Nanoparticles for Biological and Medical Imaging

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Abstract

Nanotechnology has provided considerable promise for the biological and medical fields, especially in the subjects of biological and medical imaging for the last two decades. Here, we outline different nanoparticles to contribute to biological and medical imaging disciplines. These concerned nanoparticles are soft nanoparticles, which are based on biomacromolecule/polymer or organic molecule components, hard nanoparticles that are derived from various inorganic components and hard-soft nanoparticles that are based on both inorganic components and biomacromolecule/polymer or organic molecule ones. We also discuss the imaging modalities in biology and medicine that various nanoparticles became involved in are: (1) optical imaging (OI), (2) computed tomography (CT), (3) magnetic resonance imaging (MRI), (4) ultrasonography (USG), (5) positron emission tomography (PET). We will also describe various nanoparticles to serve for one/some of those five modalities in biology and medicine imaging in this review paper.

Full Text

Preamble

Nanoparticles for Biological and Medical Imaging

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Abstract

Nanotechnology has shown considerable promise for biological and medical applications, particularly in biological and medical imaging, over the last two decades. Here, we outline the contributions of various nanoparticles to these imaging

disciplines. These nanoparticles include soft nanoparticles based on biomacromolecule/polymer or organic molecule components, hard nanoparticles derived from various inorganic components, and hard-soft nanoparticles that combine both inorganic and biomacromolecule/polymer or organic molecule components. We also discuss the imaging modalities in biology and medicine in which these nanoparticles have been applied: (1) optical imaging (OI), (2) computed tomography (CT), (3) magnetic resonance imaging (MRI), (4) ultrasonography (USG), and (5) positron emission tomography (PET). This review describes various nanoparticles that serve one or more of these five imaging modalities in biological and medical applications.

Key Words: nanoparticle, nanomedicine, soft, hard, optical imaging, computed tomography, magnetic resonance imaging, ultrasonography, positron emission tomography

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I. Introduction

Nanotechnology is a field that investigates structures at the 1-100 nm scale in one, two, or three dimensions. Over the past two decades, nanotechnology has provided a broad platform across many disciplines, including biology, medicine, chemistry, physics, materials science, and engineering. The key unit through which nanotechnology revolutionizes these scientific fields is embodied in various nanoparticles. In particular, nanoparticles show great promise for biology and medicine in applications such as detection, diagnosis, treatment, and imaging of severe diseases, including various tumors and cancers. Here, we focus on how different nanoparticles offer benefits for biological and medical imaging.

1) Various Nanoparticles for Biological and Medical Imaging

The nanoparticles relevant to biological and medical imaging include soft nanoparticles, hard nanoparticles, and hard-soft/soft-hard nanoparticles. The shapes of these nanoparticles may be spherical, rod-like, tubular, needle-like, cubic, cage-like, or prismatic. Their structures may be monolayer, core-shell, or multilayer.

(1) Soft Nanoparticles The soft nanoparticles discussed in this review are based on polymer components, organic molecule components, or mixtures of both. Polymers include generally artificial/natural macromolecules and biomacromolecules such as proteins, peptides, lipids, nucleic acids, and viruses. Organic molecules mainly include purpose-designed functional molecules.

A) Polymer Nanoparticles

Polymer nanoparticles have been produced for several decades for various applications in high-performance materials and specialty coatings, even before "nano" became a popular term. Polymer nanoparticles can be easily formed

by changing pH values or controlling specific interaction mechanisms. The extremely large surface area of polymer nanoparticles offers many opportunities to attach different functional groups to their surfaces. Another benefit of polymer nanoparticles is their compatibility with inorganic materials or different types of polymers. Commonly used polymer nanoparticles in biological and medical imaging include polymer-drug conjugates, liposomes, micelles, vesicles, dendrimers, nanogels, and nanospheres (Tong & Cheng, 2007). A third advantage of polymer nanoparticles is that good interfacial adhesion eliminates scattering and strengthens the interaction of nanoparticles with the body, increasing retention time in vivo, which benefits applications in biological and medical imaging (Schmidt & Malwitz, 2003; Ekpo MD et al., 2022).

B) Organic Nanoparticles

Organic nanoparticles have many forms, including pharmaceuticals/drugs, pigments/dyes, viruses, and protein/nucleic acid aggregates. The properties of organic nanoparticles, particularly their optical and color attributes, are controlled by their components, sizes, and supramolecular structures. Compared to hard nanoparticles, adjusting the shapes of organic nanoparticles seems to have little effect on their properties (Horn & Rieger, 2001; Wang et al., 2020).

(2) Hard Nanoparticles The hard nanoparticles discussed in this review are based on inorganic components or several types of inorganic materials. Hard nanoparticles mainly include noble metal nanoparticles such as gold and silver nanoparticles, semiconductor nanoparticles such as quantum dots (CdS, ZnS, CdSe, CdTe@ZnS) and other semiconductor nanoparticles such as TiO_2 and SiO_2, and other hard nanoparticles such as SiO_2@Au, FeCo, γ-Fe_2O_3, and Fe_3O_4.

A) Metal Nanoparticles

Metal nanoparticles, especially noble metal nanoparticles such as gold and silver, exhibit very interesting optical properties due to the phenomenon of surface plasmon resonance (SPR). This resonance of metal free electrons across the nanoparticles is induced by an electromagnetic field at a certain frequency when the size of noble metal nanoparticles is much smaller than the wavelength of light. The SPR of the metal electrons causes strong enhancement in absorption and scattering of electromagnetic radiation around the nanoparticles. The SPR of noble metal nanoparticles depends greatly on composition, size, and shape, as well as the surrounding media/substrates and inter-particle interactions (Jain, El-Sayed & El-Sayed, 2007; Li et al., 2022).

B) Semiconductor Nanoparticles

Semiconductor nanoparticles have elemental components from groups II to VI in the periodic table. The electronic energy levels in semiconductor nanoparticles are discrete and quantized, and the gap between electronic energy levels can be precisely tuned by varying their sizes and components. In chemical terms, semi-

conductor nanoparticles are considered inorganic salts or metal oxides (Thurn et al., 2007; Jiang & Tian, 2018).

(a) Quantum Dots

Quantum dots are a special type of semiconductor nanoparticle with sizes down to 10 nm, which is smaller than the bulk excitation Bohr radius of the semiconductor materials (Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/Quantum_{dot}). The small size of quantum dots results in unique photoelectron emission properties. Electrons in the valence band of a quantum dot easily hop to its conduction band after excitation under an external field. A fluorescent signal is obtained when these excited electrons with higher energy move back to the valence band, accompanied by photon emission. Consequently, quantum dots with long fluorescence lifetimes (>10 ns) and narrow emission peaks (typically 20-30 nm full width at half maximum) overcome many defects of "classical" organic fluorescent dyes, such as photoinstability and wide emission peaks. Moreover, the fluorescence emission wavelengths of quantum dots cover a wide range from UV to near-infrared light (NIR, 700-900 nm), depending on their physical size, shape, and chemical components. This is very useful for biological and medical imaging, particularly for photoluminescent labels and simultaneous multiple target detection (Fu et al., 2005; Thurn et al., 2007; Ornes, 2016).

(b) Titanium Dioxide Nanoparticles

Compared to commonly used semiconductor nanoparticles such as quantum dots, titanium dioxide nanoparticles (TiO_2) are wide-gap semiconductor nanoparticles with photocatalytic activity in the ultraviolet wavelength range (around 380 nm for 4.5 nm spherical TiO_2 nanoparticles). Upon excitation, TiO_2 nanoparticles can simultaneously trap multiple electrons, producing positively charged holes in conjugated molecules (if present) or causing formation of oxygen free radicals in the vicinity of the nanoparticle by removing electrons from water molecules in contact with the TiO_2 surface (Thurn et al., 2007). These oxygen free radicals enable oxidation of nearby biomolecules, which may be useful for therapeutic purposes in the future (Thurn et al., 2007). The surface chemistry of TiO_2 nanoparticles smaller than 20 nm depends on the formation of "corner defects" on the nanoparticle surface, which are very reactive with bidentate ligands such as adjacent hydroxyl groups with conjugation structures (Thurn et al., 2007). This offers an easy way to attach or modify molecules on the surface of TiO_2 nanoparticles (Thurn et al., 2007; Grande & Tucci, 2016).

(c) Other Semiconductor Nanoparticles

Other semiconductor nanoparticles discussed in this review include silica nanoparticles (SiO_2) and diamond nanoparticles (nanodiamond). Compared to other semiconductor nanoparticles, silica nanoparticles possess several advantages: (i) SiO_2 nanoparticles are easy to separate, modify on their surface, and treat in other solution processes; (ii) SiO_2 nanoparticles are hydrophilic

and biocompatible; (iii) SiO_2 nanoparticles do not swell or change porosity with pH changes (Wang & Tan, 2006). These properties make them ideal candidates for biological and medical imaging (Wang & Tan, 2006). Nanodiamond has highly ordered structures, is cell-like, and is soluble in aqueous solutions, which makes them clinically important (Huang et al., 2007; Wang et al., 2021).

C) Carbon Nanotubes

Carbon nanotubes are a family of tubular nanostructures rolled from one or multiple layers of covalently bonded carbon atoms—graphite (Iijima, 1991; Iijima & Ichihashi, 1993; Bethune et al., 1993). Nanotubes rolled from one layer of covalently bonded carbon atoms are called single-walled nanotubes (SWNTs), while those rolled from multiple layers are called multi-walled nanotubes (MWNTs). Due to their relatively simple structures and unique physical, mechanical, and electronic properties, SWNTs have been the focus of many researchers. Depending on the chiral angle of the formed SWNTs, they may be conductive, semiconductive, or insulating (Dekker, 1999; Manikandan et al., 2021). Semiconductive SWNTs show band gap fluorescent emission in the NIR region between 900 and 1600 nm. It is possible to detect the sharp spectra of SWNTs even in complex biological/medical environments because natural biomolecules are relatively transparent and non-emissive in this emission wavelength region.

