Nanomed Res J 8(2):127-140, Spring 2023

REVIEW ARTICLE

The most common nanostructures as a contrast agent in medical imaging

Mohamad Ghazanfari Hashemi[1], Marjan Gholami[2], Maryam Alaei[3], Maede Ghazanfari Hashemi[4], Seyedeh Nooshin Miratashi Yazdi[5*], Vahid Talebi[6], Helia Helali[7]

[1] Department of Radiology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Pharmacy, Islamic Azad University Pharmaceutical Sciences Branch, Tehran, Iran

[3] School of Medicine, Shahid Beheshti Medical University, Tehran, Iran

[4] School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

[5] Advanced Diagnostic and Interventional Radiology Research Center (ADIR),Tehran University of Medical Sciences, Tehran, Iran

[6] Department of Radiology, Cancer institute, Tehran University of Medical Sciences, Tehran, Iran

[7] Department of Psychiatry, School of Medicine, Shahid Beheshti Medical University, Tehran, Iran

ARTICLE INFO

Article History:
Received 27 Jan 2023
Accepted 19 Apr 2023
Published 01 May 2023

Keywords:
Conventional contrast limitations
Nano technology
Nanocarrier

ABSTRACT

The differentiation of certain structures from nearby tissues during medical imaging requires a sufficient amount of signals from the targeted area. The limitations of conventional contrast agents prevent the possibility of quick and accurate diagnosis of some cases and cause many problems for the patients and society. However, most of these restrictions can be surpassed through the unique physico-chemical characteristic nanotechnologyology and nano structures. Nanocarriers are abled to take the role of contrast agents or even provide the efficient delivery of these agents as carriers, while the capability of nanostructures in facilitating the simultaneous transportation of diagnostic and therapeutic agents is also undeniable. Thanks to the modern application of nanotechnology, it is possible to perform the targeted distribution of diagnostic and therapeutic agents to the desired locations. The status of in vivo surveillance and targeting efficiency can be improved by exploiting the potential benefits of nanoparticles and therefore, it is quiet expected to witness interesting characteristics from nanocarrier imaging agents for the diagnosis and staging of different diseases. This work presents a summary on the most common contrast agent nanostructures in medical imaging.

How to cite this article
Ghazanfari Hashemi M., Gholami M., Alaei M., Ghazanfari Hashemi M., Miratashi Yazdi S.N., Talebi V., Helali H. The most common nanostructures as a contrast agent in medical imaging. Nanomed Res J, 2023; 8(2): 127-140. DOI: 10.22034/nmrj.2023.02.002

INTRODUCTION

The intuitive and visual interface of imaging technic has led to its wide employment in both bio- and medical fields under the objective of facilitating the early detection and diagnosis of diseases [1]. The ongoing significant advancements in medical imaging is attributed to the improved chemistry of imaging probes and the enhanced engineering of imaging tools. Among the main goals of these projects, it is particularly intended to improve disease diagnosis and, by extension, prognosis by providing surveillance routes into tissue frameworks, dispersal of specific cell types, and even cell performance and position in real time[2]. Accordingly, great investments were made on biomedical imaging methods with the hope of finding access to molecular and cellular images for improving the quality of analysis and diagnosis. These attempts led to the emergence of the

* Corresponding Author Email: *N_miratashi@yahoo.com*

brand-new field of "molecular imaging" (MI) that integrates molecular biology and in vivo imaging and follows the objective of exploiting spectral data to track and analyze biological processes in living subjects. In contrast to the method of biopsy in providing similar information, the non-invasive manner of imaging technic in gathering data through real time has paved the way towards consecutive and longitudinal surveillances. The novel approach of MI can enable the quantification of molecular alterations related to the beginning and progression of pathologic conditions, while offering the chance of conducting advanced diagnosis and prognosis in challenging illnesses such as cancer. Among the other utilizations of this technic, one can refer to the provided possibility of studying biological procedures in living subjects and assessing therapeutic responses. X-ray computed tomography (CT), optical imaging (OI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), ultrasound, and magnetic resonance imaging are some of examples of traditional MI modalities (MRI) [3-7].

Such goals can be accomplished through a variety of imaging techniques that implicate diverse advantages and disadvantages. For instance, high sensitivity and spatial resolution are included among the features of optical imaging with scale resolution in a sub-micrometer range of absorption. However, the tissue component scattering properties are limited by the depth of penetration into the tissue, which is often less than 1 cm. One proton Similarly, the extreme sensitivity of radionuclide PET for emission tomography-based imaging technic is constrained by its spatial resolution. Furthermore, the relatively insensitive imaging approaches of CT scans and magnetic resonance imaging (MRI) are restricted in terms of sensitivity and specificity, while the interpretation of their scans lesions in regular applications is adversely reliant on clinical context. [2, 6].

Significant inherent disparity is the determining factor for distinguishing bones from their surrounding tissues under normal conditions, which is however ineffective in the case of malignancies and the normal organs or soft tissues similar to muscles and fat. The utilization of contrast agents by radiologists is a common method for procuring constructional, functional, and/or molecular data for diagnosing the illness of patients, since the in vivo scattering of contrast agent is contingent on the patient's physiological feature and the agent's qualities. [1, 8, 9].

The currently used enhancers, known as exogenous contrast compounds, are based on iodine, sulphates, chelates of gadolinium, and manganese oxide. Apparently, they were progressed subsequent to testing out the preceding Gd^{3+} and Mn^{2+}based agents, respectively [10, 11]. There are a number of drawbacks to the exertion of contrast agents for increasing the sensitivity of images, which include a short-term blood half-life, inaccurate bio-dispersal, rapid clearance, a insignificant renal toxicity, and inadequate contrast in fat patients[12]. Therefore, the development of supplements with an enhancing effect on the capabilities of available tools that provide the surveillance, diagnosis, and treatment of different diseases, similar to cancer and other cases, seems to be economically and practically more viable. Similar to the popularity of manufacturing novel contrast agents for every type of modality, there is an extending rate of investment in the advancement of detectors and imaging systems with a higher sensitivity for providing the precise and successful diagnosis of particular disease etiologies[13].

The leading product in the field of designing novel contrast agents is Nanometer-scale frameworks, or "nano-structures," with the ability to transport contrast agents. The profitable and potentially transformative tools of NP-based contrast agents are exerted for upgrading the medical diagnostics of a broad range of imaging modalities similar to positron emission tomography (PET), magnetic resonance imaging (MRI), ultrasound (US), computed tomography, (CT) and single-photon emission computed tomography (SPECT). Next to containing several advantages over small molecular contrast agents, the prospective abilities of nanoparticles can benefit the improvement of in vivo surveillance and also boost the rate of effective targeting[14]. Considering the wide range of exploited nanostructures in this field[15], we presented a review on the most common contrast agent nanostructures in medical imaging.

NANOSTRUCTURES AS A CONTRAST AGENT

The rapidly growing field of nanotechnology was initially proposed in 1959 by Richard Feynman, a Nobel Prize winner, under the objective of developing products and tools at atomic, molecular, and supramolecular levels. Considering how a nanometer refers to one billionth of a meter on

the metric system, nanoparticles can be defined as small structures with diverse physical and chemical characteristics that rely on their sizes, which are ranged from 1 to 100 nm [16, 17] . The combination of ideas from engineering, chemistry, biology, medicine, and other fields led to the emergence of nanotechnology as an attempt for conducting multidisciplinary assays to comprehend and manipulate materials. There are potential benefits to the clinical exertion of this technology. Despite the focus of most researches on in vitro and in vivo cases of animal trials, a number of recent reports identified a variety of their pre-clinical and clinical implementations. Recent developments in technology demonstrated different aspects for the significance of nanoparticles in biological imaging applications [18, 19]. The exploitation of nanoparticles (NPs) in the form of modern contrast agents can provide the opportunity of performing non-invasive diagnosis with promising results. There are different reasons that support this assert, which include (a) the accommodation of surfaces that can be functionalized by one or more targeting molecules at a broad range of densities, (b) containing a plasma circulation period that can be adjusted through different arrangements of magnitude depending on their physico-chemical features, and (c) providing the option of contrast agents and drugs addition at pre-specified ratios throughout their interior areas or surfaces. These facts prove the suitability of nanoparticulates as a platform for the progression of targeted contrast agents [20, 21].

