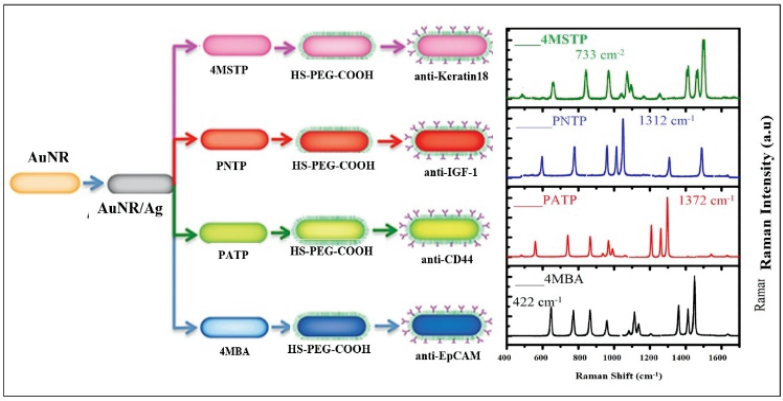

Fig. 5. Diagrammatic representation of spectral data for four SERS nano-agent groups[79]

ZINC NANOPARTICLES

Numerous studies have focused on the potential use of zinc oxide (ZnO) nanomaterials in the treatment of cancer. ZnO is a common wide band-gap semiconductor that finds use in a variety of scientific fields. Wide band-gap semiconductor features are effective at promoting the formation of ROS, whilst its inherent photoluminescence properties are valuable in biosensing applications. The most significant and distinctive characteristic of zinc oxide nanoparticles is their inborn predisposition for *in vitro* cytotoxicity against cancer cells. This trait is the result of their capacity to trigger the formation of ROS, which causes cell death[80]. Since the nanocrystal quality also declines as ZnO particle size drops, significant concentrations of gaps and/or protons are present in nanosized ZnO even in the absence of UV radiation. As a result, there are more oxygen vacancies, Zn ions, and donor/acceptor impurities in the interstitial space. These crystal flaws have the power to generate lots of electron-hole pairs, which leads to the generation of ROS (Ref. 81). ZnO nanoparticles can act synergistically with chemotherapeutic drugs and are a good option for theranostic use since they naturally possess luminescent characteristics and have selective anticancer activity. According to the investigations, ZnO nanowires are used for imaging and medication delivery. Integrin v3 on U87MG adult glioblastoma cells was optically imaged using RGD peptide-conjugated green fluorescent ZnO nanowires[82]. The scientists found that doxorubicin-loaded ZnO are created to have a synergistic antitumor effect. When

combined with doxorubicin, ZnO nanoparticles showed more cytotoxic than either drug by itself. But the cytotoxicity of drug-loaded nanoparticle was significantly higher. This demonstrated that the synergistic cytotoxicity caused by the co-administration of doxorubicin as well as zinc oxide nanoparticles resulted in increased anti-cancer activity[83].

TARGETED THERAPY

The goal of targeted therapy is to specifically treat cancer cells while sparing healthy cells any harm. This goal has rarely been met. Prior to eradicating too many healthy cells, the objective is to eradicate all malignant cells. With conventional chemotherapy, which is toxic to both healthy and malignant tissues, this is challenging. Using several processes, such as passive and active targeting, nanotechnology can be employed to increase drug accumulation specifically to the tumor location. Additionally, as the immune system is highly specialised to specifically recognise and eliminate target cells, activation of the immune system against cancer cell-specific surface markers can be exploited as a targeted therapy.

DRUG CARRIER NANOPARTICLES

By improving the medication delivery specifically to the tumor site through either passive or active techniques, NP-based therapy can offer a notable benefit over conventional chemotherapies. Clinically, the EPR effect has been used to administer drugs through passive accumulation of NPs at the tumor site using the NP formulations Myocet and DaunoXome, which are liposomal versions of the drugs doxorubicin and daunorubicin, respectively. The NP must circulate for a lengthy period in the blood for maximum tumor uptake via the EPR effect, which is frequently accomplished through PEGylation of the NP (Ref. 84). This is probably because the medication only reaches a tiny part of the tumor's cells due to low tumor penetration. Doxil's therapeutic effectiveness is enhanced both *in vitro* and *in vivo* by the attachment of a tumor-targeting antibody to its surface, which increases the drug's uptake by tumor cells[85].