D) Other Hard Nanoparticles

Other hard nanoparticles besides noble metal nanoparticles and semiconductor nanoparticles include some useful nanoparticles with special functions, such as FeCo, Gd_2O_3, Fe_3O_4, and γ-Fe_2O_3 for MRI applications, Bi_2S_3 for CT applications, and SiO_2@Au core-shell nanoparticles for optical imaging in the near-infrared field.

(3) Hard-Soft/Soft-Hard Nanoparticles The hard-soft or soft-hard nanoparticles discussed in this review are based on both inorganic components as hard layer(s) and polymer or organic molecules as soft layer(s). The hard layer(s) may be on the outside or inside of the nanoparticles depending on the application purpose.

2) Different Types of Biological and Medical Imaging

The main types of biological and medical imaging are optical imaging (OI), computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (USG), and positron emission tomography (PET). The characteristics, advantages, and disadvantages of these five imaging modalities are summarized in Table 1 .

(1) Optical Imaging (OI) Optical imaging (OI) is an imaging technique that takes advantage of visible or near-infrared light, particularly near-infrared light, to visualize objects. It usually includes two modes: diffusive optical imaging (DOI) or diffuse optical tomography (DOT) (Gibson et al., 2005) and ballistic

optical imaging (Farsiu et al., 2007). DOI or DOT is a modality that uses near-infrared light to create images of the body. This technique is sensitive to the optical absorption of some compositions in the body. The spatial resolution of DOI or DOT is around several millimeters, which competes with that of functional magnetic resonance imaging (fMRI), and the temporal resolution can reach several milliseconds. DOI or DOT provides two kinds of information: (i) detection of light absorption relevant to the concentration of chemicals in the body, and (ii) detection of light scattering relevant to physiological characteristics such as swelling of glia or neurons in the brain (Gibson et al., 2005). In contrast, ballistic optical imaging ignores diffusive photons and depends only on ballistic photons to generate high-resolution images near the diffraction limit of light through scattering media (Farsiu et al., 2007). Currently, near-infrared fluorescent imaging is the most widely used technique in medical and biological fields.

(2) Computed Tomography (CT) Computed tomography (CT) is a medical imaging technique that uses tomography where digital geometry processing creates a three-dimensional image of the internal structures of an object from many two-dimensional X-ray images (Wikipedia, the free encyclopedia: en.wikipedia.org/wiki/Computed_{tomography}). CT provides visualization of various anatomical structures based on their capability to block X-ray beams at different depths within the body. Structures at the target level are clear while other structures at different levels are blurred. Various effects can be obtained by changing the extent and path of motion with a series of depths of field and different degrees of blurring of out-of-plane structures. As a clinically practical imaging method, CT offers several advantages: (i) it excludes superimposition of images of anatomical structures outside the plane of interest, (ii) it can distinguish differences among tissues in physical density by less than 1%, and (iii) it can produce axial, coronal, or sagittal plane images depending on specific diagnostic purposes. However, CT also has disadvantages: (i) it is an ionizing radiation diagnostic technique that can cause hazards for patients, and (ii) it can induce kidney damage when contrast agents are administered intravenously to provide superior-quality images, particularly in patients with moderate kidney failure.

Furthermore, there is a special CT method—single photon emission computed tomography (SPECT)—based on a radioactive substance administered in low mass amounts and labeled with radioisotopes such as ^{99} Tc ($t_1/_2$=6 hours), ^{123}I ($t_1/_2$=13.2 hours), ^{131}I ($t_1/_2$=8.1 days), and ^{111}In ($t_1/_2$=2.8 days). This method is distinct from normal CT (Wikipedia, the free encyclopedia: en.wikipedia.org/wiki/Single_{photon}*{emission}*{computed}_{tomography}).

(3) Magnetic Resonance Imaging (MRI) Magnetic resonance imaging (MRI) is a non-invasive method that depends greatly on the relaxation properties of proton nuclei in water and lipids to produce images of the inside of an object. MRI is widely used to visualize pathological or other physiological

changes in living tissues. Compared to CT, MRI has several advantages: (i) it employs non-ionizing radio frequency (RF) signals to obtain images and is best suited for non-calcified tissues, (ii) it can detect various tissue features by varying scanning parameters, (iii) it can create cross-sectional images in any plane including oblique planes, (iv) it is superior for detecting and identifying tumors, (v) it is well suited for multiple successive examinations within short periods, and (vi) it provides multiple contrast mechanisms such as T1-weighted, T2-weighted, and T2*-weighted MR images (Wikipedia, the free encyclopedia: en.wikipedia.org/wiki/Magnetic_{resonance}_{imaging}).

In MRI, T1 relaxation (also called spin-lattice or longitudinal relaxation) is the time constant for nuclear spins returning to equilibrium. When nuclei transition from high-energy to low-energy states, they lose energy to surrounding nuclei. T1 relaxation is characterized by the longitudinal return of the net magnetization to its ground state of maximum length along the direction of the main magnetic field. T1 is usually around 1 second for tissue. T2 relaxation (also called spin-spin or transverse relaxation) is the time constant of signal decay. T2 relaxation occurs when spins in high and low energy states exchange energy without releasing energy to the surrounding lattice. The magnetic moments interact with each other, causing a decrease in transverse magnetization or decay after nuclei release their excess energy. T2 is usually less than 100 ms for general tissue. T2* is the time required for transverse magnetization to decay to 37% of its original magnitude. It occurs under an inhomogeneous magnetic field and happens in all magnets, characterized by inhomogeneous B_0 and loss of transverse magnetization at a rate greater than T2 (Wikipedia, the free encyclopedia: en.wikipedia.org/wiki/Magnetic_{resonance}_{imaging}).

(4) Ultrasonography (USG) Ultrasonography (USG) is an imaging technique based on ultrasound—a cyclic sound wave with frequency above the upper limit of human hearing (about 25 kilohertz)—to visualize muscles, tendons, and other internal organs, including their size, structure, and any pathological lesions, with tomographic images in real time (Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Medical_{ultrasonography}). The typical clinical diagnostic imaging frequency for ultrasound is 1-10 MHz, providing submillimeter to millimeter spatial resolution. At higher frequencies (20-50 MHz), ultrasound images provide higher resolution down to tens of micrometers, suitable for imaging specific organs such as in ophthalmology or with intravascular probes. At very low frequencies (1-3 MHz), ultrasound images allow deep penetration within the body, while high frequencies provide only limited penetration, generally several millimeters (Klibanov, 2005). As the most widely used imaging technique, USG is relatively inexpensive and portable compared to CT or MRI. To date, USG has posed no known risks to patients because it does not use ionizing radiation. However, ultrasound can cause two potential physiological effects: (i) production of microscopic bubbles in living tissues that distort cell membranes and influence ion fluxes and intracellular activity, and (ii) generation of small pockets of gas in body fluids or tissues that swell and contract

under high-intensity ultrasound.

(5) Positron Emission Tomography (PET) Positron emission tomography (PET) is a non-invasive imaging technique involving exposure to ionizing radiation that creates a three-dimensional map of functional processes in living subjects at nano- and picomolar levels. It detects gamma rays emitted indirectly by a positron-emitting radioisotope that enters the body on metabolically active molecules before an image of metabolic activity in space is reconstructed by computer analysis. Usually PET is used in combination with CT to obtain both anatomic and metabolic information in the body. It is very useful for visualizing details of moving organs or structures with higher amounts of anatomical variation (Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Positron_{emission}_{tomography}).

II. Nanoparticles for Optical Imaging (OI)

Nanoparticles that contribute to optical imaging in biology and medicine are primarily hard nanoparticles such as noble metal nanoparticles, quantum dots (QDs), titanium dioxide nanoparticles, carbon nanotubes, and composite SiO_2 core-Au shell nanoparticles, or hard-soft nanoparticles such as peptide-modified QDs, antibody-modified QDs, PEGylated Au, and oligonucleotide-coated silver nanoparticles.

1) Metal Nanoparticles and Hard-Soft Nanoparticles Based on Metal

Noble metal nanoparticles such as Au and Ag are superior to traditional absorbing and fluorescence dyes used in biological and medical imaging due to the SPR phenomenon. For instance, Mie theory calculates that the optical cross-section of gold nanoparticles is approximately 4-5 orders of magnitude higher than those of organic dyes (Mie, 1908). The SPR-enhanced scattering from gold nanoparticles makes them promising optical probes and labels for cancer detection based on imaging. Sokolov and coworkers used immunotargeted gold nanoparticles with a diameter of 12 nm to image cervical epithelial cancer cells (SiHa cells) known to overexpress the transmembrane glycoprotein epidermal growth factor receptor (EGFR) (Sokolov, 1999). They employed anti-EGFR monoclonal antibodies via electrostatic interaction of the antibody molecules with the negatively charged surface of gold nanoparticles. The scattering from non-labeled SiHa cells was about 50-fold lower than that from labeled cells. The scattering images of the labeled cells showed that binding of the gold nanoparticle-antibodies occurred mainly on the cell membrane surface, confirming the molecular-specific interaction of this labeling technique.