The manufacturing of these NPs platforms as contrast agents in medical imaging requires the consideration of some major parameters such as the long-duration fate, limited non-specified binding and assimilation, selective binding to designated cell surface receptors, efficient removal from body, and the slight or lack of toxic impacts on the body. The occurrence of improper bio-dispersals and incomplete clearances in the course of biological interactions throughout the body may result in toxic difficulties similar to the induction of progressive and reproductive risks, acute/chronic toxicity, immunotoxicity, and carcinogenicity. The safety of certain substances cannot be confirmed due to their in vivo degradation into highly hazardous components[22-24].

The performance of an efficient transportation to a designated target by nanoparticles relies on their significant features such as particle charge, size, framework, and hydrophilicity [25]. The accumulation and interference of contrast agent nano-materials are critically significant. Since a major proportion of particles smaller than 5.5 nm are cleared by the kidneys, it is important to ascertain the size sufficiency of applied particles in order to prevent their quick excretion by these organs. The crucial impact of particles surface characteristics next to their sizes for the uptake of RES is undeniable. According to discoveries, neutral and hydrophilic surfaces are typically less prone to opsonization and adsorption, leading to their more "stealthy" status for complement systems [23, 26-28].

In line with the capabilities of nanotechnology in diagnosing diseases, providing their concurrent treatment, and monitoring the obtained results (Figure 1), nanoparticles can also accurately distinguish and destroy the cause of illnesses (such as cancer cells) without damaging their healthy neighboring cells. The advances of nanotechnology are accelerating the progress of dual and multifunctional nanoparticles, which have challenged the dissimilarities of diagnostic and therapeutic agents. Contrast agents with the ability to deliver targeted drugs to particular receptors are an example for this statement [16]. There are also benefits offered by imaging nanoparticles that implicate nanoplatforms for the conjugation of targeted agents such as antibodies or ligands. Apparently, this approach can facilitate the in vivo visualization of single cells or complete organisms [29].

The most common contrast agent nano-structures for medical imaging

Solid lipid nanoparticles, liposomes, micelles, nanotubes, metallic nanoparticles, quantum dots, dendrimers, polymeric nanoparticles, and iodinated nanoparticles are included among the list of nano products that are being assessed as potential contrast agents for medical imaging purposes. The following section is mainly focused on the most common contrast agent nano structures in the mentioned field)involving quantum dots, gold nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs), and liposomes(.

Quantum dots

The approximately spherical products of quantum dots (QDs) are known as virtually crystalline semiconductor particles that contain

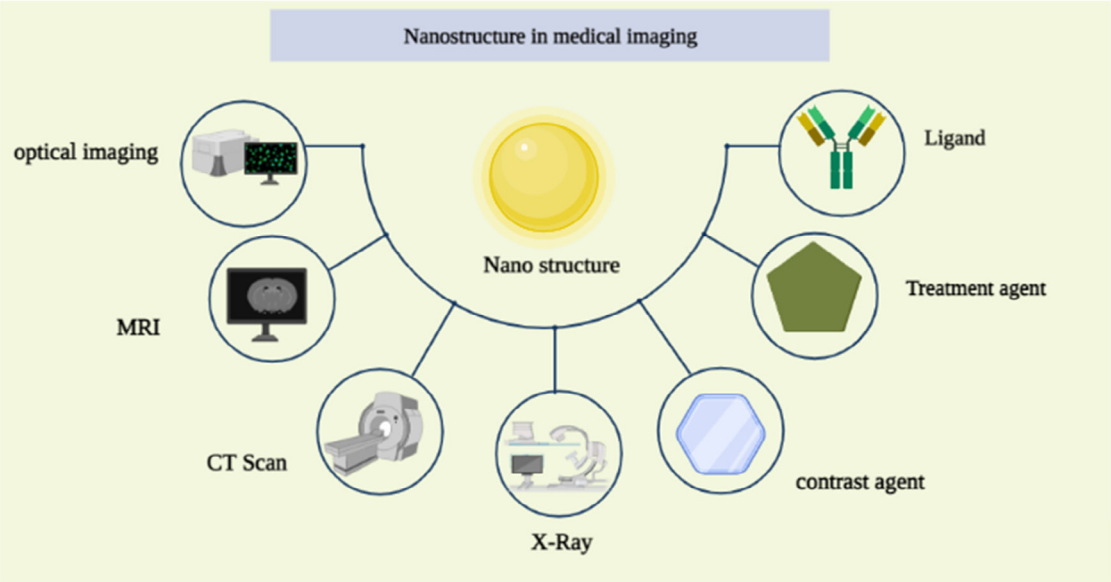

Fig. 1. Application of nanostructures in medical imaging (in the form of a contrast agent, a carrier for a diagnostic agent, a carrier for a diagnostic and therapeutic agent)

an smaller average diameter value of 10 nm along with a mass of 200–1,000 atoms, which were assessed in solar cells, digital cameras, and light-emitting diodes. A dependency on composition was observed from the band gap energy of these semiconductors, which refers to the least amount of required energy needed to raise an electron from ground state towards a higher position. The emitting of a photon causes the occurrence of a visible fluorescence as the election unwinds and moves back towards the ground state. Since the rate of band gap energy can be influenced by the particle size of applied semiconductor, the optical features of QDs can be adjusted by changing their sizes. In contrast to different fluorescent proteins and natural dyes, the exhibition of an enhanced signal brightness up to 10-100 times brighter by QDs, as well as a superior photobleaching resistance (offering long-duration stability for the probes), forced the conduction of numerous investigations on their capabilities. Moreover, several florescence colours can be produced through the concurrent excitation of a single light source [25, 30-32]. The exerted unnatural centres of quantum dots for imaging purposes are commonly acquired from cadmium or selenium and contain an inhibitory coating towards toxic impacts, while providing suitable attaching conditions for antibodies, peptides, or other moieties to determine the targeted cells or biomolecules for interacting with quantum dots [33]. Only a few special optical characteristics are ideal for in vivo imaging. As a result of confinement effects, the factor of size can arrange a precise control over the emission colour of QDs throughout the range of ultraviolet to near-infrared. This product is also practical for multiplexing due to accommodating a broad absorption band and a narrow emission band. Furthermore, the production of multimodality imaging probes can be facilitated through the large surface area of QDs that can enable the required assembly of different contrast agents. There are reports on the triumphant exertion of biocompatible QD conjugates in the cases of tumour targeting, tumour an giogenesis imaging, sentinel lymph node mapping, and metastatic cell tracking[34]. A number of quantum dots implementations in medical imaging is presented by Table 1.

Gold nanoparticles

An extensive amount of research was conducted on the performance of gold nanoparticles (AuNP) as therapeutic and contrast agents to be exploited in a variety of biomedical imaging routes. The profitable utilization of AuNP in the form of medicinal components is attributed to their inertness, biocompatibility, and simple surface modification of ligand capping. Additionally, the