DRUG CARRIER STEM CELL

For usage as drug and NP carriers, adult stem cells including mesenchymal and neural stem cells have recently attracted a lot of attention. The objective is to actively deliver the therapeutic payload or imaging agent to the tumor site by taking use of the tumor homing abilities of these stem cells. Stem cells can find their way to the tumor location, whereas NPs with active targeting improve the likelihood of adhering to and being internalised by tumor cells. This active targeting is distinct from the active targeting accomplished with NPs alone. Mesenchymal stem cells (MSCs) and neural stem cells are two forms of adult stem cells that have been investigated (NSCs). Both can be implanted into rats and loaded with NPs without impairing their normal cellular function. For at least 6 weeks following implantation, both can be monitored

using MRI (Ref. 86). Combining stem cells and NPs can enhance stem cell-mediated drug delivery through imaging and encourage the active targeting of NPs to a greater percentage of cancer cells.

T-CELL BASED IMMUNOTHERAPY

Some NP-based treatments for diabetes, rheumatoid arthritis, and transplant rejection target T cells[87]. In these situations, the intention is to suppress the immune response in order to avoid infection or transplant or implant rejection. On the other hand, cancer immunotherapy calls for reversing the immune system's usual suppression in the tumor microenvironment[88]. Immune system white blood cells called T cells play a role in cell-mediated immunity. In order to promote specific cancer cell killing, adoptive T cell therapy entails extracting T cells from patients and activating them against a tumor antigen *ex vivo* before putting them back into the patient[89]. This autologous T cell therapy has demonstrated promise in some melanoma patients[90] and in fact, it is now the norm of care for some cancer patients who have experienced relapses. By offering a method of real-time imaging, the application of nanotechnology to T cell-based immunotherapies can help advance knowledge of T cell trafficking and enhance therapy as an adjuvant.

DENDRITIC CELL BASED IMMUNOTHERAPY

A DC vaccine (a DC laden with antigen) is used in dendritic cell (DC)-based immunotherapy, and this DC must travel to lymph nodes in order to present antigens to T cells, which in turn trigger an immune response. Antigen is typically ex vivo loaded into autologous DCs before being injected back into the patient as a therapy. Since only a few numbers of activated DCs can trigger a potent immune response, this pathway for cancer immunotherapy can be quite robust. Although only in a small subset of patients, a handful of clinical trials using DC immunotherapy against cancer have demonstrated feasibility and effectiveness[91]. By enabling real-time tracking to identify hazards and monitor response, the introduction of nanoscale imaging methods to DC-based medicines should hasten their widespread translation into the clinic more clearly.

CONCLUSIONS

Oncology is one of the disciplines that have benefited the most from nanotechnology. A wide acceptance of cancer nanotechnology will come from a better understanding of how nanoparticles interact with biological systems; how multiple functions, including imaging and therapy, can be incorporated in a single nanoplatform; and how to harness the unique physicochemical properties of nanoparticles that do not otherwise exist in small-molecular-weight molecules for the detection and destruction of cancer cells with high selectivity and efficiency. Whereas researchers have successfully introduced a few nanotechnology-based anticancer therapeutic agents, such as liposomal doxorubicin (Doxil) and human serum albumin-bound paclitaxel

(Abraxane), into the clinic, targeted delivery of nanoparticles for treatment of cancer has yet to live up to its promise. The major challenges in successful clinical translation of targeted delivery of nanoparticles include overcoming various biological barriers and demonstrating better therapeutic efficacy than that of the current standard of care in the clinic. Understanding these challenges is imperative for effectively moving the field of cancer nanotheranostics forward.