El-Sayed et al. successfully demonstrated detection and differentiation of cancerous cells from normal cells using SPR scattering imaging and SPR absorption spectroscopy of 35 nm gold nanoparticles with anti-EGFR antibodies immunotargeted to two epithelial cell lines: human oral squamous carcinomas HOC

313 clone 8 and HSC 3 (El-Sayed et al., 2005). The SPR scattering imaging confirmed specific binding of the antibodies to EGFR overexpressed on the surface of cancerous cells and accumulation of the nanoparticle conjugates in cytoplasmic membrane areas. As a control, benign keratinocyte cell lines (HaCaT) incubated with the gold bionanoconjugates showed non-specific labeling with random distribution of nanoparticles on the HaCaT cells. Moreover, the strong SPR absorption of gold nanoparticles offers a new method for sensing and quantifying molecular-specific binding of nanoparticles by microabsorption spectroscopy. Both HOC and HSC cells showed a red shift of 9 nm after labeling with gold nanoparticles in solution. This change results from the local dielectric environment around the gold nanoparticles due to binding of the conjugated antibodies with their targets. They also demonstrated that specific and homogeneous binding of antibody-conjugated gold nanoparticles to the cancer cell surface leads to a sharper SPR absorption peak for cancerous cells compared to benign cells, where nanoparticles bind inhomogeneously due to non-specific interactions. Additionally, the El-Sayed group showed the efficiency of immunotargeted gold nanoparticles as photothermal agents in living cells in vitro using laser microscopy images with the aforementioned cell lines. The malignant HOC and HSC cellular lines suffered photothermal damage within 4 minutes at laser energy thresholds, while none of the healthy HaCaT cell lines without gold treatment showed any photothermal damage (El-Sayed et al., 2006; Huang et al., 2006a).

Commonly used gold nanoparticles enable imaging in visible light and can be extended to skin or surface-type cancers in vitro; however, in vivo imaging applications for deeper tissues require near-infrared (NIR) light where tissues have the highest transmissivity (Weissleder, 2001). Depending on tissue type, light penetration depth can be up to several centimeters in the spectral region of 700-900 nm, known as the biological NIR window. To overcome this limitation of spherical gold nanoparticles, two methods can make them suitable for in vivo imaging: (i) changing the shape of gold nanoparticles from spherical to rod or cage, and (ii) changing the composition from pure metal to silica core-gold shell.

The El-Sayed group prepared and employed Au nanorods conjugated to anti-EGFR antibodies for NIR cancer cell imaging (shown in Figure 1 [Figure 1: see original paper]) and selective photothermal therapy (Huang et al., 2006b). Using both SPR scattering and absorption properties of gold nanorods, the Cheng group also showed that gold nanorods strongly enhance fluorescence, enabling in vivo imaging using a two-photon NIR excitation scheme (Wang et al., 2005). The Xia group reported gold nanocages and their applications in biomedical imaging (Chen et al., 2005; Cang et al., 2005; Chen et al., 2007). They synthesized 45 nm gold nanocages and precisely tuned the SPR peaks to 810 nm to match the center wavelength of laser irradiation for photothermal cancer treatment. The nanocages were easily modified with thiolated PEG and then conjugated with HER2-antibody to target EGFR2 overexpressed on the surface of SK-BR-3 breast cancer cells. Their results showed good promise for immuno gold nanocages smaller than 50 nm as a new class of photothermal

therapeutic agents for cancer treatment. The Halas group at Rice University designed a nanostructure called nanoshells, composed of a silica core and a thin Au shell, to obtain desirable optical tunability (Fortina et al., 2007). The nanoshells can be designed to possess high SPR scattering and/or absorption in the NIR region to facilitate in vivo applications in optical imaging and therapy. Together with coworkers, this group showed that human breast cancer cells incubated with nanoshells undergo photothermal damage upon exposure to NIR laser light. They injected thiolated PEG-coated silica-Au nanoshells into mouse tumors. Low doses of NIR laser light caused high temperatures localized in tumor regions sufficient to induce irreversible tissue damage. In contrast, control tissues exposed to NIR light without nanoshell injection showed very low temperature rise without any tissue damage (Hirsch et al., 2003a). In further experiments on breast cancer cell lines in vitro, NIR laser photothermal therapy showed greater selectivity via molecular-specific labeling of cancer cells with nanoshells conjugated with antibodies to HER2 (Loo et al., 2005a). This group performed a series of studies based on nanoshell imaging, including whole immunoassay (Hirsch et al., 2003b; Hirsch et al., 2005), photothermal tumor ablation (Hirsch et al., 2003a; O' Neal et al., 2004), cancer imaging (Loo et al., 2004; Loo et al., 2005a; Loo et al., 2005b; Fu et al., 2008), and tissue welding (Gobin et al., 2005).

Compared to gold nanoparticles, applications of silver nanoparticles in biological and medical imaging are limited. Here we list two cases. One is from the Dickson group, who employed strongly emissive individual DNA-coated Ag nanoparticles as single-molecule fluorophores in the NIR region, offering great potential for future in vitro or in vivo single-molecule studies (Vosch et al., 2007). Another case is from Xu and colleagues (Xu et al., 2004). Very recently, this group directly characterized the transport of single silver nanoparticles into an in vivo model system—the zebrafish embryo—and investigated their effects on early embryonic development at single-nanoparticle resolution in real time (shown in Figure 2 [Figure 2: see original paper]). They found that single Ag nanoparticles (5–46 nm) are transported into and out of embryos through chorion pore canals (CPCs) and exhibit Brownian diffusion (not active transport), with the diffusion coefficient inside the chorionic space approximately 26 times lower than that in egg water. In contrast, silver nanoparticles trapped inside CPCs and the inner mass of the embryos showed restricted diffusion. Their results demonstrated that the biocompatibility and toxicity of Ag nanoparticles and types of abnormalities observed in zebrafish are highly dependent on the dose of Ag nanoparticles, with a critical concentration of 0.19 nM. Unlike other chemicals, single silver nanoparticles can be directly imaged inside developing embryos at nanometer spatial resolution, offering new opportunities to unravel the pathways that lead to abnormalities in biological and medical imaging (Lee et al., 2007a).

2) Quantum Dots (QDs) and Hard-Soft Nanoparticles Based on QDs

Compared to metal nanoparticles, QDs have two biological windows for optical imaging in living subjects: one at 700-900 nm and another at 1200-1600 nm. QDs are ideal candidates for multiphoton imaging in live animal models. In 1998, two groups simultaneously reported QD-based applications in biological and medical imaging (Bruchez et al., 1998; Chan et al., 1998). Since then, QDs have been linked to various biomolecules such as peptides (Biju et al., 2007), antibodies (Goldman et al., 2002a; Goldman et al., 2002b; Lidke et al., 2004; Winter et al., 2001), streptavidin (Dahan et al., 2003; Wu et al., 2003), nucleic acids (Mahtab et al., 2000), epidermal growth factor (EGF) (Lidke et al., 2004; Derfus et al., 2004a), and other ligands (Rosenthal et al., 2002) for fluorescent imaging applications. Excellent review papers on the use of QD nanocrystals for biological labeling, detection, and imaging are available (Alivisatos, 2004; Chan et al., 2002; Nie et al., 2007).

Another area of QD application involves testing in fixed cells over the last few years. QDs conjugated with signal peptides or transfection agents enable transport of biomacromolecules to specific organelles in living cells. Hoshino et al. used oligopeptides to penetrate cellular membranes utilizing their protein transduction domains and to locate specific organelles (Hoshino et al., 2004a). Derfus and coworkers utilized electroporation or transfection reagents conjugated with QDs to cross cell membranes and track organelles (Derfus et al., 2004b). To date, there have been no truly successful cases to overcome this challenge. The best method for cytoplasmic translocation of QDs remains direct injection in living cells. This approach allows targeting of QDs to subcellular compartments such as mitochondria or the nucleus using targeting peptides (Chen & Gerion, 2004). However, cell injection, though useful for single-cell observation, is tedious when many cells need to be labeled. A method that enables homogeneous distribution of QDs in the cytoplasm of cells would be highly desirable. Moreover, Parak et al. reported that QDs could be used as reagents for imaging phagokinetic tracks in cells (Parak et al., 2002). Two groups also used QDs to label live cells and demonstrated their utility for long-term multicolor imaging of live cells (Jaiswal et al., 2002; Hoshino et al., 2004b). For more details, an excellent review on the synthesis, solubilization, and functionalization of QDs and their applications to cell and animal biology is available (Michalet et al., 2005). These published results suggest that QD fluorescent probes are useful not only as imaging tools for tracing target cells but also for long-term retention in vivo, which is very helpful for living animal experiments.

Progress in animal experiments involving QDs has been made due to rapid development in the synthesis, solubilization, and functionalization of QDs over the last several years. The first animal study using peptide-QD conjugates to target receptors on blood vessels with exquisite binding specificity was reported by the Ruoslahti group (Akerman et al., 2002). In their pioneering work, ex vivo histological data showed that QD-peptide conjugates were specifically directed to tumor vasculature and other targets. A study by Kim et al. in 2004 presented

the first experiment using near-infrared QDs in animal surgical procedures in vivo (Kim et al., 2004). This is a good example of QDs in medical applications because they first discovered that near-infrared-emitting type-II QDs enable in vivo fluorescence imaging of lymph nodes at up to 1 cm depth. In the same year, the Nie group reported a new class of multifunctional QD probes for simultaneous tumor targeting and imaging in live animal models (shown in Figure 3 [Figure 3: see original paper]) (Gao et al., 2004). More recently, Cai et al. studied in vivo specific targeted imaging of tumor vasculature using QD705-RGD conjugates (Cai et al., 2006). At this time, it is not realistic to directly translate QD-based in vivo imaging in small animal models to patients because of (i) limited optical signal penetration depth, (ii) concerns about QD toxicity, (iii) poor delivery, and (iv) lack of quantification.