Table 1. Application of QDs throughout varying medical imaging methods

Nano structure	Type of imaging method	Application	Reference
QD	fluorescence imaging	Multifunctional nanoparticle probes based on semiconductor quantum dots (QDs) for cancer targeting and imaging	[35]
109Cd -core/shell of QDs	SPECT	- long circulation half-life - stability with weak cytotoxic effects	[36]
RGD–Quantum Dot	intravital microscopy	- Real-Time Intravital Imaging	[37]
DOTA–QD–RGD	PET/NIRF imaging	- decreased probable toxicity - surpasses the tissue penetrating restrictions of optical imaging	[38]
QD	microPET	- Targeted imaging in deep tissue - Bio-dispersal of Quantum Dots in alive Mice	[39]
18F-FP-QD-RGD-BBN	PET/near-infrared fluorescence (NIRF) probe	- Dual-targeting probe for the surveillance of tumors throughout alive samples	[40]
QD	fluorescence imaging	-Sentinel lymph node mapping	[41]
QD(CdTe core, CdSe shell)	fluorescence imaging	-Sentinel Lymph Node Mapping	[22]
Self-illuminating quantum dot	luminesce imaging	-improved sensitivity in small animal imaging, accompanied by an in vivo signal-to-background	[42]
QD	Fluorescence microscopy	- Tracking metastatic tumor cell extravasation	[43]
QD	Fluorescence microscopy	- synchronous imaging and contrasted tumor vessels from perivascular cells and the matrix	[44]
64Cu-labeled QDs	Micro positron emission tomography	- Bio-dispersal of Quantum Dots in alive Mice	[45]
QD	Fluorescence microscopy	- Sensing the local chemical surrounding of cellular receptor	[46]
Compact Cysteine-Coated CdSe(ZnCdS) Quantum Dots	Fluorescence microscopy	- Biological compatibility, exceptional compactness, high fluorescent, and simple functionalization for in Vivo Applications	[47]
QD	optical imaging	- cause the production of Reactive Oxygen Species to damage the Multiple Organelle and induce Cell annihilation	[48]

other diverse traits of these particles promoted their application in biological settings, which include their uncomplicated synthesis, numerous surface functionalization probabilities, and colloidal stability, as well as having the option of using biomolecules such as peptides and antibodies for modifying the surface characteristics of GNPs [49-52]. The medicinal exertion of gold nanoparticles (AuNP) are suggested for a wide range of purposes. Despite the existing preference for bigger AuNP (>5.5 nm) due to containing a prolonged blood-circulation and accretion in sick tissues, the necessity of small AuNP (<5.5 nm) for the eliminating performances of kidney is undeniable [53].

GNPs can be created in a diverse range of shapes, sizes, and compositions that consequently result in their optical properties. Nanospheres, nanorods, nanoshells, nanocages, nanoclusters, nanoroses, and nanostars are some of the several types of employed nanostructures [54]. The therapeutic profitability of GNPs is supported by their physico-chemical qualities, while their multifaceted and forthright chemistry implement the attachment of varying biomolecules to their surfaces. Furthermore, the adjoining of diverse biopharmaceuticals similar to monoclonal antibodies, peptides, lower-molecular-weight molecules, and aptamers to the surfaces of these nanoparticles can increase the effectiveness of tumour targeting [55, 56]. Recognized as an optical phenomenon, the operation of surface plasmon resonance (SPR) relies on the interacting effects of electromagnetic waves with conduction electrons in metals, which can aid the diagnosis and curing process of varying illnesses [57, 58]. The exploitation of GNPs physicochemical features by researchers led to the design of GNP imaging probes for optical imaging, photoacoustic (PA) imaging, magnetic resonance imaging (MRI), X-ray imaging, single photon emission computed tomography (SPECT), and positron emission tomography (PET). In addition, this product can also be employed to offer molecular data and optical assistance for different kinds of malignancies. The adjustable absorbing and scattering impacts of GNPs can pave the way for a variety of imaging modalities [59-62]. Table 2 presents some of the gold nanoparticles applications in various imaging methods.

superparamagnetic iron oxide nanoparticles (SPIONs)

Throughout the category of magnetic particles, superparamagnetic iron oxide nanoparticles (SPIONs) contain an average diameter of 10 nm and proved to be capable of displaying exceptional magnetic features, which turned them into the most powerful nanostructures for various applications, especially imaging[78-80]. The core of these nanoparticles (SPIONs) is incorporated of an iron oxide while containing a hydrophilic coating; however, the core is sometimes comprised of Fe3O4 (magnetite) or -Fe2O3 (maghemite). Super para magnetism essentially serves as an activation mechanism as the magnetization vanishes upon the dispatching of external magnetic field. Next to their capability to operate as multipurpose agents, the surfaces of SPIONs are designed to perform a variety of simultaneous biomedical-related functionalities such as drug delivery, MRI contrast agents, and local heat inducement (hyperthermia). The modernly emerged technic of "molecular imaging" requires the creation of high affinity ligands and their grafting on SPIONs in order to enable the in vivo visualisation of molecular activities at cellular levels. In addition to their effectiveness as bioconjugates, there is a broad list for the clinical utilities of SPIONs that implicate the imaging of liver and spleen, inflammation, and many other physiological processes. The possibility of visualizing magnetic nanoparticles through the employment of MR imaging stands as their primary benefit; in this regard, the potential of SPIONs to create magnetic field gradients capable of changing the characteristics of proton relaxation can act as a source of contrast for MR imaging (MRI) [81-85].

The biocompatibility of SPIONs is attributable to their in vivo degradation into nontoxic iron ions, as well as their effortless spreading throughout biological mediums. In contrast to several other products, the effectiveness of contrast agent SPIONS remains unaffected by the surrounding conditions [86, 87].

The most widely exerted T2 MRI contrast agents are the Iron oxide superparamagnetic T2 contrast agents. The classical outer-sphere relaxation theory is the proper explanation for the relaxing impacts in regards to the relaxation rates of water protons throughout their diffusion in particle magnetization fields. SPIO nanoparticles were initially created as T2 agents capable of providing a dark (negative) contrast in images. The factors of colloidal stability and biocompatibility are essential prerequisites for clinical applications. Iron oxide nanoparticles are often comprised of a stabilizing coating out

Table 2. Application of Gold nanoparticles in various medical imaging methods

Nano structure	Type of imaging method	Application	Reference
PEGylated GNPs-F19 Ab	optical imaging	- selective Labeling Agents for Human Pancreatic Carcinoma Tissues	[51]
Gold nanoparticles as carriers for gadolinium chelates	MRI	- in the form of contrast agents for MRI	[63]
124I-TA-Au@AuNPs	positron emission tomography (PET)	- An efficient Nuclear Medicine Imaging Agent to traffic the Dendritic Cells	[64]
Gold half-shell coated hyaluronic acid-doxorubicin conjugate	optical imaging	- exerted in theranostic means	[65]
Erlotinib conjugated gold nanocluster enveloped magnetic iron oxide nanoparticles	optical imaging	-to image the pancreatic cancer cells	[66]
Gold nanoparticles	Photoacoustic Imaging and Plasmon Resonance	-For Selective Detection of Cancer	[67]
mesoporous silica-coated gold nanorods	optoacoustic tomography	-Detection of pancreatic tumor S	[68]
Gd(III)-Dithiolane Gold Nanoparticles	MRI	-to provide the imaging of T1-Weighted Magnetic Resonance of Pancreas	[69]
Gold nanoparticle cluster	fluorescence imaging and X-ray computed tomograph	- exerted in X-ray computed tomography–fluorescence dual-mode imaging of tumors	[70]
Gold Nanorods	optical imaging	-in the role of absorption contrast agents to non-invasively detect the arterial vascular disorders	[71]
Gold Nanoparticles	computed tomography (CT)	-Molecular CT Imaging of Cancer	[72]
Gold Nanoparticles	X-ray fluorescence (XRF) imaging	- As a radiosensitizer and a drug-delivery agent	[73]
Gold Nanoparticles	X-Ray Imaging	- X-Ray Imaging and Proton therapy Improvements	[74]
Gold nanorod	photoacoustic imaging	- Contrast agent to provide surveillance on prostate cancer	[75]
Gold nanoparticles (GNPs)	X-ray imaging	- As X-ray imaging contrast agents and radiosensitizers	[76]
Anti-CD4-targeted Gold Nanoparticles	X-ray Computed Tomography	- cause Specific Contrast enhancing effects in Peripheral Lymph Nodes	[77]

Table 3. Application of iron oxide nanoparticles throughout diverse medical imaging methods