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REFERENCES

1. F. F. BRAY, J. FERLAY, I. SOERJOMATARAM, R. L. SIEGEL, L. A. TORRE, A. J. JEMAL: Erratum: Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, **70** (4), 313 (2020).
2. J. SHI, P. W. KANTOFF, R. WOOSTER, O. C. FAROKHZAD: Cancer Nanomedicine: Progress, Challenges and Opportunities. Nat Rev Cancer, **17** (1), 20 (2017).
3. H. CHEN, W. ZHANG, G. ZHU, J. XIE, X. CHEN: Rethinking Cancer Nanotheranostics. Nat Rev Mater, **2** (7), 1 (2017).
4. A. WICKI, D. WITZIGMANN, V. BALASUBRAMANIAN, J. HUWYLER: Nanomedicine in Cancer Therapy: Challenges, Opportunities, and Clinical Applications. Journal of Controlled Release (JCR), **200**, 138 (2015).
5. S. MURA, P. COUVREUR: Nanotheranostics for Personalized Medicine. Adv Drug Del Rev, 64 (13), 1394 (2012).
6. B. OUYANG, W. POON, Y. N. ZHANG, Z. P. LIN, B. R. KINGSTON et al.: The Dose Threshold for Nanoparticle Tumour Delivery. Nat Mater, **19** (12), 1362 (2020).
7. W. POON, B.R. KINGSTON, B. OUYANG, W. NGO, W.C. CHAN: A Framework for Designing Delivery Systems. Nat Nanotechnol, **15** (10), 819 (2020).
8. S. M. JANIB, A. S. MOSES, J. A. McKAY: Imaging and Drug Delivery Using Theranostic Nanoparticles. Adv Drug Del Rev, **62** (11), 1052 (2010).
9. D. E. LEE, H. KOO, I. C. SUN, J. H. RYU, K. KIM, I. C. KWON: Multifunctional Nanoparticles for Multimodal Imaging and Theragnosis. Chem Soc Rev, **41** (7), 2656 (2012).
10. X. XUE, Y. HUANG, R. BO, B. JIA, H. WU et al.: Trojan Horse Nanotheranostics with Dual Transformability and Multifunctionality for Highly Effective Cancer Treatment. Nat Commun, **9** (1), 1 (2018).
11. R. OUN, Y. E. MOUSSA, N. J. WHEATE: The Side Effects of Platinum-based Chemotherapy Drugs: a Review for Chemists. Dalton Trans, **47** (19), 6645 (2018).
12. D. SHAHBAZI-GAHROUEI, P. M. KHANIABADI, S. SHAHBAZI-GAHROUEI, A. KHORASANI, F. MAHMOUDI: A Literature Review on Multimodality Molecular Imaging Nanoprobes for Cancer Detection. Polish Journal of Medical Physics and Engineering (PJMPE), **25** (2), 57 (2019).
13. D. A. MANKOFF: Molecular Imaging as a Tool for Translating Breast Cancer Science. Breast Cancer Res, **10** (1), 1 (2008).
14. M. H. MAHMUD: Effects of Contrast-enhanced Positron Emission Tomography. Computed Tomography in Cancer Imaging. 2015.
15. M. F. KIRCHER, J. K WILLMANN: Molecular Body Imaging: MR Imaging, CT, and US. Part I. Principles. Radiology, **263** (3), 633 (2012).