3) Titanium Dioxide

Titanium dioxide nanoparticles for biological and medical imaging have been reported by two laboratories: the Woloschak group and the Cheon group. In the Woloschak laboratory, they showed the effects of TiO_2 nanoparticles conjugating oligonucleotides to the surface of TiO_2 nanoparticles that target different organelles in living cells. X-ray fluorescence microscopy (XFM) (Paunesku et al., 2006) and TEM data confirmed that by varying the oligonucleotide sequence bound to the nanoparticle, the subcellular localization of the TiO_2-DNA nanoconjugate can change based on the location of available complementary cellular DNA (Paunesku et al., 2003; Paunesku et al., 2007). Titanium signals were found by XFM and TEM within the nucleus when breast cancer MCF-7/WS8 cells were treated with TiO_2 nanoconjugates complementary to genomic DNA encoding 18S rRNA (of which 200–300 copies reside in the nucleolus (Makalowski, 2001)). In contrast, both XFM and TEM detected a more dispersed Ti signal in mitochondria throughout the cytoplasm when the oligonucleotide sequence bound to the TiO_2 nanoparticle was complementary to mitochondrial DNA (shown in Figure 4 [Figure 4: see original paper]) (Paunesku et al., 2007). A third experiment combined XFM and confocal fluorescence microscopy to image the same cell treated with a TiO_2-DNA nanoconjugate whose nucleic acid component was labeled with tetramethylrhodamine (TAMRA). Both titanium signal and fluorescent TAMRA signal were clearly shown in the nucleus and perinuclear region (Thurn et al., 2007). This result strongly suggested that TiO_2-DNA nanoconjugates not only penetrate cell membranes and enter cells but also remain stable inside cells. Moreover, they conjugated TiO_2-DNA with Gd-based compounds to obtain T1-weighted MRI signal, representing a further step toward medical application (Endres et al., 2007). The Cheon group used titanium dioxide nanorods while the Woloschak group used nanospheres. Their data clearly showed high photocatalytic effects upon skin cancer cell tests using confocal fluorescence microscopy (Seo et al., 2007).

4) Carbon Nanotubes

In 2004, Bianco and coworkers demonstrated for the first time that functionalized carbon nanotubes can cross the cell membrane (Pantarotto et al., 2004a). Fluorescent images clearly showed that carbon nanotubes are a promising carrier system for drug delivery and targeted therapy, acting as nanovehicles and enabling evaluation of the biological functions of covalently linked molecules after cellular uptake. Single-walled nanotubes (SWNTs) cross the cell membrane via endocytosis to deliver molecular cargoes including therapeutic agents (Murakami et al., 2004; Bianco et al., 2005; Cai et al., 2005; Zhu et al., 2005), lipids (Singh et al., 2006), near-infrared agents (Cherukuri et al., 2004; Kam et al., 2005), peptides (Pantarotto et al., 2003; Pantarotto et al., 2004a), proteins (Kam et al., 2004; Kam & Dai, 2005), and nucleic acids such as plasmid DNA (Pantarotto et al., 2004b; Liu et al., 2005; Singh et al., 2005), RNA (Lu et al., 2004), and short interfering RNA (siRNA) (Kam, Liu & Dai, 2005). To investigate the mechanism of SWNT penetration into cells and its toxicity, Porter et al. showed that it is possible to map the location of intracellular SWNTs using TEM and confocal microscopy (Porter et al., 2007). They successfully imaged individual SWNTs within lysosomes and crossing cell membranes. They demonstrated two possible pathways for SWNT entry into cells: energy-dependent phagocytosis or endocytosis, and passive diffusion across lipid bilayers. They showed that direct imaging of SWNTs within cells is achievable and essential to complement cytotoxicity assays to understand localized effects. Moreover, a recent rabbit study by Cherukuri et al. used NIR fluorescence to monitor SWNT pharmacokinetics following intravenous administration, showing that nanotube fluorescence is being used in novel biomedical research (shown in Figure 5 [Figure 5: see original paper]) (Cherukuri et al., 2006). As a step toward developing biomedical applications based on nanotube fluorescence, Leeuw and colleagues explored the effects and fate of SWNTs orally administered to Drosophila melanogaster, the preeminent model organism in biology (Leeuw et al., 2007). This demonstrates nanotube imaging within a living organism. Additionally, two groups published articles on the biodistribution of chemically functionalized carbon nanotubes intravenously injected into animals based on biological imaging (Wang et al., 2004; Singh et al., 2006). Both groups reported that SWNTs functionalized by various methods behaved like small molecules in mice and were rapidly cleared through urine with little uptake by the liver, kidney, lung, muscle, skin, spleen, blood, bone, and heart of the reticuloendothelial system (RES).

5) Other Hard or Hard-Soft Nanoparticles

(1) Silica-based Nanoparticles Silica-based nanoparticles are widely used in bioanalytics and biological/medical imaging because they show less aggregation, minimal dye leakage, easily versatile surface functionalization methods, and excellent photostability (Kim et al., 1999; Smith et al., 2006; Tan et al., 2004a). Various targets such as proteins, cells, and bacteria have been de-

tected using these silica nanoparticles (Wang et al., 2005; Santra et al., 2001; Houser, 1990; Deng et al., 2006; Tan et al., 2004b; Zhao et al., 2004; He et al., 2004). For example, using a covalent bond, Santra et al. (Santra et al., 2001) attached mouse anti-human CD10 antibody to surface-modified, Rubpy-doped silica nanoparticles and then incubated them with mononuclear lymphoid target cells, confirming the effectiveness of this method for selective detection of leukemia cells. In another case, Deng and coworkers (Deng et al., 2006) doped the silica matrix with a near-infrared fluorescent dye, methylene blue. NIR imaging showed that the doped silica nanoparticles conjugated with monoclonal anti-alpha fetoprotein (AFP, a cancer marker) antibody could make fluorescence-anisotropy measurements directly on whole blood samples. Eu-doped silica nanoparticles were also used for targeting human squamous cancer cells (SCC-9) and imaging with confocal fluorescence microscopy (Santra et al., 2005).

(2) Diamond Nanoparticles (Nanodiamond) Nanodiamond is superior in physical and biocompatible properties and has emerged as a promising material for biomedical applications. For example, fluorescent nanodiamonds (35-100 nm) are stable biomarkers for bioimaging (Narayan et al., 2006; Yu et al., 2005; Fu et al., 2007). Very recently, Ho and coworkers attached an anticancer agent—doxorubicin hydrochloride (DOX)—for therapeutic delivery, confirmed by optical imaging results (Huang et al., 2007).

III. Nanoparticles for CT

Nanoparticles that contribute to CT have focused on iodine/surfactant-based liposome soft nanoparticles (Thomsen & Morcos, 2000), gadolinium-based liposome soft nanoparticles (Henson et al., 2004; Chryssidis, Davies & Tie, 2002; Quinn et al., 1994), barium sulfate hard nanoparticles, and newly developed metallofullerene hard nanoparticles (Miyamoto et al., 2006), gold hard nanoparticles (Hainfeld et al., 2006; Kannan et al., 2006; Kattumuri et al., 2007; Kim et al., 2007; Cai et al., 2007a), and bismuth sulfide hard nanoparticles (Rabin et al., 2006). Barium sulfate has been used as a contrast agent to improve visualization of the gastrointestinal tract in X-ray images since the 1920s (Patton, 1994). Iodine-based liposome soft nanoparticles are divided into ionic and non-ionic contrast media depending on the iodine type in the compounds (Thomsen & Morcos, 2000). Metallofullerenes, gold nanoparticles, and bismuth sulfide nanoparticles have only recently appeared and have not yet been applied in clinics, unlike barium sulfate and iodinated agents that have been FDA-approved for many years.

A unique example is the report by Miyamoto et al. on aqueous-soluble metallofullerenes as CT contrast agents (Miyamoto et al., 2006). Furthermore, Hainfeld et al. studied unmodified gold nanoparticles as a new CT contrast agent and applied them to a mouse model (Hainfeld et al., 2006). Two groups used polymer-modified gold nanoparticles as CT contrast agents (Kim et al., 2007;

Cai et al., 2007a), while Katti and colleagues are developing a CT contrast agent based on non-toxic phytochemical gum arabic matrix-coated gold to increase gold nanoparticle concentration and gold isotope 198 for future therapeutic purposes (Kannan et al., 2006; Kattumuri et al., 2007). Notably, measurement of the X-ray absorption coefficient in vitro revealed that the attenuation of different PEG-gold nanoparticles is over five times higher than that of current iodine-based CT contrast agents (shown in Figure 6 [Figure 6: see original paper]) (Kim et al., 2007).

Mukundan and coworkers used liposomal iodinated nanoparticles for preclinical CT in a mouse model (Mukundan et al., 2006). McIntire et al. investigated four types of iodinated nanoparticles in rabbit lymph nodes after subcutaneous injection (McIntire et al., 2000). They found that: (1) all four agents provided adequate enhancement of both popliteal and axillary lymph nodes in rabbits (i.e., $>$ Δ100 HU); (2) lymph node volume appears related to clearance of insoluble, iodinated nanoparticle contrast agents, which can be modulated by changes in the agent' s structure; and (3) using the same agent, smaller particles deliver material to lymph nodes more quickly and clear more rapidly. Hyafil and colleagues studied detection of macrophages in atherosclerotic plaques of rabbits using a clinical X-ray CT scanner after intravenous injection of a contrast agent formed from iodinated nanoparticles (N1177) dispersed with surfactant. This contrast agent may become a key adjunct to clinical evaluation of coronary arteries with CT (shown in Figure 7 [Figure 7: see original paper]) (Hyafil et al., 2007). Kao et al. tested liposomal iohexol nanoparticles and found that the liposomal iohexol formulation had sufficient residence time for blood pool imaging in a rabbit model (Kao et al., 2003). Further experiments with long-residence-time iohexol formulations might lead to applications in cardiac imaging and early tumor detection. Suga et al. investigated whether quick and accurate localization of sentinel lymph node stations based on detailed underlying lung anatomy using indirect computed tomographic lymphography (CT-LG) might guide selective lymph node dissection for minimally invasive surgery in non-small cell lung cancer (Suga et al., 2004). Wisner and coworkers found that a surface-modified, iodinated chylomicron remnant-like emulsion provided marked, selective enhancement of targeted lymph nodes after subcutaneous administration (Wisner et al., 2002). Moreover, the formulation produced significant opacification of more distant node groups from a single injection. Wolf and coworkers estimated in vivo extraction of lymphographic material in the popliteal node of rabbits using radiopaque nanoparticles (Wolf et al., 1999). Gazelle et al. evaluated the efficacy of a nanoparticulate CT contrast agent—ethyl ester of diatrizoic acid (EEDA)—in an animal model of focal liver disease (Gazelle et al., 1995). They found that liver-directed agents such as EEDA may prove more efficacious than currently available extracellular agents designed for liver CT scanning. Wisner et al. also evaluated the imaging characteristics of an iodinated particulate contrast agent for indirect CT lymphography of normal subdiaphragmatic lymph nodes in dogs (Wisner et al., 1995). The CT images showed enhancement of regional lymph nodes draining various injection sites.