Nano structure	Type of imaging method	Application	Reference
magnetic nanoparticles-siRNA	MRI and NIRF	-In vivo imaging of siRNA transportation and silencing at tumors	[92]
MN-anti-miR10b	PET–MRI	- delivery demonstration to metastatic lesions in a murine case of metastatic breast cancer	[93]
Cy5.5 TCL-SPION	magnetic resonance/optical	- Tumor detection in vivo	[87]
Glutathione capped hybrid ytterbium/iron oxide nanoparticles	imaging in magnetic resonance and X-ray computerized tomography	- in the form of multiplatform contrast agent at medical imaging technic	[94]
Iron Oxide Nanoparticles	Magnetic Resonance Imaging	- in vivo Tracking of Stem Cells	[95]
Iron oxide nanoparticles	Magnetic Resonance Imaging	- in the role of magnetic resonance contrast agent for imaging the tumor	[96]
64Cu-DOTA-Cy5.5-HSA-IONPs	PET/NIRF/MRI	- the precise performance of Tri-modality imaging, ex vivo assessments, and histological evaluations to assay the in vivo manner of nano-structures	[97]
Iron oxide nanoparticles	computed tomography (CT) and magnetic resonance imaging (MRI)	- In vivo imaging and quantifying the uptake and bio-dispersal of iron oxide nanoparticles	[98]
anti-PSMA antibody- iron oxide nanoparticles	magnetic resonance imaging (MRI)	- For Prostate Cancer Imaging	[99]
LHRH-conjugated Magnetic Iron Oxide Nanoparticles	magnetic resonance imaging (MRI)	- To operate in vivo MR imaging and extend the sensitivity of surveillance on metastases and disseminated cells in lymph nodes, bones and peripheral organs	[100]
PEG- iron oxide nanoparticle (IO)	MRI	- In Vivo MRI surveillance of Gliomas by Chlorotoxin-Conjugated Superparamagnetic Nanoprobes	[101]
RGD-Conjugated Superparamagnetic Iron Oxide	MRI	- Specific Targeting of Tumor Angiogenesis	[102]
iron oxide nanoparticles	MRI	- MR molecular imaging of Her-2/neu receptor in breast cancer cells	[103]
Monoclonal antibody A7-superparamagnetic iron oxide	MR	- in the form of contrast agent for MR imaging of rectal carcinoma	[104]
RGD-4C- Fn - Ferrimagnetic Ferritin Cage Nanoparticles	optical imaging	- As a multi-performance nanoscale container for concurrent iron oxide loading and cell-particular targeting	[105]

Table 4. Application of Liposomes in various medical imaging methods

Nano structure	Type of imaging method	Application	Reference
Cetuximab-labeled liposomes containing near-infrared probe	optical imaging	- For imaging and diagnostic purposes	[117]
Liposomes with 64Cu	PET	- For molecular imaging and monitoring drug transportation	[118]
liposomes containing iohexol and gadoteridol	CT	- Quantitative CT imaging of the spatial and temporal dispersal of liposomes	[119]
Liposomal-Iodine	CT	- Atherosclerotic plaques in a mouse sample by exerting a liposomal-Iodine nanoparticle contrast agent	[120]
Liposomal-Iodine	CT	- As contrast agent in companion dogs with naturally induced cancer	[121]
Liposomal-Iodine	CT	-As a contrast agent for the preclinical CT of mice	[122]
Liposomes- Gd- KCCYSL peptide	MRI	- As therapeutic and diagnostic agents for targeting agents for HER-2-overexpressing tumor cells	[123]
liposomes -manganese-52	PET	- in the role of a contrast agent	[124]
Liposomes- ^{89} Zr	PET	- For PET-trackable tumor-targeted theranostics	[125]
64Cu-Liposome	PET	- Drug transportation to tumors and predicting the feedbacks to cancer	[126]
Liposomes - DOXIL -Mn(oxinate)	PET	- For labelling and tracking DOXIL in vivo	[127]
Liposomes- indocyanine green (ICG)	optical imaging	- As the light sensitizing compound	[128]
Glycosylated liposomes loading carbon dots	optical imaging	- for the Selective tracking and efficient labelling of cancer cells	[129]
Liposomal Quantum Dots	optical imaging	- Via monocytes for inflamed tissues imaging	[130]
Perfluorooctyl bromide & indocyanine green co-loaded nanoliposomes	optical imaging	- to perform upgraded multimodal imaging-guided phototherapy	[131]
Bio-inspired melanin-based nanoliposomes (Lip-Mel)	PA/ MR	- fabricated theranostic agents for concurrent photoacoustic (PA) imaging- and T1-weighted magnetic resonance (MR) imaging-guided photothermal ablation of tumors	[132]
Liposom	photoacoustic inflammation imaging	-As nanoprobe functionality in photoacoustic inflammation imaging and tumor theranostics through an in vivo chromogenic trial	[133]
Liposome-Conjugated Mesoporous Silica Nanoparticles	NIRFI/PAI	-Theranostic nanoplatform for imaging-guided synergistic cancer therapy	[134]

of dextran, citrate, or PEG along with a core that contains one or more magnetic crystallites [80, 88-91]. Table 3 demonstrates some of the iron oxide nanoparticles utilizations in different imaging methods.

Liposomes

The suspension of numerous individual lipids and their mixtures in an aqueous state results in the spontaneous formation of bi layered structures as the hydrophobic sections of their molecules turn inwards followed by the exposure of hydrophilic areas to their aqueous surrounding. These materials are referred to as liposomes[106-108], which are concentric bleeder vesicles with an aqueous volume that is surrounded by a membranous lipid bilayer. Typically, bilayer lipid membranes are comprised of phospholipids with a hydrophobic ending and a hydrophilic head. The volume and type of lipid components can significantly impact the spherical or multilayered spherical framework of synthesized liposomes. The production of bilayer lipids creates an equivalent amount of water chambers while containing a concentric pattern[109, 110].

The promising stance of liposomes as drugs and diagnostic agent carriers in regards to the physico-chemical characteristics of the drug is attributable to the following reasons: capable of trapping any drug or diagnostic agent in their internal water compartment or membrane, offering complete biocompatibility, providing protection for the incorporated pharmaceuticals within the liposomes from the deactivating effects of outer circumstances without inducing any unwanted side-reactions, and offering a distinct route for the transportation of pharmaceuticals to cells or even discrete cellular compartments. The appending of components to a lipid mixture can simply alter the size, charge, and surface characteristics of liposomes [111, 112]. Numerous investigations were conducted on the encapsulation of liposomes for designing suitable transportation systems capable of entrapping unstable compounds. The existing antimicrobial, antioxidant, hydrophobic, and hydrophilic chemicals in the invertebrate components of liposome particles can be exploited for preventing compositions and functioning disruption of targeted delivery systems[113, 114].

Thin-film hydration, reverse-phase evaporation, ethanol injection route, microfluidics technics, and other methods can be used for the formation of liposomes. The incapability of liposomes in functioning as an imaging probe can be resolved through the incorporation of imaging probes in order to provide imaging properties. The addition of probes in the course or subsequent to the production of liposomes, referred to as passive and active loadings respectively, can aid the creation of liposome-based probes. Despite the possibility of performing passive loading for nearly every type of probes, yet there is a significant variance in encapsulation competence based on the probes framework and the formulation of liposome. However, the initial step of active loading process is the formation of liposomes that is followed by loading of probes. This approach is commonly more complex and useful for a restricted number of probes, which is however accompanied by a high encapsulation effectiveness of greater than 90% that is caused by the strong contact between the produced liposomes and probes [115, 116]. Table 4 displays some of the liposomes applications in various imaging methods.

CONCLUSIONS

Nanostructures are exerted for filling the role of contrast agents, as well as the delivery carriers of contrast agents and the carrier of concurrent delivery of diagnostic and therapeutic agents. The designed imaging probes by nanotechnology can be used for the diagnosis of various diseases. The application of contrast agents nano structures can overcome the limitations of conventional contrast agents, which can also provide guidance for therapy-based probes. The usage of these products can extend the rates of cellular consumption and target tissue accretion through the routes of passive and active targeting. The implementation of nanotechnology in medical diagnostics can open new horizons for performing the rapid diagnosis of many diseases.