16. F. AMINOLROAYEAI, D. SHAHBAZI-GAHROUEI, S. SHAHBAZI-GAHROUEI, N. RASOULI: Recent Nanotheranostics Applications for Cancer Therapy and Diagnosis: a Review. IET Nanobiotechnol, **15** (3), 247 (2021).
17. M. R. BASHIR, L. BHATTI, D. MARTIN, R. C. NELSON: Emerging Applications for Ferumoxytol as a Contrast Agent in MRI. J Magn Reson Imaging, **41** (4), 884 (2015).
18. S. ZANGANEH, G. HUTTER, R. SPITLER, O. LENKOV, M. MAHMOUDI et al.: Iron Oxide Nanoparticles Inhibit Tumour Growth by Inducing Pro-inflammatory Macrophage Polarization in Tumour Tissues. Nat Nanotechnol, **11** (11), C986 (2016).
19. P. M. KHANIABADI, D. SHAHBAZI-GAHROUEI, A. M. MAJID, B. M. KHANIABADI: Study the Anti-MUC1 Antibody-based Iron Oxide Nanoparticles on Three-dimension Spheroid and Breast Cancer (MCF-7) Cell Imaging. Polish Journal of Medical Physics and Engineering (PJMPE), **25** (2), 69 (2019).
20. R. M. PATIL, N. D. THORAT, P. B. SHETE, P. A BEDGE, S. GAVDE et al.: Comprehensive Cytotoxicity Studies of Superparamagnetic Iron Oxide Nanoparticles. Biochem Biophys Rep, **1** (13), 63 (2018).
21. F. H. BEIGI, S. FATAHIAN, S. SHAHBAZI-GAHROUEI, D. SHAHBAZI-GAHROUEI, A. FARZADNIYA: Assessment of Ploy Dopamine Coated Fe3O4 Nanoparticles for Melanoma (B16-F10 and A-375) Cells Detection. Anti-cancer Agents Med Chem (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), **20** (16), 1918 (2020).
22. F. GHAHREMANI, A. KEFAYAT, D. SHAHBAZI-GAHROUEI, H. MOTAGHI, M. A. MEHRGARDI, S. HAGHJOOY-JAVANMARD: AS1411 Aptamer-Targeted Gold Nanoclusters Effect on the Enhancement of Radiation Therapy Efficacy in Breast Tumor-bearing Mice. Nanomedicine, **13** (20), 2563 (2018).
23. J. B. VINES, J. H. YOON, N. E. RYU, D. J. LIM, H. PARK: Gold Nanoparticles for Photothermal Cancer Therapy. Front Chem, **7**, 167 (2019).
24. J. LIU, M.YU, C. ZHOU, S. YANG, X. NING, J. ZHENG: Passive Tumor Targeting of Renal-clearable Luminescent Gold Nanoparticles: Long Tumor Retention and Fast Normal Tissue Clearance. J Am Chem Soc, **135** (13), 4978 (2013).