Additional applications of different nanoparticles as CT contrast agents are described in excellent reviews on potential CT contrast media (Yu & Watson, 1999) and newly presented contrast agents (Blankenberg, 2003).

IV. Nanoparticles for MRI

Nanoparticles as contrast agents for MRI have greatly benefited medical examinations because T1-weighted, T2-weighted, or T2-*weighted images alone sometimes do not adequately show anatomy or pathology. Frequently used Gd-liposome (Mulder et al., 2006), Gd-polymer (Kobayashi & Brechbiel, 2005), Gd-DNA (Endres et al., 2007), and Gd-protein (Chan & Wong, 2007) based soft nanoparticles serve as T1-enhanced contrast agents in MRI, while iron oxide (Mulder et al., 2007) or other (super)paramagnetic hard nanoparticles (Seo et al., 2006; Babinec & Babincová, 2007) usually act as T2, particularly T2*-enhanced contrast agents. It should be noted that small iron oxide or other superparamagnetic hard nanoparticles may enhance T1 signal as well as T2 and T2* (Cunningham et al., 2005; Mani et al., 2006). A summary of different contrast agents for MRI is shown in Table 2 .

1) T1-Contrast Agents for MRI

Gd-based T1 contrast agents were first introduced in MRI by Young et al. after Levy and coworkers confirmed enhancement in the magnetic resonance field (Levy, Dechter, & Kowalewski, 1978; Young et al., 1981; Carr et al., 1984). Gadolinium-based MRI contrast agents (CAs) of various sizes and chemical properties prepared via relatively simple chemistry can provide sufficient contrast enhancement for various applications (Kobayashi & Brechbiel, 2005). Regarding different sizes of Gd-based contrast agents, they show different functions: (1) small-sized polyamidoamine (PAMAM) dendrimer-core agents (<3 nm) easily leak across vascular walls, causing rapid perfusion; (2) 3-6 nm agents are quickly excreted through the kidney, showing promise for functional renal contrast enhancement; (3) 7-12 nm agents can be used as blood pool contrast agents because they are retained in circulation; (4) 12-15 nm agents are easily recognized by the reticuloendothelial system (RES) rather than by vascular walls or excretion routes; and (5) 15-20 nm agents exhibit different behaviors in the body. Regarding different chemical properties, Gd-based contrast agents also show various functions: (1) agents with a hydrophobic core of polypropylenimine diaminobutane (DAB) dendrimer easily accumulate in the liver and can be used as liver contrast agents; and (2) hydrophilic contrast agents can be used for lymphatic imaging. Finally, contrast agents targeted to antibodies (Sipkins et al., 1998), receptors (Lipinski et al., 2006), DNA (Endres et al., 2007), or functional peptides (Tesauro et al., 2007) can act as tumor-specific agents with dual diagnostic and therapeutic functions (Winter et al., 2006) based on gadolinium components (Kobayashi & Brechbiel, 2005; Lee et al., 2007b).

Gd-based agents have numerous applications as MRI contrast agents for imaging functional anatomy of tumor blood vessels, such as contrast agents for micro-MR

angiography of normal and intratumoral vessels (Kobayashi et al., 2001a), detection of alterations in tumor vessel permeability induced by radiation (Kobayashi et al., 2004a), specific organs such as liver (Kobayashi et al., 2001b), kidney (Kobayashi et al., 2002; Kobayashi et al., 2004b), and brain (Ito et al., 2006), and the lymphatic node system (Kobayashi et al., 2003; Kobayashi et al., 2006). Previous results of liver and kidney targeting, or lymphatic, particularly sentinel node imaging (Kobayashi et al., 2004c), showed that Gd-based contrast agents have been applied in further preclinical studies or clinical practices (Kobayashi & Brechbiel, 2005; Laurent, Vander Elst & Muller, 2006; Xu et al., 2007).

An exceptional case of T1 contrast agents based on gadolinium is Gd_2O_3 solid nanoparticles (Burnett et al., 1985; Bridot et al., 2007). These luminescent hybrid nanoparticles of Gd_2O_3 coated with a polysiloxane shell include organic fluorophores and carboxylated PEG covalently immobilized on the surfaces of the inorganic nanoparticles. Experimental data showed that these particles induce enhanced positive contrast in MRI compared to commonly used positive contrast agents like Gd-DOTA in clinical MRI practice (shown in Figure 8 [Figure 8: see original paper]). These solid T1 nanoparticles may also have good promise for diagnostic and neutron-capture therapy applications.

2) T2-Contrast Agents for MRI

T2/T2* contrast agents were first developed by the Lauterbur group in 1983, and they and other groups subsequently used superparamagnetic particles for MRI (Mendonca-Dias, Gaggelli & Lauterbur, 1983; Lauffer et al., 1985; Mendoca-Dias & Lauterbur, 1986; Saini et al., 1987; Stark et al., 1988; Corot et al., 2006). The currently used ultrasmall superparamagnetic iron-oxide nanoparticles (USPIOs) for T2/T2* contrast agents were introduced by Weissleder and coworkers in 1990 (Weissleder et al., 1990a). USPIOs usually have cores of 4-6 nm with hydrated dynamic particle diameters of 10-40 nm (Wang, Hussain & Krestin, 2001; Wu, Tang & Jensen, 2004). (U)SPIOs generally produce very strong transverse and longitudinal relaxation effects in vivo compared with Gd-based contrast agents (Corot et al., 2006). For instance, a dose of 7 μmol iron/kg of a USPIO agent (NC100150) yielded a signal drop almost equal to that of a standard 0.2 mmol/kg gadodiamide injection in bolus tracking measurements of cerebral blood volume (CBV) and cerebral blood flow (CBF) (Simonsen et al., 1999; Wu, Tang & Jensen, 2004). To date, (U)SPIO nanoparticles via targeted or non-targeted approaches have been widely used in various biological or clinical applications such as imaging of small molecules (Weissleder et al., 2005), targeted receptors (Weissleder et al., 1991), magnetically labeled cells (Schulze et al., 1995), cell migration (Lewin et al., 2000), atherosclerotic plaque (Kooi et al., 2003; Frias et al., 2004), cell inflammation (Dunn et al., 2005), tissue inflammation (Turvey et al., 2005), reticuloendothelial systems (RES) (Chavanpatil, Khdair & Panyam, 2006) including liver (Harisinghani et al., 2001) and spleen (Ferrucci & Stark, 1990; Kim et al., 2006), lymph nodes (Weissleder et al., 1990b; Harisinghani et al., 2003), perfusion imaging of brain (Enochs et al., 1999), myocardium

(Weissleder et al., 1992), and kidney (Grenier, Pedersen & Hauger, 2006), MR angiography (Barrett et al., 2006; Warmuth et al., 2007), and tumor vascular imaging (Bentzen et al., 2005).

Currently, few nanoparticles for biomedical imaging applications of T2 contrast agents have been reported in animal models besides USPIOs and SPIOs, such as the FeCo core/single graphitic-shell nanoparticles reported by the Dai group (Seo et al., 2006) and the spinel ferrite nanoparticles discovered by the Cheon group (Lee et al., 2007c). The Dai group found that FeCo/C core-shell nanoparticles show ultrahigh saturation magnetization and r1/r2 relaxivities. Preliminary in vivo results demonstrated long-lasting positive contrast enhancement for vascular MRI in a rabbit model. This core-shell nanoparticle may serve as a combined agent for integrated diagnosis and therapeutic applications. The Cheon group used artificial engineering methods to prepare spinel ferrite nanoparticles conjugated with antibodies that showed enhanced T2 signal for detection of cancer markers compared with normal probes. They also successfully visualized small tumors in a mouse model (shown in Figure 9 [Figure 9: see original paper]). These high-performance magnetic nanoparticle systems could play a key role in real-time imaging of biological/medical events such as cell trafficking, cancer metastasis, cellular signaling, and tumor diagnostics.

3) A Combination of T1 and T2-Contrast Agents for MRI

Some groups have tested simultaneous acquisition of T1-weighted and T2-weighted images in MRI. Burnett and coworkers demonstrated the utility of gadolinium oxide (Gd_2O_3) nanoparticles as liver, spleen, and lung contrast-enhancing agents with marked increases in signal intensity in both T1 and T2 relaxation acceleration even at small quantities (Burnett et al., 1985). Moreover, Chapon et al. showed that accurate characterization of myocardial infarction volume and detection of myocardial viability post-infarction in rats is possible (Chapon et al., 2005). Yuan et al. identified lipid-rich necrotic cores with 85% sensitivity and 92% specificity in advanced human carotid arteries using multi-contrast techniques in vivo MRI (Yuan et al., 2001). Benefiting from combinations of multiple contrast techniques, it is possible to recognize plaque anatomy and its fine structures or even compositions in animal models (Skinner et al., 1995; Helft et al., 2001), and distinguish the aorta (Fayad et al., 2000) and carotid artery (Toussaint et al., 1996) in humans.