CONFLICT OF INTEREST

None

REFERENCES

1. He, W., K. Ai, and L. Lu, Nanoparticulate X-ray CT contrast agents. Science China Chemistry, 2015. 58(5): p. 753-760. https://doi.org/10.1007/s11426-015-5351-8
2. Faulkner, S. and N.J. Long, Radiopharmaceuticals for imaging and therapy. Dalton Transactions, 2011. 40(23): p. 6067-6067. https://doi.org/10.1039/c1dt90067f
3. Huang, Y., et al., Biomedical nanomaterials for imaging-guided cancer therapy. Nanoscale, 2012. 4(20): p. 6135-6149. https://doi.org/10.1039/c2nr31715j
4. James, M.L. and S.S. Gambhir, A molecular imaging primer: modalities, imaging agents, and applications. Physiological

reviews, 2012. 92(2): p. 897-965. https://doi.org/10.1152/physrev.00049.2010
5. Kherlopian, A.R., et al., A review of imaging techniques for systems biology. BMC systems biology, 2008. 2(1): p. 1-18. https://doi.org/10.1186/1752-0509-2-74
6. Massoud, T.F. and S.S. Gambhir, Molecular imaging in living subjects: seeing fundamental biological processes in a new light. Genes & development, 2003. 17(5): p. 545-580. https://doi.org/10.1101/gad.1047403
7. Rudin, M. and R. Weissleder, Molecular imaging in drug discovery and development. Nature reviews Drug discovery, 2003. 2(2): p. 123-131. https://doi.org/10.1038/nrd1007
8. Cormode, D.P., et al., Modified natural nanoparticles as contrast agents for medical imaging. Advanced drug delivery reviews, 2010. 62(3): p. 329-338. https://doi.org/10.1016/j.addr.2009.11.005
9. Bremer, C., V. Ntziachristos, and R. Weissleder, Optical-based molecular imaging: contrast agents and potential medical applications. European radiology, 2003. 13(2): p. 231-243. https://doi.org/10.1007/s00330-002-1610-0
10. Du, Y., et al., Design of superparamagnetic nanoparticles for magnetic particle imaging (MPI). International journal of molecular sciences, 2013. 14(9): p. 18682-18710. https://doi.org/10.3390/ijms140918682
11. Lee, S.H., et al., Paramagnetic inorganic nanoparticles as T1 MRI contrast agents. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 2014. 6(2): p. 196-209. https://doi.org/10.1002/wnan.1243
12. Razi, M., et al., The peep of nanotechnology in reproductive medicine: a mini-review. International Journal of Medical Laboratory, 2015. 2(1): p. 1-15.
13. Krupinski, E.A. and Y. Jiang, Anniversary paper: evaluation of medical imaging systems. Medical physics, 2008. 35(2): p. 645-659. https://doi.org/10.1118/1.2830376
14. Vivero-Escoto, J.L., R.C. Huxford-Phillips, and W. Lin, Silica-based nanoprobes for biomedical imaging and theranostic applications. Chemical Society Reviews, 2012. 41(7): p. 2673-2685. https://doi.org/10.1039/c2cs15229k
15. Janib, S.M., A.S. Moses, and J.A. MacKay, Imaging and drug delivery using theranostic nanoparticles. Advanced drug delivery reviews, 2010. 62(11): p. 1052-1063. https://doi.org/10.1016/j.addr.2010.08.004
16. Gunasekera, U.A., Q.A. Pankhurst, and M. Douek, Imaging applications of nanotechnology in cancer. Targeted Oncology, 2009. 4(3): p. 169-181. https://doi.org/10.1007/s11523-009-0118-9
17. Sanvicens, N. and M.P. Marco, Multifunctional nanoparticles-properties and prospects for their use in human medicine. Trends in biotechnology, 2008. 26(8): p. 425-433. https://doi.org/10.1016/j.tibtech.2008.04.005
18. Morais, M.G.d., et al., Biological applications of nanobiotechnology. Journal of nanoscience and nanotechnology, 2014. 14(1): p. 1007-1017. https://doi.org/10.1166/jnn.2014.8748
19. Wang, X., et al., Application of nanotechnology in cancer therapy and imaging. CA: a cancer journal for clinicians, 2008. 58(2): p. 97-110. https://doi.org/10.3322/CA.2007.0003
20. Sajja, H.K., et al., Development of multifunctional nanoparticles for targeted drug delivery and noninvasive imaging of therapeutic effect. Current drug discovery technologies, 2009. 6(1): p. 43-51. https://doi.org/10.2174/157016309787581066
21. Yang, X., et al., cRGD-functionalized, DOX-conjugated, and 64Cu-labeled superparamagnetic iron oxide nanoparticles for targeted anticancer drug delivery and PET/MR imaging. Biomaterials, 2011. 32(17): p. 4151-4160. https://doi.org/10.1016/j.biomaterials.2011.02.006
22. Frangioni, J.V., et al., Sentinel lymph node mapping with type-II quantum dots, in Quantum Dots. 2007, Springer. p. 147-159. https://doi.org/10.1385/1-59745-369-2:147
23. Sun, C., J.S. Lee, and M. Zhang, Magnetic nanoparticles in MR imaging and drug delivery. Advanced drug delivery reviews, 2008. 60(11): p. 1252-1265. https://doi.org/10.1016/j.addr.2008.03.018
24. Surendiran, A., et al., Novel applications of nanotechnology in medicine. Indian Journal of Medical Research, 2009. 130(6).
25. Fountaine, T.J., et al., Multispectral imaging of clinically relevant cellular targets in tonsil and lymphoid tissue using semiconductor quantum dots. Modern Pathology, 2006. 19(9): p. 1181-1191. https://doi.org/10.1038/modpathol.3800628
26. Farajzadeh, R., et al., Nano-encapsulated metformin-curcumin in PLGA/PEG inhibits synergistically growth and hTERT gene expression in human breast cancer cells. Artificial cells, nanomedicine, and biotechnology, 2018. 46(5): p. 917-925. https://doi.org/10.1080/21691401.2017.1347879
27. Mohammadian, F., et al., Effects of chrysin-PLGA-PEG nanoparticles on proliferation and gene expression of miRNAs in gastric cancer cell line. Iranian journal of cancer prevention, 2016. 9(4). https://doi.org/10.17795/ijcp-4190
28. Mohammadian, F., et al., Upregulation of Mir-34a in AGS gastric cancer cells by a PLGA-PEG-PLGA chrysin nano formulation. Asian Pacific Journal of Cancer Prevention, 2016. 16(18): p. 8259-8263. https://doi.org/10.7314/APJCP.2015.16.18.8259
29. Kumar, R., et al., Covalently dye-linked, surface-controlled, and bioconjugated organically modified silica nanoparticles as targeted probes for optical imaging. ACS nano, 2008. 2(3): p. 449-456. https://doi.org/10.1021/nn700370b
30. Nagasaki, Y., et al., Novel Molecular Recognition via Fluorescent Resonance Energy Transfer Using a Biotin–PEG/Polyamine Stabilized CdS Quantum Dot. Langmuir, 2004. 20(15): p. 6396-6400. https://doi.org/10.1021/la036034c
31. Rhyner, M.N., et al., Quantum dots and multifunctional nanoparticles: new contrast agents for tumor imaging. 2006. https://doi.org/10.2217/17435889.1.2.209
32. Smith, A.M., et al., Bioconjugated quantum dots for in vivo molecular and cellular imaging. Advanced drug delivery reviews, 2008. 60(11): p. 1226-1240. https://doi.org/10.1016/j.addr.2008.03.015
33. Baker, M., Nanotechnology imaging probes: smaller and more stable. Nature methods, 2010. 7(12): p. 957-962. https://doi.org/10.1038/nmeth1210-957
34. Bentolila, L.A., Y. Ebenstein, and S. Weiss, Quantum dots for in vivo small-animal imaging. Journal of Nuclear Medicine, 2009. 50(4): p. 493-496. https://doi.org/10.2967/jnumed.108.053561
35. Gao, X., et al., In vivo cancer targeting and imaging with semiconductor quantum dots. Nature biotechnology, 2004. 22(8): p. 969-976. https://doi.org/10.1038/nbt994
36. Cai, W. and H. Hong, In a "nutshell": intrinsically radio-labeled quantum dots. American Journal of Nuclear Medicine and Molecular Imaging, 2012. 2(2): p. 136.
37. Smith, B.R., et al., Real-time intravital imaging of RGD–quantum dot binding to luminal endothelium in mouse tumor neovasculature. Nano letters, 2008. 8(9): p. 2599-2606. https://doi.org/10.1021/nl080141f
38. Cai, W., et al., Dual-function probe for PET and near-infrared fluorescence imaging of tumor vasculature. Journal of Nuclear Medicine, 2007. 48(11): p. 1862-1870. https://doi.org/10.2967/jnumed.107.043216
39. Schipper, M.L., et al., microPET-based biodistribution of quantum dots in living mice. Journal of Nuclear Medicine,