25. L. L. KNITTEL, H. ZHAO, A. NGUYEN, A. MIRANDA, P. SCHUCK, A. A. SOUSA: Ultrasmall Gold Nanoparticles Coated with Zwitterionic Glutathione Monoethyl Ester: a Model Platform for the Incorporation of Functional Peptides. J Phys Chem B, **124** (19), 3892 (2020).
26. H. J. WEINMANN, R. C. BRASCH, W. R. PRESS, G. E. WESBEY: Characteristics of Gadolinium-DTPA Complex: a Potential NMR Contrast Agent. Am J Roentgenol, **142** (3), 619 (1984).
27. R. JENJOB, N. KUN, J. Y. GHEE, Z. SHEN, X. WU et. al: Enhanced Conjugation Stability and Blood Circulation Time of Macromolecular Gadolinium-DTPA Contrast Agent. Mater Sci Eng: C, **61**, 659 (2016).
28. R. C. SEMELKA, M. RAMALHO, M. ALOBAIDY, J. RAMALHO: Gadolinium in Humans: a Family of Disorders. Am J Roentgenol, **207** (2), 229 (2016).
29. D. PAN, S. D. CARUTHERS, G. HU, A. SENPAN, M. J. SCOTT et al.: Ligand-directed Nanobialys as Theranostic Agent for Drug Delivery and Manganese-based Magnetic Resonance Imaging of Vascular Targets. J Am Chem Soc, **130** (29), 9186 (2008).
30. J. PENG, M. DONG, B. RAN, W. LI, Y. HAO et al.: "One-For-All"-Type, Biodegradable Prussian Blue/Manganese Dioxide Hybrid Nanocrystal for Trimodal Imaging-guided Photothermal Therapy and Oxygen Regulation of Breast Cancer. ACS Appl Mater Interfaces, **9** (16), 13875 (2017).
31. X. CAI, Q. ZHU, Y. ZENG, Q. ZENG, X. CHEN, Y. ZHAN: Manganese Oxide Nanoparticles as MRI Contrast Agents in Tumor Multimodal Imaging and Therapy. Int J Nanomed, **14**, 8321 (2019).
32. N. CHEN, C. SHAO, Y. QU, S. LI, W. GU et al.: Folic Acid-conjugated Mno Nanoparticles as a T 1 Contrast Agent for Magnetic Resonance Imaging of Tiny Brain Gliomas. ACS Appl Mater Interfaces, **6** (22), 19850 (2014).
33. X. HU, Y. JI, M. WANG, F. MIAO, H. MA et al.: Water-soluble and Biocompatible Mno@ PVP Nanoparticles for MR Imaging *in vitro* and *in vivo*. J Biomed Nanotechnol, **9** (6), 976 (2013).
34. W. CHEN, R. ZHENG, P. D. BAADE, S. ZHANG, H. ZENG et al.: Cancer Statistics in China, 2015. CA: a Cancer Journal for Clinicians, **66** (2), 115 (2016).