V. Nanoparticles for USG

Ultrasonography (ultrasound imaging) of tissues and borders between tissues relies mainly on differences in the product of the speed of sound in the medium multiplied by the density of that medium—i.e., acoustic impedance mismatch (Leighton, 1997). Contrast agent particles with the highest echo response would be those with the greatest acoustic impedance mismatch between the bulk medium (e.g., blood, which has acoustic impedance quite close to water) and a

microphase composed of contrast agents. Several types of contrast agents in ultrasound imaging based on nanoparticles/microparticles include hard nanoparticles such as solid silica/polymer nanoparticles (Liu et al., 2006; Liu et al., 2007a), metal oxide nanoparticles (Nolte et al., 2005), and noble metal nanoparticles (Willard & Van Bommel, 2005), and soft nanoparticles such as liquid-core microemulsions and nanoemulsions (Lanza et al., 1996), liposomes (Alkan-Onyuksel et al., 1996), and gas-filled microbubbles with average sizes of several micrometers (Fritz et al., 1997; Meza et al., 1996). The use of hard nanoparticles for ultrasound imaging is in its preliminary phase, with few studies reported, so we will not discuss them in detail.

Among soft nanoparticle/microparticle contrast agents, gas-filled microbubbles provide the highest contrast signal in ultrasound imaging (Klibanov et al., 2002). Liquid contrast emulsion nanoparticles/microparticles show lower contrast signal but enhanced stability and prolonged circulation time (Lanza et al., 1996). As for multilamellar liposome-based agents, they were initially thought to offer different acoustic responses due to their multilamellar lipid structures (Alkan-Onyuksel et al., 1996); later studies showed that their acoustic responses were caused by incorporated pockets of gas phase (Huang et al., 2002). The signal enhancement provided by liposome particles is several orders of magnitude lower than that of microbubble-based agents (Coussios et al., 2004; Klibanov, 2005). Since microbubbles show the best detection sensitivity and some of these contrast agents are already FDA-approved for blood pool indications, we will focus our discussion on microbubble-based contrast media in ultrasound imaging applications.

Gramiak and Shah first showed that gas microbubbles could be used to enhance ultrasound contrast in 1968 (Gramiak & Shah, 1968). Usually, gas microbubbles need to be coated with a layer of material or targeted to receptors or ligands to serve as stable and specific contrast agents in ultrasound imaging. In the 1980s, ultrasound contrast agents were coated with an adsorbed layer of saccharide (Feinstein et al., 1984) or protein (Feinstein et al., 1990). Albumin-coated microbubbles such as Albunex® and Optison™ (GE Healthcare) were the first commercially available and FDA-approved contrast agents. The first successful targeted ultrasound contrast agents were developed in the late 1990s using avidin-biotin adhesion (Lanza et al., 1997; Klibanov, 1999). For in vivo imaging, Lanza group developed a three-step process (Lanza et al., 1997): step one, a biotinylated monoclonal antibody was administered and bound to fibrin within the clot; step two, avidin molecules were administered that bound the biotin on the monoclonal antibody; step three, biotinylated ultrasound contrast agents were given that bound the exposed end of the avidin molecule. This targeting ultrasound contrast caused a four-fold increase in acoustic signal from clots (Lanza et al., 1997). To date, various targeted ultrasound probes such as ICAM1 (Song et al., 2002), VCAM1 (Hamilton et al., 2004), P-selectin (Lindner et al., 2001), fibrin (Lanza et al., 1997; Demos et al., 1999), avidin (Korpanty et al., 2005), genetic payloads (Frenkel et al., 2002; Lentacker et al., 2006), and integrins (Leong-Poi et al., 2003) have been successfully tested. In clinical ultrasound sys-

tems, these stabilized microbubbles have been used to enhance the reflectivity of perfused tissues in applications spanning cardiology, neuroscience, and radiology. Targeted contrast agents have not yet been applied clinically (Sakamoto et al., 2005; Kruger Hagen et al., 2000), but preclinical studies have successfully demonstrated applications in angiogenesis and vascular inflammation, and these microbubbles may be good candidates for targeted delivery of therapeutic agents. For details on contrast agents in ultrasonography, readers are referred to an outstanding review by Ferrara et al. (Ferrara, Pollard & Borden, 2007).

VI. Nanoparticles for PET

In PET, radiolabeled nuclides are conjugated to receptors, enzymes, transporters, ion channels, siRNA, mRNA, and specific substrate-associated sites such as β-amyloid plaques found in Alzheimer' s disease to form soft nanoparticles (Collier et al., 2002; Groves et al., 2007; Holschbach & Olsson, 2002; Jarkas et al., 2005; Wilson et al., 2002). Radiolabeled nuclides are also attached to the surfaces of some hard nanoparticles such as carbon nanotubes (Liu et al., 2007b). Commonly used positron-emitting radionuclides include ^{11}C ($t_1/_2$=20.4 min), ^{13}N ($t_1/_2$=9.96 min), ^{15}O ($t_1/_2$=2.03 min), ^{18}F ($t_1/_2$=109.8 min), ^{64}Cu ($t_1/_2$=12.7 hours), ^{68}Ga ($t_1/_2$=68 min), ^{76}Br ($t_1/_2$=16.1 hours), ^{86}Y ($t_1/_2$=14.7 hours), ^{89}Zr ($t_1/_2$=3.3 days), ^{94} Tc ($t_1/_2$=52.5 min), ^{94}Tc ($t_1/_2$=293 min), ^{124}I ($t_1/_2$=4.3 days), and ^{177}Lu ($t_1/_2$=6.7 days) (Roeda et al., 2007; Räty et al., 2007; Barker et al., 2001; Cai, Niu & Chen, 2007). Depending on the injected radionuclides, many biological and metabolic processes can be visualized using PET, including glucose metabolism (^{18}F-deoxyglucose (^{18}F-FDG)), DNA synthesis (^{11}C-thymidine) and consumption (^{18}F-thymidine (^{18}F-FLT)), amino acid transport and metabolism (^{11}C-methionine) in cells, ER expression (^{18}F-16α-fluorestradiol (FES)), bone formation and mineralization (^{18}F-fluoride), thymidine kinase activity (^{18}F-fluorothymidine (FLT)), blood flow and perfusion ($H_2{}^{15}O$, ^{82}Rubidium, and $^{13}NH_3$), or tissue hypoxia (^{18}F-misonidazole) (Machtens et al., 2007; Långström, Itsenko & Rahman, 2007; Mankoff & Eubank, 2006).

Among these radionuclides, ^{18}F, specifically ^{18}F-fluorodeoxyglucose ([^{18}F]FDG), is the most widely used tracer in oncology and clinical diagnosis, with many review papers available for this agent (de Geus-Oei et al., 2007; Ido et al., 1978; Nutt, 2007; Vallabhajosula, 2007). Here, we present some cases for ^{64}Cu-labeled nanoparticles in PET. Pressly et al. reported ^{64}Cu-labeled nanoparticles comprised of amphiphilic block graft copolymers and studied the pharmacokinetics and enhanced blood lifetime based on the labeled nanoparticles (Pressly et al., 2007). The Dai and Chen groups co-investigated the biodistribution of ^{64}Cu-labeled SWNTs in mice by in vivo PET, ex vivo biodistribution, and Raman spectroscopy (Liu et al., 2007b). They found that effectively PEGylated SWNTs show relatively long blood circulation time, low uptake by the reticuloendothelial system (RES), and high tumor accumulation (shown in Figure 10 [Figure 10: see original paper]). Sun et al. developed a novel strategy to construct

shell-crosslinked nanoparticles with large numbers of DOTA-lysines per particle (>400) that were accessible for ^{64}Cu radiolabeling, showing good promise as in vivo PET tracers at low administered doses (Sun et al., 2007). The Davis group conjugated 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to the 5'end of targeted siRNA nanoparticles, enabling labeling with ^{64}Cu for PET imaging. They found that transferrin-targeted siRNA nanoparticles reduced tumor luciferase activity by 50% relative to non-targeted siRNA nanoparticles one day after injection (Bartlett et al., 2007). Chakrabarti et al. imaged oncogene mRNAs with radiolabeled ^{64}Cu PNA-peptide nanoparticles by PET and found that targeted nanoparticles provide specific oncogene expression in pancreas cancer xenografts (Chakrabarti et al., 2007).

VII. Nanoparticles for Multimodality Imaging

Among all biological and medical imaging modalities, no single modality is perfect or sufficient to obtain all necessary information (Massoud & Gambhir, 2003). For instance, it is difficult to accurately quantify optical signals in living subjects, especially in deep tissues; MRI suffers from low sensitivity despite high resolution; radionuclide-based imaging techniques such as PET and SPECT have very high sensitivity but relatively poor resolution; USG offers a very inexpensive and convenient method but has poor resolution and cannot image hard tissues; and CT, while having high resolution, involves X-ray exposure for patients in clinical diagnosis. Combining multiple biological and medical imaging modalities can provide many advantages over any single modality. On one hand, combining optical imaging with 3D tomographic techniques such as PET, CT (including SPECT), or MRI can enable noninvasive in vivo imaging with higher sensitivity and/or accuracy. On the other hand, various nanoparticles with large surface areas can incorporate multiple functional units for multimodality imaging (Cai & Chen, 2007; Stell et al., 2007).