2007. 48(9): p. 1511-1518. https://doi.org/10.2967/jnumed.107.040071
40. Hu, K., et al., In vivo cancer dual-targeting and dual-modality imaging with functionalized quantum dots. Journal of Nuclear Medicine, 2015. 56(8): p. 1278-1284. https://doi.org/10.2967/jnumed.115.158873
41. Kim, S., et al., Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. Nature biotechnology, 2004. 22(1): p. 93-97. https://doi.org/10.1038/nbt920
42. So, M.-K., et al., Self-illuminating quantum dot conjugates for in vivo imaging. Nature biotechnology, 2006. 24(3): p. 339-343. https://doi.org/10.1038/nbt1188
43. Voura, E.B., et al., Tracking metastatic tumor cell extravasation with quantum dot nanocrystals and fluorescence emission-scanning microscopy. Nature medicine, 2004. 10(9): p. 993-998. https://doi.org/10.1038/nm1096
44. Stroh, M., et al., Quantum dots spectrally distinguish multiple species within the tumor milieu in vivo. Nature medicine, 2005. 11(6): p. 678-682. https://doi.org/10.1038/nm1247
45. Schipper, M.L., et al., Particle size, surface coating, and PEGylation influence the biodistribution of quantum dots in living mice. Small, 2009. 5(1): p. 126-134. https://doi.org/10.1002/smll.200800003
46. Liu, W., et al., Compact biocompatible quantum dots functionalized for cellular imaging. Journal of the American Chemical Society, 2008. 130(4): p. 1274-1284. https://doi.org/10.1021/ja076069p
47. Liu, W., et al., Compact cysteine-coated CdSe (ZnCdS) quantum dots for in vivo applications. Journal of the American Chemical Society, 2007. 129(47): p. 14530-14531. https://doi.org/10.1021/ja073790m
48. Lovrić, J., et al., Unmodified cadmium telluride quantum dots induce reactive oxygen species formation leading to multiple organelle damage and cell death. Chemistry & biology, 2005. 12(11): p. 1227-1234. https://doi.org/10.1016/j.chembiol.2005.09.008
49. Naha, P.C., P. Chhour, and D.P. Cormode, Systematic in vitro toxicological screening of gold nanoparticles designed for nanomedicine applications. Toxicology in Vitro, 2015. 29(7): p. 1445-1453. https://doi.org/10.1016/j.tiv.2015.05.022
50. Thakor, A., et al., Gold nanoparticles: a revival in precious metal administration to patients. Nano letters, 2011. 11(10): p. 4029-4036. https://doi.org/10.1021/nl202559p
51. Eck, W., et al., PEGylated gold nanoparticles conjugated to monoclonal F19 antibodies as targeted labeling agents for human pancreatic carcinoma tissue. ACS nano, 2008. 2(11): p. 2263-2272. https://doi.org/10.1021/nn800429d
52. Li, X., et al., Nanostructured scaffolds for bone tissue engineering. Journal of biomedical materials research Part A, 2013. 101(8): p. 2424-2435. https://doi.org/10.1002/jbm.a.34539
53. Cheheltani, R., et al., Tunable, biodegradable gold nanoparticles as contrast agents for computed tomography and photoacoustic imaging. Biomaterials, 2016. 102: p. 87-97. https://doi.org/10.1016/j.biomaterials.2016.06.015
54. Banstola, A., et al., Current applications of gold nanoparticles for medical imaging and as treatment agents for managing pancreatic cancer. Macromolecular Research, 2018. 26(11): p. 955-964. https://doi.org/10.1007/s13233-018-6139-4
55. Lu, W., Xiong c., Zhang G., Huang Q., Zhang r., Zhang JZ, Li c. clin. cancer res, 2009. 15: p. 876-886. https://doi.org/10.1158/1078-0432.CCR-08-1480
56. Lu, W., et al., II, Huang Q, Gelovani JG and Li C: Tumor site-specific silencing of NF-kappaB p65 by targeted hollow gold nanosphere-mediated photothermal transfection. Cancer Res, 2010. 70(8): p. 3177-3188. https://doi.org/10.1158/0008-5472.CAN-09-3379
57. Liu, L., N. Xia, and J. Wang, Potential applications of SPR in early diagnosis and progression of Alzheimer's disease. Rsc Advances, 2012. 2(6): p. 2200-2204. https://doi.org/10.1039/c2ra00667g
58. Souto, D.E., et al., A brief review on the strategy of developing SPR-based biosensors for application to the diagnosis of neglected tropical diseases. Talanta, 2019. 205: p. 120122. https://doi.org/10.1016/j.talanta.2019.120122
59. England, C.G., et al., Molecular imaging of pancreatic cancer with antibodies. Molecular pharmaceutics, 2016. 13(1): p. 8-24. https://doi.org/10.1021/acs.molpharmaceut.5b00626
60. Guo Y., et al., Photothermal ablation of pancreatic cancer cells with hybrid iron-oxide core gold-shell nanoparticles. International journal of nanomedicine, 2013: p. 3437-3446. https://doi.org/10.2147/IJN.S47585
61. Hainfeld, J., et al., Gold nanoparticles: a new X-ray contrast agent. The British journal of radiology, 2006. 79(939): p. 248-253. https://doi.org/10.1259/bjr/13169882
62. Houghton, J.L., et al., Site-specifically labeled CA19. 9-targeted immunoconjugates for the PET, NIRF, and multimodal PET/NIRF imaging of pancreatic cancer. Proceedings of the National Academy of Sciences, 2015. 112(52): p. 15850-15855. https://doi.org/10.1073/pnas.1506542112
63. Debouttière, P.J., et al., Design of gold nanoparticles for magnetic resonance imaging. Advanced Functional Materials, 2006. 16(18): p. 2330-2339. https://doi.org/10.1002/adfm.200600242
64. Lee, S.B., et al., Engineering of radioiodine-labeled gold core-shell nanoparticles as efficient nuclear medicine imaging agents for trafficking of dendritic cells. ACS applied materials & interfaces, 2017. 9(10): p. 8480-8489. https://doi.org/10.1021/acsami.6b14800
65. Kim, K.S., et al., Gold half-shell coated hyaluronic acid-doxorubicin conjugate micelles for theranostic applications. Macromolecular Research, 2012. 20(3): p. 277-282. https://doi.org/10.1007/s13233-012-0062-x
66. Nebu, J., et al., Erlotinib conjugated gold nanocluster enveloped magnetic iron oxide nanoparticles-A targeted probe for imaging pancreatic cancer cells. Sensors and Actuators B: Chemical, 2018. 257: p. 1035-1043. https://doi.org/10.1016/j.snb.2017.11.017
67. Mallidi, S., et al., Multiwavelength photoacoustic imaging and plasmon resonance coupling of gold nanoparticles for selective detection of cancer. Nano letters, 2009. 9(8): p. 2825-2831. https://doi.org/10.1021/nl802929u
68. Khanal, A., et al., Detection of pancreatic tumors in vivo with tumor targeted mesoporous silica-coated gold nanorods by multispectral optoacoustic tomography. Nano Res., 2015. 8: p. 3864-3877. https://doi.org/10.1007/s12274-015-0886-8
69. Holbrook, R.J., et al., Gd (III)-dithiolane gold nanoparticles for T 1-weighted magnetic resonance imaging of the pancreas. Nano letters, 2016. 16(5): p. 3202-3209. https://doi.org/10.1021/acs.nanolett.6b00599
70. Hayashi, K., et al., Gold nanoparticle cluster-plasmon-enhanced fluorescent silica core-shell nanoparticles for X-ray computed tomography-fluorescence dual-mode imaging of tumors. Chemical communications, 2013. 49(46): p. 5334-5336. https://doi.org/10.1039/c3cc41876f
71. Ankri, R., et al., Gold nanorods as absorption contrast agents for the noninvasive detection of arterial vascular disorders based on diffusion reflection measurements. Nano letters, 2014. 14(5): p. 2681-2687. https://doi.org/10.1021/nl500573d
72. Popovtzer, R., et al., Targeted gold nanoparticles enable molecular CT imaging of cancer. Nano letters, 2008. 8(12): p. 4593-4596. https://doi.org/10.1021/nl8029114
73. Jung, S., et al., Dynamic in vivo X-ray fluorescence imaging of gold in living mice exposed to gold nanoparticles. IEEE transactions on medical imaging, 2019. 39(2): p. 526-533. https://doi.org/10.1109/TMI.2019.2932014