35. L. WANG, H. YIN, R. BI, G. GAO, K. LI, H. L. LIU: ENO1-targeted Superparamagnetic Iron Oxide Nanoparticles for Detecting Pancreatic Cancer by Magnetic Resonance Imaging. Journal Of Cellular and Molecular Medicine (JCMM), **24** (10), 5751 (2020).
36. Z. WANG, R. QIAO, N. TANG, Z. LU, H. WANG et al.: Active Targeting Theranostic Iron Oxide Nanoparticles for MRI and Magnetic Resonance-guided Focused Ultrasound Ablation of Lung Cancer. Biomaterials. **127**, 25 (2017).
37. N. RAPOPORT, A. PAYNE, C. DILLON, J. SHEA, C. SCAIFE, R. GUPTA: Focused Ultrasound-mediated Drug Delivery to Pancreatic Cancer in a Mouse Model. J Ther Ultrasound, **1** (1), 11 (2013).
38. R. JENJOB, T. PHAKKEEREE, F. SEIDI, M. THEERASILP, D. CRESPY: Emulsion Techniques for the Production of Pharmacological Nanoparticles. Macromol Biosci, **19** (6), 1900063 (2019).
39. M. KESHTKAR, D. SHAHBAZI-GAHROUEI, A. MAHMOUDABADI: Synthesis and Application of Fe_3O_4 Au Composite Nanoparticles as Magnetic Resonance/Computed Tomography Dual-modality Contrast Agent. Journal of Medical Signals and Sensors (JMMS), **10** (3), 201 (2020).
40. D. SHAHBAZI-GAHROUEI, P. M. KHANIABADI, B. M. KHANIABADI, S. SHAHBAZI-GAHROUEI: Medical Imaging Modalities Using Nanoprobes for Cancer Diagnosis: a Literature Review on Recent Findings. Journal of Research in Medical Sciences (the Official Journal of Isfahan University of Medical Sciences), **24**, (2019).
41. M. FAN, Y. HAN, S. GAO, H. YAN, L. CAO et al.: Ultrasmall Gold Nanoparticles in Cancer Diagnosis and Therapy. Theranostics, **10** (11), 4944 (2020).
42. M. FAZEL-GHAZIYANI, D. SHAHBAZI-GAHROUEI, M. POURHASSAN-MOGHADDAM, B. BARADARAN, M. GHAVAMI: Targeted Detection of the Cancer Cells Using the Anti-CD24 Bio Modified Pegylated Gold Nanoparticles: the Application of CD24 as a Vital Cancer Biomarker. Nanomed J, **5** (3), 172 (2018).
43. D. RAND, V. ORTIZ, Y. LIU, Z. DERDAK, J. R. WANDS et al.: Nanomaterials for X-Ray Imaging: Gold Nanoparticle Enhancement of X-Ray Scatter Imaging of Hepatocellular Carcinoma. Nano Letters, **11** (7), 2678 (2011).
44. J. MORAES, K. OHNO, T. MASCHMEYER, S. PERRIER: Monodisperse, Charge-stabilized, Core–Shell Particles via Silica-supported Reversible Addition–Fragmentation Chain Transfer Polymerization for Cell Imaging. Chem Mater, **25** (17), 3522 (2017).
45. R. ZHANG, C. QIAO, Q. JIA, Y. WANG, H. HUANG et al.: Highly Stable and Long-circulating Metal-organic Frameworks Nanoprobes for Sensitive Tumor Detection *in vivo*. Adv Healthc Mater, **8** (19), 1900761 (2019).
46. S. HAN, R. BOUCHARD, K. V. SOKOLOV: Molecular Photoacoustic Imaging with Ultra-small Gold Nanoparticles. Biomed Optics Express, **10** (7), 3472 (2019).
47. M. HAJIRAMEZANALI, F. ATYABI, M. MOSAYEBNIA, M. AKHLAGHI, P. GERAMIFAR et al.: 68Ga-radiolabeled Bombesin-conjugated to Trimethyl Chitosan-coated Superparamagnetic Nanoparticles for Molecular Imaging: Preparation, Characterization and Biological Evaluation. Int J Nanomed, **14**, 2591 (2019).
48. Y. ZHAO, B. PANG, H. LUEHMANN, L. DETERING, X. YANG et al.: Gold Nanoparticles Doped with 199Au Atoms and Their Use for Targeted Cancer Imaging by SPECT. Adv Healthc Mater, **5** (8), 928 (2016).
49. Z. WEI, X. LIN, M. WU, B. ZHAO, R. LIN et al.: Core-Shell Nagdf4@ CaCO3 Nanoparticles for Enhanced Magnetic Resonance/Ultrasonic Dual-modal Imaging via Tumor Acidic Micro-environment Triggering. Sci Rep, **7** (1), 1 (2017).
50. S. ZHENG, M. ZHANG, H. BAI, M. HE, L. DONG et al.: Preparation of AS1411 Aptamer Modified Mn-MoS2 QDs for Targeted MR Imaging and Fluorescence Labelling of Renal Cell Carcinoma. Int J Nanomed, **14**, 9513(2019).
51. C. ANDREOU, S. PAL, L. ROTTER, J. YANG, M. F. KIRCHER: Molecular Imaging in Nanotechnology and Theranostics. Mol Imaging Biol, **19** (3), 363 (2017).
52. X. D. ZHANG, Z. LUO, J. CHEN, X. SHEN, S. SONG et al.: Ultrasmall Au10− 12 (SG) 10− 12 Nanomolecules for High Tumor Specificity and Cancer Radiotherapy. Adv Mater, **26** (26), 4565 (2018).