(1) MRI & Optical Imaging

Several groups used various magnetic nanoparticles conjugated with optically active components for magnetic-opto bimodal imaging (Talanov et al., 2006; Neuwelt et al., 2004; Veiseh et al., 2005). Cy5.5-PEG-iron oxide soft-hard nanoparticles were coated with chlorotoxin, a glioma tumor-targeting peptide of 36 amino acids, to improve tumor-specific binding of multimodal imaging probes (Kircher et al., 2003; Veiseh et al., 2005). A cellular uptake study of 9L glioma cells (positive control) and rat cardiomyocyte (rCM) cells (negative control) showed tumor-specific binding and internalization of the targeted nanoparticles by glioma cells. Choi et al. conjugated magnetic iron oxide nanoparticles with near-infrared (NIR) fluorescent single-walled carbon nanotubes (SWNT), forming heterostructured complexes that can be used as bimodal bioimaging agents (Choi et al., 2007). These nanoparticulate complexes have longer spin-spin relaxation times than typical ferromagnetic particles due to the smaller size of their magnetic component while retaining SWNT optical signals. DNA-

wrapped nanoparticulate complexes taken up by macrophage cells were imaged using MRI and NIR mapping, demonstrating that these multifunctional nanostructures could be useful in multimodal biomedical imaging. The Hilger group used fluorescent magnetosomes as bimodal contrast agents for diagnostic purposes, showing the excellent spatial resolution of MRI and high sensitivity of fluorescence imaging (Lisy et al., 2007). Yang et al. reported Gd(III)-functionalized fluorescent quantum dots as multimodal imaging probes (Yang et al., 2006). These multimodal probes exhibit yellow fluorescence and strong paramagnetic signals. Van Tilborg et al. used Annexin A5-conjugated magnetic nanoparticles, which significantly increased the relaxation rates of apoptotic cell pellets compared to untreated control cells and apoptotic cells treated with non-conjugated nanoparticles (van Tilborg et al., 2006). Moreover, Jaffer et al. showed that atherosclerosis-targeted magnetic nanoparticles provide a foundation for imaging genetic and/or pharmacological perturbations of cellular inflammation in atherosclerosis by MRI and optical imaging (Jaffer et al., 2006).

(2) MRI & SPECT/CT

Zheng et al. evaluated the in vivo performance of a liposome formulation coencapsulating iohexol and gadoteridol as a bimodal contrast agent for CT and MR-based image guidance applications (Zheng et al., 2007). The long in vivo circulation lifetime and simultaneous CT and MR signal enhancement provided by this liposome system make it a good candidate for image guidance applications. Watkin et al. synthesized gadolinium oxide albumin microspheres (GOAM) and conducted preliminary imaging studies utilizing ultrasound, MR, and CT (Watkin et al., 2002). Zielhuis et al. designed nanosized liposomes labeled with radionuclides holmium-166 (both a beta- and gamma-emitter and highly paramagnetic) or technetium-99m, and coloaded with paramagnetic gadolinium, enabling multimodal SPECT and MR imaging and radionuclide therapy within a single agent. These nanoparticulate liposomes allow for multimodality imaging and therapy, making these new agents highly attractive for future applications (Zielhuis et al., 2006).

(3) MRI & Ultrasound Imaging

Nolte et al. evaluated whether SPIO particles improved detection and demarcation of experimental gliomas on sonograms, which may improve intraoperative neuronavigation with sonography and provide a way to enhance both MRI and US imaging (Nolte et al., 2005).

(4) PET & Optical Imaging

The Chen group quantitatively developed a tumor-targeting efficacy study of a dual-function QD-based probe using PET and near-infrared fluorescent imaging (Cai et al., 2007b). This dual-function probe significantly reduced potential toxicity and overcame the tissue penetration limitation of optical imaging, enabling quantitative targeted imaging in deep tissue.

(5) PET & CT

Bartlett et al. employed PET and CT to monitor whole-body biodistribution kinetics and tumor localization of siRNA nanoparticles while simultaneously using bioluminescent imaging (BLI) to measure luciferase knockdown by the delivered siRNA molecules (Bartlett et al., 2007). By formulating nanoparticles with or without transferrin targeting ligands, the effect of cell-specific targeting on both biodistribution and function could be studied simultaneously within the same animal. Antoch et al. evaluated whether mannitol-LBG might be used as a negative oral contrast agent in PET/CT scanning because it provides excellent bowel distention while avoiding contrast material-induced PET artifacts (Antoch et al., 2004).

VIII. Perspective

Although molecular imaging can effectively detect small lesions in the human body, fundamental questions remain: Where are the boundaries of atoms in various biomolecules? Where are the boundaries of molecules in organelles? Where are the boundaries between cells in tissues? Where are the boundaries between organelles in cells? Where are the boundaries between tissues in organs? Where is the boundary between healthy tissues and lesions such as tumors and cerebrovascular diseases? How do lesion tissues evolve and migrate? Where are the boundaries between organs?

Beyond the human body, where are the boundaries between people (physical and spiritual)? Where are the boundaries on land, mountains, lakes, and forests? Where are the boundaries between groups? Where is the boundary between living and inanimate? Where is the boundary between land and sea? Where is the boundary between life and death? Where are the borders between countries? How are boundaries between social units divided, changed, evolved, and migrated? Where is the boundary between Earth and the Moon? Where are the boundaries of the solar system? How do boundaries of all things in nature move, transform, and change? How do units in the universe evolve? Where are the boundaries between religions? Where are the boundaries between social ideologies? Where are the boundaries of the universe? Where are the boundaries of the Milky Way? Where is the boundary between consciousness and matter? Where is the boundary between philosophy and natural sciences? When boundaries are unclear, conflicts arise between individuals, social organizations, nations, spirit and matter, galaxies, stars and moons. How can we avoid conflicts from boundary constraints? While this review covers imaging of lesions, especially tumors, using molecular imaging probes that clearly show boundaries between tumors and healthy tissues, many more boundaries can be considered and explored.

IX. Conclusions

Nanotechnology has contributed to all areas of biological and medical imaging as discussed in this review. (1) For optical imaging (OI), different shapes of gold nanoparticles and various types of QDs have been focused on in non-targeted or targeted in vitro/vivo experiments, besides other nanoparticles. These results show good promise, but there is still a long way to reach clinical application due to concerns such as eliminating QD toxicity in the body. (2) For computed tomography, commercial barium-based hard particles and iodinated liposome/micelle nanoparticles have been used in clinical practice for many years, though some side effects remain for patients. Other types of nanoparticulate materials such as Bi_2S_3 and heavy metal nanoparticles (e.g., gold) are just beginning in vivo experiments. (3) For magnetic resonance imaging, the most well-investigated Gd-based nanoparticle T1 contrast agents have been FDA-approved and used clinically for years. Meanwhile, the most used iron oxide nanoparticle T2 contrast agents are already in clinical practice or phase III clinical trials. (4) For ultrasonography, various microbubbles have been used clinically for many years, but few nanosized particles are in clinical use, though several liposome-based nanoparticles have been tested in vivo. (5) For positron emission tomography, a series of radiolabeled nuclei attached to liposome or other nanoparticle surfaces have been tested in vivo and in vitro. (6) Very recently, multifunctional nanoparticles for multimodal imaging have appeared. MRI/OI, MRI/SPECT/CT, MRI/USG, PET/OI, and PET/CT have shown good promise in vitro, ex vivo, and even in vivo (Cai & Chen, 2007).

In summary, the future of various nanoparticles for biological and medical imaging will be multifunctional, targeted, and combined with therapeutic function (Cai & Chen, 2007). There is good promise for nanoparticles in biological and medical imaging, but there is still a long way to go. The ultimate goal is that nanoparticle-based agents will enable efficient, targeted in vivo delivery of therapeutically functional drugs with minimal or no toxicity to patients, while allowing the therapy process to be monitored non-invasively over time.

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Figure Legends

Figure 1. (A) Light scattering images of anti-EGFR/Au nanospheres after incubation with cells for 30 min at room temperature. (B) Light scattering images of anti-EGFR/Au nanorods after incubation with cells for 30 min at room temperature. (C) Average extinction spectra of anti-EGFR/Au nanospheres from 20 different single cells for each kind. (D) Average extinction spectra of anti-EGFR/Au nanorods from 20 different single cells for each kind. From gold nanospheres, the green to yellow color is most dominant, corresponding to the surface plasmonic enhancement of scattering light in the visible region, and from gold nanorods, the orange to red color is most dominant, corresponding to the surface plasmonic enhancement of the longitudinal oscillation in the near-infrared region (With permission adapted from Huang et al., 2006b; Copyright © 2006 American Chemical Society).

Figure 2. Characterization of individual Ag nanoparticles embedded inside a fully developed (120 hpf) zebrafish using dark-field SNOMS. (A) Optical image of a fixed, normally developed zebrafish. The rectangles highlight representative areas: (i) retina, (ii) brain (mesencephalon cavity), (iii) heart, (iv) gill arches, and (v) tail. (B) Zoom-in optical images of single Ag nanoparticles embedded in those tissue sections outlined in (A). Dashed circles outline the representative embedded individual Ag nanoparticles. Scale bar = 400 μm (A) and 4 μm (B)

(With permission adapted from Lee et al., 2007a; Copyright © 2007 American Chemical Society).

Imaging Figures

Figure 3. In vivo fluorescence images of tumor-bearing mice using QD probes with three different surface modifications: carboxylic acid groups (left), PEG groups (middle) and PEG-PSMA Ab conjugates (right). For each surface modification, a color image (top), two fluorescence spectra from QD and animal skin (middle) and a spectrally resolved image (bottom) were obtained from the live mouse models bearing C4-2 human prostate tumors of similar sizes (0.5−1.0 cm in diameter). The amounts of injected QDs and the lengths of circulation were: 6 nmol and 6 h for the COOH probe; 6 nmol and 24 h for the PEG probe; and 0.4 nmol and 2 h for the PSMA probe. The site of QD injection was observed as a red spot on the mouse tail. The spectral feature at 700 nm (red curve, middle panel) was an artifact caused by mathematical fitting of the original QD spectrum, which has little or no effect on background removal (With permission adapted from Gao et al., 2004; Copyright © 2004 Nature Publishing Group).