74. Torrisi, L., N. Restuccia, and I. Paterniti, Gold nanoparticles by laser ablation for X-ray imaging and protontherapy improvements. Recent patents on Nanotechnology, 2018. 12(1): p. 59-69. https://doi.org/10.2174/1872210511666170609093433
75. Agarwal, A., et al., Targeted gold nanorod contrast agent for prostate cancer detection by photoacoustic imaging. Journal of applied physics, 2007. 102(6): p. 064701. https://doi.org/10.1063/1.2777127
76. Li, W., et al. Monte Carlo simulations of dose enhancement around gold nanoparticles used as x-ray imaging contrast agents and radiosensitizers. in Medical Imaging 2014: Physics of Medical Imaging. 2014. SPIE. https://doi.org/10.1117/12.2043687
77. Eck, W., et al., Anti-CD4-targeted gold nanoparticles induce specific contrast enhancement of peripheral lymph nodes in X-ray computed tomography of live mice. Nano letters, 2010. 10(7): p. 2318-2322. https://doi.org/10.1021/nl101019s
78. Kouhbanani, M.A.J., et al., Green synthesis of iron oxide nanoparticles using Artemisia vulgaris leaf extract and their application as a heterogeneous Fenton-like catalyst for the degradation of methyl orange. Materials Research Express, 2018. 5(11): p. 115013. https://doi.org/10.1088/2053-1591/aadde8
79. Kouhbanani, M.A.J., et al., One-step green synthesis and characterization of iron oxide nanoparticles using aqueous leaf extract of Teucrium polium and their catalytic application in dye degradation. Advances in Natural Sciences: Nanoscience and Nanotechnology, 2019. 10(1): p. 015007. https://doi.org/10.1088/2043-6254/aafe74
80. Laurent, S. and M. Mahmoudi, Superparamagnetic iron oxide nanoparticles: promises for diagnosis and treatment of cancer. International journal of molecular epidemiology and genetics, 2011. 2(4): p. 367.
81. Thorek, D.L., et al., Superparamagnetic iron oxide nanoparticle probes for molecular imaging. Annals of biomedical engineering, 2006. 34(1): p. 23-38. https://doi.org/10.1007/s10439-005-9002-7
82. Yu, M.K., et al., Drug-loaded superparamagnetic iron oxide nanoparticles for combined cancer imaging and therapy in vivo. Angewandte Chemie International Edition, 2008. 47(29): p. 5362-5365. https://doi.org/10.1002/anie.200800857
83. Mahmoudi, M., et al., Superparamagnetic iron oxide nanoparticles: promises for diagnosis and treatment of multiple sclerosis. ACS chemical neuroscience, 2011. 2(3): p. 118-140. https://doi.org/10.1021/cn100100e
84. Mahmoudi, M., A. Simchi, and M. Imani, Recent advances in surface engineering of superparamagnetic iron oxide nanoparticles for biomedical applications. Journal of the Iranian Chemical Society, 2010. 7(2): p. S1-S27. https://doi.org/10.1007/BF03246181
85. Mahmoudi, M., et al., Optimal design and characterization of superparamagnetic iron oxide nanoparticles coated with polyvinyl alcohol for targeted delivery and imaging. The Journal of Physical Chemistry B, 2008. 112(46): p. 14470-14481. https://doi.org/10.1021/jp803016n
86. Gupta, A.K., et al., Recent advances on surface engineering of magnetic iron oxide nanoparticles and their biomedical applications. 2007. https://doi.org/10.2217/17435889.2.1.23
87. Lee, H., et al., Thermally cross-linked superparamagnetic iron oxide nanoparticles: synthesis and application as a dual imaging probe for cancer in vivo. Journal of the American Chemical Society, 2007. 129(42): p. 12739-12745. https://doi.org/10.1021/ja072210i
88. Kellar, K.E., et al., NC100150 injection, a preparation of optimized iron oxide nanoparticles for positive-contrast MR angiography. Journal of Magnetic Resonance Imaging, 2000. 11(5): p. 488-494. https://doi.org/10.1002/(SICI)1522-2586(200005)11:5<488::AID-JMRI4>3.0.CO;2-V
89. L. Villaraza, A.J., A. Bumb, and M.W. Brechbiel, Macromolecules, dendrimers, and nanomaterials in magnetic resonance imaging: the interplay between size, function, and pharmacokinetics. Chemical reviews, 2010. 110(5): p. 2921-2959. https://doi.org/10.1021/cr900232t
90. LaConte, L., N. Nitin, and G. Bao, Magnetic nanoparticle probes. Materials today, 2005. 8(5): p. 32-38. https://doi.org/10.1016/S1369-7021(05)00893-X
91. Laurent, S., et al., Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chemical reviews, 2008. 108(6): p. 2064-2110. https://doi.org/10.1021/cr068445e
92. Medarova, Z., et al., In vivo imaging of siRNA delivery and silencing in tumors. Nature medicine, 2007. 13(3): p. 372-377. https://doi.org/10.1038/nm1486
93. Le Fur, M., et al., Radiolabeling and PET-MRI microdosing of the experimental cancer therapeutic, MN-anti-miR10b, demonstrates delivery to metastatic lesions in a murine model of metastatic breast cancer. Cancer nanotechnology, 2021. 12(1): p. 1-15. https://doi.org/10.1186/s12645-021-00089-5
94. Yeste, M., et al., Solvothermal synthesis and characterization of ytterbium/iron mixed oxide nanoparticles with potential functionalities for applications as multiplatform contrast agent in medical image techniques. Ceramics International, 2022. 48(21): p. 31191-31202. https://doi.org/10.1016/j.ceramint.2022.06.194
95. Mahmoudi, M., et al., Magnetic resonance imaging tracking of stem cells in vivo using iron oxide nanoparticles as a tool for the advancement of clinical regenerative medicine. Chemical reviews, 2011. 111(2): p. 253-280. https://doi.org/10.1021/cr1001832
96. Choi, H., et al., Iron oxide nanoparticles as magnetic resonance contrast agent for tumor imaging via folate receptor-targeted delivery1. Academic radiology, 2004. 11(9): p. 996-1004. https://doi.org/10.1016/j.acra.2004.04.018
97. Xie, J., et al., PET/NIRF/MRI triple functional iron oxide nanoparticles. Biomaterials, 2010. 31(11): p. 3016-3022. https://doi.org/10.1016/j.biomaterials.2010.01.010
98. Hoopes, P.J., et al. In vivo imaging and quantification of iron oxide nanoparticle uptake and biodistribution. in Medical Imaging 2012: Biomedical Applications in Molecular, Structural, and Functional Imaging. 2012. SPIE. https://doi.org/10.1117/12.916097
99. Serda, R.E., et al., Targeting and cellular trafficking of magnetic nanoparticles for prostate cancer imaging. Molecular imaging, 2007. 6(4): p. 7290.2007. 00025. https://doi.org/10.2310/7290.2007.00025
100. Leuschner, C., et al., LHRH-conjugated magnetic iron oxide nanoparticles for detection of breast cancer metastases. Breast cancer research and treatment, 2006. 99(2): p. 163-176. https://doi.org/10.1007/s10549-006-9199-7
101. Sun, C., et al., In vivo MRI detection of gliomas by chlorotoxin-conjugated superparamagnetic nanoprobes. Small, 2008. 4(3): p. 372-379. https://doi.org/10.1002/smll.200700784
102. Zhang, C., et al., Specific targeting of tumor angiogenesis by RGD-conjugated ultrasmall superparamagnetic iron oxide particles using a clinical 1.5-T magnetic resonance scanner. Cancer research, 2007. 67(4): p. 1555-1562. https://doi.org/10.1158/0008-5472.CAN-06-1668
103. Artemov, D., et al., MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 2003. 49(3): p. 403-408. https://doi.org/10.1002/