53. K. CHATTERJEE, S. SARKAR, K. J. RAO, S. PARIA: Core/Shell Nanoparticles in Biomedical Applications. Adv Colloid Interface Sci, **209**, 8 (2014).
54. W. E. ABD El HADY, E. A. MOHAMED, O. A. SOLIMAN, H. M. El-SABBAGH: *In vitro–in vivo* Evaluation of Chitosan-PLGA Nanoparticles for Potentiated Gastric Retention and Anti-Ulcer Activity of Diosmin. Int J Nanomed,. **14**, 7191 (2019).
55. N. TONG, Z. ZHANG, W. ZHANG, Y. QIU, Y. GONG et al.: Diosmin Alleviates Retinal Edema by Protecting the Blood-retinal Barrier and Reducing Retinal Vascular Permeability during Ischemia/Reperfusion Injury. Plos One, **8** (4), e61794 (2013).
56. N. J. VICKERS: Animal Communication: When I'm Calling You, Will You Answer Too?. Curr Biol, **27** (14), R713 (2017).
57. L. H. CHUAH, N. BILLA, C. J. ROBERTS, J. C. BURLEY, S. MANICKAM: Curcumin-containing Chitosan Nanoparticles as a Potential Mucoadhesive Delivery System to the Colon. Pharm Dev Technol, **18** (3), 591 (2013).
58. J. REJMAN, V. OBERLE, I. S. ZUHORN, D. HOEKSTRA: Size-dependent Internalization of Particles via the Pathways of Clathrin- and Caveolae-mediated Endocytosis. Biochem J, **377** (1), 159 (2004).
59. S. TENZER, D. DOCTER, J. KUHAREV, A. MUSYANOVYCH, V. FETZ et al.: Rapid Formation of Plasma Protein Corona Critically Affects Nanoparticle Pathophysiology. In: Nano-Enabled Medical Applications. Jenny Stanford Publishing, 2020, 251–278.
60. H. HATAKEYAMA, E. ITO, H. AKITA, M. OISHI, Y. NAGASAKI et al.: A Ph-sensitive Fusogenic Peptide Facilitates Endosomal Escape and Greatly Enhances the Gene Silencing of Sirna-containing Nanoparticles *in vitro* and in vivo. Journal of Controlled Release (JCR), **139** (2), 127 (2009).
61. B. D. CHITHRANI, W. C. CHAN: Elucidating the Mechanism of Cellular Uptake and Removal of Protein-coated Gold Nanoparticles of Different Sizes and Shapes. Nano Letters, **7** (6), 1542 (2007).
62. C. S. KIM, N. D. LE, Y. XING, B. YAN, G. Y. TONGA et al.: The Role of Surface Functionality In Nanoparticle Exocytosis. Adv Healthc Mater, **3** (8), 1200 (2014).
63. L. BABES, B. DENIZOT, G. TANGUY, J. J. LE JEUNE, P. JALLET: Synthesis of Iron Oxide Nanoparticles Used as MRI Contrast Agents: a Parametric Study. J Colloid Interface Sci, **212** (2), 474 (1999).
64. M. E. KOOI, V. C. CAPPENDIJK, K. B. CLEUTJENS, A. G. KESSELS, P. J. KITSLAAR et al.: Accumulation of Ultrasmall Superparamagnetic Particles of Iron Oxide in Human Atherosclerotic Plaques Can Be Detected by *in vivo* Magnetic Resonance Imaging. Circulation. **107** (19), 2453 (2003).
65. A. SINGH, S.K. SAHOO: Magnetic Nanoparticles: a Novel Platform for Cancer Theranostics. Drug Discov Today, **19** (4), 474 (2014).
66. D. K. CHATTERJEE, P. DIAGARADJANE, S. KRISHNAN: Nanoparticle-mediated Hyperthermia in Cancer Therapy. Ther Deliv, **2** (8), 1001 (2011).
67. C. SUN, C. FANG, Z. STEPHEN, O. VEISEH, S. HANSEN et al.: Tumor-targeted Drug Delivery and MRI Contrast Enhancement by Chlorotoxin-conjugated Iron Oxide Nanoparticles. 2008, 495–505.
68. X. WANG, X. XING, B. ZHANG, F. LIU, Y. CHENG, D. SHI: Surface Engineered Antifouling Optomagnetic Spions for Bimodal Targeted Imaging of Pancreatic Cancer Cells. Int J Nanomed, **9**, 1601 (2014).
69. M. S. KHAN, G. D. VISHAKANTE, H. SIDDARAMAIAH: Gold Nanoparticles: a Paradigm Shift in Biomedical Applications. Adv Colloid Interface Sci, **199**, 44 (2013).
70. J. LI, S. GUPTA, C. LI: Research Perspectives: Gold Nanoparticles in Cancer Theranostics. Quantitative Imaging in Medicine And Surgery (QIMS), **3** (6), 284 (2013).
71. B. KANG, M. A. MACKEY, M. A. El-SAYED: Nuclear Targeting of Gold Nanoparticles in Cancer Cells Induces DNA Damage, Causing Cytokinesis Arrest and Apoptosis. J Am Chem Soc, **132** (5), 1517 (2010).
72. B. D. BUSBEE, S. O. OBARE, C. J. MURPHY: An Improved Synthesis of High-Aspect-ratio Gold Nanorods. Adv Mater, **15** (5), 414 (2003).