Figure 4. XFM maps of whole PC12 cell transfected with mitochondria-specific nanoconjugates using natural uptake. (a) Elemental maps of P, S, Cl, K, Ca, Ti, Mn, Fe, Cu, and Zn in PC12 cell treated with nanoconjugates carrying ND2s oligonucleotide for 24 h and then "washed" for 24 h in nanoconjugate-free medium. Elemental maps show the range of concentrations in the sample in a rainbow color scale from highest (red) to lowest (black) signal. Scan area was 13 µm × 12.8 µm, with 0.2 µm step. Scanning was done at 2ID-D beamline at the APS. Elemental concentrations are given in µg per cm^2. White size bar is 2 µm. (b) Enlarged Ti maps of the cells in (a) and a detailed XFM map of a mitochondria inside the cell. Left: enlarged Ti map of the whole cell. Right: S, Ti, Mn and overlap maps for the mitochondria-shaped form from the left panel. The scan area was 1.5 µm × 1.5 µm with 50 nm step. Scanning was done at 2ID-D beamline at the APS. White size bar is 100 nm (With permission adapted from Paunesku et al., 2007; Copyright © 2007 American Chemical Society).

Figure 5. Micrographs at two magnifications of liver tissue from rabbits killed 24 h after i.v. administration of suspended SWNTs. (A and B) Near-IR SWNT fluorescence images with field widths of 390 µm (A) and 83 µm (B). Scattered isolated bright pixels are artifacts from defective sensor elements in the near-IR camera; all larger features represent emission from SWNTs. In C and D, the SWNT fluorescence from A and B is shown overlaid as false-color green onto visible bright-field images from adjacent 3-µm-thick specimen slices that had been stained with hematoxylin and eosin (With permission adapted from Cherukuri et al., 2006, Copyright © 2006 by the National Academy of Sciences).

Figure 6. Serial CT images in a rat hepatoma model following injection of 400 µL of PEG-coated GNPs (100 mg/mL) into the tail vein. Images were obtained at (a) 0 h (before injection) and (b) 5 min, (c) 1 h, (d) 2 h, (e) 4

h, and (f) 12 h after injection. Arrows indicate the hepatoma regions, and the arrowheads indicate the aorta. Numbers in brackets are the HU values of the hepatoma regions (left) and the surrounding normal liver parenchyma (right) (With permission adapted from Kim et al., 2007, Copyright © 2007 by American Chemical Society).

Figure 7. Kinetics and distribution of N1177 in nonatherosclerotic rabbits. (a,b) Axial view (acquired by CT) of a nonatherosclerotic rabbit 5 min after the injection of N1177 (a) showing the enhancement of the aorta (white arrowhead) and vena cava (white arrow), allowing for the reconstruction of three-dimensional CT angiograms (b). (c) Two hours after the injection of N1177, a strong enhancement was detected in the spleen (asterisk), as shown in the axial CT view of the rabbit. (d) The regions of high densities were identified on a three-dimensional reconstruction of the CT scan using a color scale. Note the strong enhancement of the spleen and the liver 2 h after the injection of N1177. The same level and width windows were used for images a and c. Inserts in b and d indicate the color scale of densities in HU. (e) Densities in HU of the different organs (assessed by CT) before and at different time points after the injection of N1177 (squares) or a conventional iodinated contrast agent (circles). Densities measured in macrophage-rich organs were significantly higher 2 h after the injection of N1177 compared to precontrast values, whereas no enhancement was detected in these organs 2 h after the injection of a conventional CT contrast agent. Black arrows denote the time of injection (With permission adapted from Hyafil et al., 2007; Copyright © 2007 Nature Publishing Group).

Figure 8. Fluorescence reflectance imaging of a nude mouse (a, b, c) before and (d, e, f) 3 hours after the injection of GadoSiPEG2C (K, kidneys; B, bladder). Fluorescence reflectance imaging of some organs after dissection (g) of a control mouse (no particles injection) and (h) of the nude mouse visualized on pictures (a-f). (i) Fluorescence reflectance imaging of a nude mouse after the injection of GadoSi2C (particles without PEG). Each image is acquired with an exposure time of 200 ms (With permission adapted from Bridot et al., 2007; Copyright © 2007 American Chemical Society).

Figure 9. In vivo MR detection of cancer using magnetic nanoparticle–Herceptin conjugates. (a–f) Color maps of T2-weighted MR images of a mouse implanted with the cancer cell line NIH3T6.7, at different time points after injection of MnMEIO-Herceptin conjugates or CLIO-Herceptin conjugates (preinjection (a,d); and 1 h (b,e) or 2 h (c,f) after injection). In a–c, gradual color changes at the tumor site, from red (that is, low R2) to blue (that is, high R2), indicate progressive targeting by MnMEIO-Herceptin conjugates. In contrast, almost no change was seen in the mouse treated with CLIO-Herceptin conjugate (d–f). (g) Plot of R2 change versus time. In the mouse treated with MnMEIO-Herceptin conjugate (squares), significant R2 changes (up to 34%) were observed with time after treatment. In contrast, R2 changed by <5% after treatment with CLIO-Herceptin conjugate (dots) and by <13% after treatment with 12-nm-MEIO–Herceptin conjugate (triangles). (h) Ex vivo MR images (i–

iii) of explanted tumors (8 h) and their color maps (iv–vi). Tumor explanted after treatment with MnMEIO-Herceptin conjugate (i) is dark; that explanted following CLIO-Herceptin conjugate treatment (ii) or no treatment (iii) shows no contrast. Consistently, in the image color-coded according to R2, the tumor explanted after MnMEIO-Herceptin conjugate treatment is blue (iv) whereas that after CLIO-Herceptin conjugate treatment (v) or no treatment (vi) is red (With permission adapted from Lee et al., 2007c; Copyright © 2007 Nature Publishing Group).

Figure 10. Functionalization-dependent biodistribution and blood circulation of intravenously injected SWNTs in mice bearing the U87MG human glioblastoma tumour. a, MicroPET images of two mice at various time points post tail-vein injection of 64Cu-labelled SWNT–PEG2000 and SWNT–PEG5400, respectively. The arrows point to the tumours. b, Liver uptake curves over time as measured by PET for the two SWNT conjugates. c, Blood activity curves for the two conjugates. All data points represent three animals per group (four mice per group for c) (With permission adapted from Liu et al., 2007b; Copyright © 2007 Nature Publishing Group).

Comparison of Imaging Modalities

Table 1. Comparison of various biological and medical imaging modalities (Adapted partly from Hengerer et al., 2005; Elliott & Thrush, 1996; Ferrara, Pollard & Borden, 2007).

Modality	Molecular Info	Functional Info	Anatomical Info	Resolution	Depth Limit	Contrast Conc.	Comments
SPECT	+++	+++	+++	<0.0001–1.1 mm (Axial/Lateral)	No Limit	pM–nM	Very sensitive, Range of nuclides and energies
PET	+++	+++	+++	Frequency dependent	No Limit	<pM–nM	Very sensitive, Quantitation

Modality	Molecular Info	Functional Info	Anatomical Info	Resolution	Depth Limit	Contrast Conc.	Comments
MRI	No radiation, smart contrast agents	Molec. Func. Anat. Info.	+++	<0.0001–1.1 mm (Axial/Lateral)	Frequency-dependent	mM–µM	No radiation, smart contrast agents
OI	No radiation, Small devices, Multi-Wavelength Imaging, Smart contrast agents	+++	+++	Frequency-dependent	Limit, Depth-dependent	pM–nM	No radiation, smart contrast agents
USG	No radiation, smart contrast agents	Molec. Func. Anat. Info.	+++	Frequency-dependent	Limit, Depth-dependent	<0.0001–1.1 mm (Axial/Lateral)	Very sensitive, Range of nuclides and energies, Anat. Info.

CT: Computed Tomography; SPECT: Single-Photon Emission Computed Tomography; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; OI: Optical Imaging; USG: Ultrasonography; Molec. Info.: Molecular Information; Anat. Info.: Anatomical Information; Contrast Conc.: Contrast Concentration

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Comparison of MRI Contrast Media

Table 2. Comparison of some contrast media for MRI applications (Adapted partly from Barrett et al., 2006).

Contrast Media	Size	MR Applications	Comments
Albumin-(Gd-DTPA)30	92 kDa	Tumor angiogenesis, Angiography, Mammography	High polydispersity. Also used to coat liposomes and iron oxide
MS-325	68 kDa	Angiography, Lymphangiography	Blood pool, High vascular residence time
Dextran-(Gd-DTPA)15	75 kDa	Experimental only	Also used in anti-angiogenesis drug research
Dextran-(Gd-DTPA)187	—	Angiography, Cardiac perfusion studies	High polydispersity
MMCMs	165 kDa	Liver and spleen imaging, Lymphangiography	High polydispersity. Good potential for drug delivery
Liposomes (Gd or Iron)	20–400 nm	Angiogenesis, Lymphangiography, Tumor vasculature	Developmental stages only. Potential for targeting imaging and drug delivery
Viral particles (CCMV)	28 nm	Liver metastases	Potential for drug delivery, targeted imaging and stem cell imaging
Dendrimers	15 kDa (G2), 88 kDa (G5), 3820 kDa (G10)	Lymphangiography, Tumor vasculature	Potential for targeting imaging and drug delivery

Contrast Media	Size	MR Applications	Comments
SPIO	50–150 nm	Liver imaging	Negative contrast agents. Ferumoxides licensed for liver imaging
USPIO	10–50 nm	Lymphangiography, Tumor angiogenesis	Potential for drug delivery, targeted imaging and stem cell imaging
VSOP	2–10 nm	Angiography	Negative contrast agents

MMCM: Macromolecular contrast media; Gd: Gadolinium; kDa: kilo-Daltons; nm: nanometers; CCMV: cowpea chlorotic mottle virus; SPIO: superparamagnetic iron oxide; USPIO: ultrasmall superparamagnetic iron oxide; VSOP: very small superparamagnetic iron oxide

Note: Figure translations are in progress. See original paper for figures.