mrm.10406
104. Toma, A., et al., Monoclonal antibody A7-superparamagnetic iron oxide as contrast agent of MR imaging of rectal carcinoma. British journal of cancer, 2005. 93(1): p. 131-136. https://doi.org/10.1038/sj.bjc.6602668
105. Uchida, M., et al., Targeting of cancer cells with ferrimagnetic ferritin cage nanoparticles. Journal of the American Chemical Society, 2006. 128(51): p. 16626-16633. https://doi.org/10.1021/ja0655690
106. Nakhaei, P., et al., Liposomes: structure, biomedical applications, and stability parameters with emphasis on cholesterol. Frontiers in Bioengineering and Biotechnology, 2021: p. 748. https://doi.org/10.3389/fbioe.2021.705886
107. Pratt, L.R. and A. Pohorille, Hydrophobic effects and modeling of biophysical aqueous solution interfaces. Chemical Reviews, 2002. 102(8): p. 2671-2692. https://doi.org/10.1021/cr000692+
108. Tu, Y., et al., Mimicking the cell: bio-inspired functions of supramolecular assemblies. Chemical reviews, 2016. 116(4): p. 2023-2078. https://doi.org/10.1021/acs.chemrev.5b00344
109. Chetoni, P., et al., Comparison of liposome-encapsulated acyclovir with acyclovir ointment: ocular pharmacokinetics in rabbits. Journal of ocular pharmacology and therapeutics, 2004. 20(2): p. 169-177. https://doi.org/10.1089/108076804773710849
110. Rovira-Bru, M., D.H. Thompson, and I. Szleifer, Size and structure of spontaneously forming liposomes in lipid/PEG-lipid mixtures. Biophysical Journal, 2002. 83(5): p. 2419-2439. https://doi.org/10.1016/S0006-3495(02)75255-7
111. Silindir, M., et al., Liposomes and their applications in molecular imaging. Journal of drug targeting, 2012. 20(5): p. 401-415. https://doi.org/10.3109/1061186X.2012.685477
112. Torchilin, V.P., Recent advances with liposomes as pharmaceutical carriers. Nature reviews Drug discovery, 2005. 4(2): p. 145-160. https://doi.org/10.1038/nrd1632
113. Benech, R.-O., et al., Inhibition of Listeria innocua in cheddar cheese by addition of nisin Z in liposomes or by in situ production in mixed culture. Applied and environmental microbiology, 2002. 68(8): p. 3683-3690. https://doi.org/10.1128/AEM.68.8.3683-3690.2002
114. Shehata, T., et al., Prolongation of residence time of liposome by surface-modification with mixture of hydrophilic polymers. International journal of pharmaceutics, 2008. 359(1-2): p. 272-279. https://doi.org/10.1016/j.ijpharm.2008.04.004
115. Pattni, B.S., V.V. Chupin, and V.P. Torchilin, New developments in liposomal drug delivery. Chemical reviews, 2015. 115(19): p. 10938-10966. https://doi.org/10.1021/acs.chemrev.5b00046
116. Xia, Y., et al., Liposome-based probes for molecular imaging: from basic research to the bedside. Nanoscale, 2019. 11(13): p. 5822-5838. https://doi.org/10.1039/C9NR00207C
117. Portnoy, E., et al., Cetuximab-labeled liposomes containing near-infrared probe for in vivo imaging. Nanomedicine: Nanotechnology, Biology and Medicine, 2011. 7(4): p. 480-488. https://doi.org/10.1016/j.nano.2011.01.001
118. Seo, J.W., et al., A novel method to label preformed liposomes with 64Cu for positron emission tomography (PET) imaging. Bioconjugate chemistry, 2008. 19(12): p. 2577-2584. https://doi.org/10.1021/bc8002937
119. Zheng, J., D. Jaffray, and C. Allen, Quantitative CT imaging of the spatial and temporal distribution of liposomes in a rabbit tumor model. Molecular Pharmaceutics, 2009. 6(2): p. 571-580. https://doi.org/10.1021/mp800234r
120. Bhavane, R., et al., Dual-energy computed tomography imaging of atherosclerotic plaques in a mouse model using a liposomal-iodine nanoparticle contrast agent. Circulation: Cardiovascular Imaging, 2013. 6(2): p. 285-294. https://doi.org/10.1161/CIRCIMAGING.112.000119
121. Ghaghada, K.B., et al., Computed tomography imaging of solid tumors using a liposomal-iodine contrast agent in companion dogs with naturally occurring cancer. PloS one, 2016. 11(3): p. e0152718. https://doi.org/10.1371/journal.pone.0152718
122. Mukundan Jr, S., et al., A liposomal nanoscale contrast agent for preclinical CT in mice. American Journal of Roentgenology, 2006. 186(2): p. 300-307. https://doi.org/10.2214/AJR.05.0523
123. Ringhieri, P., et al., Liposomes derivatized with multimeric copies of KCCYSL peptide as targeting agents for HER-2-overexpressing tumor cells. International journal of nanomedicine, 2017. 12: p. 501. https://doi.org/10.2147/IJN.S113607
124. Jensen, A.I., et al., Remote-loading of liposomes with manganese-52 and in vivo evaluation of the stabilities of 52Mn-DOTA and 64Cu-DOTA using radiolabelled liposomes and PET imaging. Journal of Controlled Release, 2018. 269: p. 100-109. https://doi.org/10.1016/j.jconrel.2017.11.006
125. Yu, B., et al., Reassembly of 89Zr-Labeled Cancer Cell Membranes into Multicompartment Membrane-Derived Liposomes for PET-Trackable Tumor-Targeted Theranostics. Advanced Materials, 2018. 30(13): p. 1704934. https://doi.org/10.1002/adma.201704934
126. Lee, H., et al., Companion diagnostic 64Cu-liposome positron emission tomography enables characterization of drug delivery to tumors and predicts response to cancer nanomedicines. Theranostics, 2018. 8(9): p. 2300. https://doi.org/10.7150/thno.21670
127. Gawne, P., et al., Manganese-52: applications in cell radiolabelling and liposomal nanomedicine PET imaging using oxine (8-hydroxyquinoline) as an ionophore. Dalton Transactions, 2018. 47(28): p. 9283-9293. https://doi.org/10.1039/C8DT00100F
128. Lajunen, T., et al., The effect of light sensitizer localization on the stability of indocyanine green liposomes. Journal of Controlled Release, 2018. 284: p. 213-223. https://doi.org/10.1016/j.jconrel.2018.06.029
129. Guan, C., et al., Glycosylated liposomes loading carbon dots for targeted recognition to HepG2 cells. Talanta, 2018. 182: p. 314-323. https://doi.org/10.1016/j.talanta.2018.01.069
130. Aizik, G., et al., Delivery of liposomal quantum dots via monocytes for imaging of inflamed tissue. ACS nano, 2017. 11(3): p. 3038-3051. https://doi.org/10.1021/acsnano.7b00016
131. Sheng, D., et al., Perfluorooctyl bromide & indocyanine green co-loaded nanoliposomes for enhanced multimodal imaging-guided phototherapy. Biomaterials, 2018. 165: p. 1-13. https://doi.org/10.1016/j.biomaterials.2018.02.041
132. Zhang, L., et al., Bioinspired multifunctional melanin-based nanoliposome for photoacoustic/magnetic resonance imaging-guided efficient photothermal ablation of cancer. Theranostics, 2018. 8(6): p. 1591. https://doi.org/10.7150/thno.22430
133. Chen, Q., et al., H2O2-responsive liposomal nanoprobe for photoacoustic inflammation imaging and tumor theranostics via in vivo chromogenic assay. Proceedings of the National Academy of Sciences, 2017. 114(21): p. 5343-5348. https://doi.org/10.1073/pnas.1701976114
134. Sun, Q., et al., Theranostic nanoplatform: triple-modal imaging-guided synergistic cancer therapy based on liposome-conjugated mesoporous silica nanoparticles. ACS applied materials & interfaces, 2018. 10(2): p. 1963-1975. https://doi.org/10.1021/acsami.7b13651