73. P. K. JAIN, K. S. LEE, I. H. El-SAYED, M. A. El-SAYED: Calculated Absorption and Scattering Properties of Gold Nanoparticles of Different Size, Shape, and Composition: Applications in Biological Imaging and Biomedicine. J Phys Chem B, **110** (14), 7238 (2006).
74. A. K. SAHOO, S. BANERJEE, S. S. GHOSH, A. CHATTOPADHYAY: Simultaneous RGB Emitting Au Nanoclusters in Chitosan Nanoparticles for Anticancer Gene Theranostics. ACS Appl Mater Interfaces, **6** (1), 712 (2014).
75. W. NGWA, R. KUMAR, S. SRIDHAR, H. KORIDECK, P. ZYGMANSKI et al.: Targeted Radiotherapy with Gold Nanoparticles: Current Status and Future Perspectives. Nanomed, **9** (7), 1063 (2014).
76. J. L. ELECHIGUERRA, J. L. BURT, J. R. MORONES, A. CAMACHO-BRAGADO, X. GAO, H. H. LARA et al.: Interaction of Silver Nanoparticles with HIV-1. J Nanobiotechnol, **3**, 6 (2005).
77. S. BOCA-FARCAU, M. POTARA, T. SIMON, A. JUHEM, P. BALDECK, S. ASTILEAN: Folic Acid-conjugated, SERS-labeled Silver Nanotriangles for Multimodal Detection and Targeted Photothermal Treatment on Human Ovarian Cancer Cells. Mol Pharm, **11** (2), 391 (2014).
78. Z. A. NIMA, M. MAHMOOD, Y. XU, T. MUSTAFA, F. WATANABE et al.: Circulating Tumor Cell Identification by Functionalized Silver-Gold Nanorods with Multicolor, Super-enhanced SERS and Photothermal Resonances. Sci Rep, **4** (1), 1 (2014).
79. J. W. RASMUSSEN, E. MARTINEZ, P. LOUKA, D. G. WINGETT: Zinc Oxide Nanoparticles for Selective Destruction of Tumor Cells and Potential for Drug Delivery Applications. Expert Opin Drug Deliv, **7** (9), 1063 (2010).
80. S. K. SHARMA, P. K. PUJARI, K. SUDARSHAN, D. DUTTA, M. MAHAPATRA et al.: Positron Annihilation Studies in ZnO Nanoparticles. Solid State Commun, **149** (13–14), 550 (2009).
81. H. HONG, J. SHI, Y. YANG, Y. ZHANG, J. W. ENGLE et al.: Cancer-targeted Optical Imaging with Fluorescent Zinc Oxide Nanowires. Nano Lett, **11** (9), 3744 (2011).
82. H. SHARMA et al.: Development and Characterization of Metal Oxide Nanoparticles for the Delivery of Anticancer Drug. Artif Cells Nanomed Biotechnol, (2014).
83. C. LI, C. LAI, Q. QIU, X. LUO, L. HU et al.: Dual-ligand Modification of Pegylated Liposomes Used for Targeted Doxorubicin Delivery to Enhance Anticancer Efficacy. AAPS Pharmscitech, **20** (5), 1 (2019).
84. A. N. LUKYANOV, T. A. ELBAYOUMI, A. R. CHAKILAM, V. P. TORCHILIN: Tumor-targeted Liposomes: Doxorubicin-loaded Long-circulating Liposomes Modified with Anti-cancer Antibody. Journal of Controlled Release (JCR), **100** (1), 135 (2004).
85. J. W. BULTE, T. DOUGLAS, B. WITWER, S. C. ZHANG, E. STRABLE et al.: Magnetodendrimers Allow Endosomal Magnetic Labeling and *in vivo* Tracking of Stem Cells. Nat Biotechnol, **19** (12), 1141 (2001).
86. T. M. FAHMY, P. M. FONG, J. PARK, T. CONSTABLE, W. M. SALTZMAN: Nanosystems for Simultaneous Imaging and Drug Delivery to T Cells. AAPS J, **9** (2), E171 (2007).
87. M. GARLEY, E. JABŁOŃSKA, D. DĄBROWSKA: Nets in Cancer. Tumor Biology, **37** (11), 14355 (2016).
88. M. K. BRENNER, H. E. HESLOP: Adoptive T Cell Therapy of Cancer. Curr Opin Immunol, **22** (2), 251 (2010).
89. M. E. DUDLEY, J. R. WUNDERLICH, P. F. ROBBINS, J. C. YANG, P. HWU et al.: Cancer Regression and Autoimmunity in Patients after Clonal Repopulation with Antitumor Lymphocytes. Science, **298** (5594), 850 (2002).
90. H. DEWITTE, B. GEERS, S. LIANG, U. HIMMELREICH, J. DEMEESTER et al.: Design and Evaluation of Theranostic Perfluorocarbon Particles for Simultaneous Antigen-loading and 19F-MRI Tracking of Dendritic Cells. Journal of Controlled Release (JCR), **169** (1–2), 141 (2013).
91. F. O. NESTLE, J. BANCHEREAU, D. HART: Dendritic Cells: on the Move from Bench to Bedside. Nat Med, **7** (7), 761 (2001).

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