Egypt. J. Chem. **Vol. 65**, No. 6. pp. 199 - 205 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

A review of the applications of nanotechnology in medical imaging with contrast nanoparticle synthesis and probe design

Firas Ali Hussein Alhameedawi[a], Mohammed Khlaif Challab[b],Salam Hussein Al-Alaq[c*]

a - Directorate of Education in the holy Karbala

b - Directorate of Education in the holy Karbala

c- Directorate of Education in the holy Karbala*

Abstract

Molecular imaging is one of the major focuses in diagnostic medicine. Nanoparticles enable the effective imaging of various particles the high-contradiction cells. In this research, different effect that must be affects in the synthesis of nanoparticles contrast were investigated and several important examples were presented.This research was a literary analysis. Because the research is a review and while reviewing several important studies and analyzing their content, was discussed and concluded.In this report, most nanoparticles have been used to produce new contrast materials, especially for molecular imaging and discovery of cellular processes. The advantages of using these nanoparticles include the ability to produce high contrast, ease of integration of various features, long time in the blood circulation and the ability to carry large volumes of substances (such as medicine). The production and supply of nanocomposites has evolved over the years, and in the latest study, nanoscale contrast agents with marophage paramagnetic properties and quantum properties have the ability to produce. Atomic and molecular fractions have been reported to move more toward nanomaterials. Micro-MRE emulsions have been used for this purpose, including pharmaceutical and blood vessel use.However, few products have reached the stage of commercialization and marketing. Work on producing MRI machines with more and newer capabilities has been limited, and many contrast-enhancing factors have been the result of scientific and laboratory findings. In addition, many of the magnetic nanoparticles used in imaging are not of the desired size and accuracy, resulting in unexpected results. This is a good opportunity for in-house researchers to produce devices with higher quality and better image resolution, and as a result to turn their scientific products into technology. One of the main focuses in diagnostic medicine is molecular imaging. As discussed by Kudhawi et al. (1). Molecular imaging can help us diagnose diseases early, identify diseases in the early stages, provide important information about the pathology of processes.

Keywords: Nanoparticles, Magnetic Resonance Imaging (MRI), Molecule Imaging, medicine, Gene.

Introduction

Over the past decades, extensive research has been conducted to provide and develop newer and more capable methods for early and better diagnosis of diseases, among which imaging methods have a special place among other diagnostic methods. [1] MRI is one of these methods that has a long history in medicine. Due to the advantages and major applications of MRI in different stages of treatment of diseases, attention to new imaging methods in order to target and increase the sensitivity of this imaging method, is increasing day by day. This method is more than 50 years old. This method has made many advances during this period and has won several Nobel Prizes. In 1937, the first MRI test was performed. About seven years later, a man named Robbie submitted a work report on MRI and won the

*Corresponding author, e-mail: mohammadchellab@gmail.com:(Mohammed Khlaif Challab)
Receive Date: 15 October 2021, Revise Date: 08 February 2022, Accept Date: 21 February 2022
DOI: 10.21608/EJCHEM.2022.101148.4701

Nobel Prize in Medicine. The phenomenon of intensification in the case of atomic nuclei was first discovered by Blanche and Bursell in 1946. The two scientists were awarded the Nobel Prize in 1952 for this work. Jenrick took a two-dimensional MRI image in 1971 and two heterosexual images in 1973, and the first image of a living animal was taken in 1974, and the technology was finally seriously established in the 1980s (1). Finally, the 2003 Nobel Prize went to Paul Lutherber and Peter Mansfield for their work on MRI. Paul Lutherber showed that the use of gradients in a magnetic field makes it possible to create two-dimensional images. Peter Mansfield used a gradient in a magnetic field to be able to accurately show resonance differences. This was the main step in creating a practical illustration method. The multiplicity of Nobel Prizes in MRI illustrates the importance of this issue. This method provides high-precision images of body parts and is widely used in the world today and can replace previous methods (2).

An MRI machine is a tube surrounded by a circular magnet. This magnet creates a magnetic field. Here a radio wave with different wavelengths sweeps the surface of the sample. The end of the sample, by absorbing energy from a radio wave of the same frequency as it rotates, goes to a higher energy state and is in the direction of the external magnetic field. When the field is cut off, these nuclei return to their original state. It is at this point that electromagnetic waves are emitted from the material at radio frequencies, which are received by a coil called a coil. This wire converts incoming waves into electric current. These currents are then amplified and given to the computer as MRI signals. The computer converts this data into an image using a conversion system called Fourier transform (2).

MRI imaging is not destructive, does not emit harmful radiation, and its resolution is very high. However, the sensitivity of this method is low. Therefore, newer devices must be provided to increase the sensitivity and quality of images. This method can be used for diagnosis, treatment and development of diseases, especially cancer (3, 4, 5). The first step in effectively controlling and coping with different types of cancer is early detection of the disease. By identifying the disease in the early stages, the disease can be controlled and treated to a very high extent. Therefore, during the past decades, extensive research has been done to present and develop newer and more capable methods for early diagnosis of this disease. In addition, it is possible to see the injected drug using MRI, which allows doctors to make sure the drug has reached the desired location and to monitor the progress of treatment.

Finding

A) The latest innovation in contrast nanoparticle design

In the past, the MRI machine only diagnosed cancer after the body became involved with it, and because it lacked the necessary sensitivity, it could not detect small tumors. This inability is related to the nature of the method that MRI uses to distinguish between healthy and damaged tissue. To solve this problem, the scientists decided to use nanostructures loaded with different magnetic metal particles. Among the most important magnetic particles used in MRI are iron oxide, manganese oxide and gadolinium [2]. In fact, the use of these particles, which act as signal amplifiers in conjunction with MRI, will significantly improve its signal (6). However, some of these metals have toxic effects on the body and cannot be used. Especially gadolinium ion, which has high toxic effects, especially on the kidneys, and its use can cause some negative side effects, such as nephrogenic systemic fibrosis [3] (this complication is a large fibrosis of connective tissue that widely affects the skin, joints, eyes and internal tissues. Involved in patients. For this reason, the US Food and Drug Administration (FDA) has placed restrictions on the use of gadolinium in clinical applications (7). Therefore, structures of gadolinium must be produced that prevent the metal from coming into direct contact with the body. This biocompatibility problem was solved by developing a nanoparticle system (8). In addition, the combination of these ions with nanoparticles has created a structure that can dramatically increase the resolution of MRI images (9).

These nanoparticles are contrast enhancers, each with its own unique properties that enhance image quality. A group of these agents that are at least 10 times more effective than the best available agents currently are nanodiamonds. Nanodiamonds are highly efficient at adsorbing water molecules to their surface, which improves the properties of the nanodiamond gadolinium-(III) complex. Maybe that's why these complexes are so bright and have good image resolution. In addition, the biocompatibility of the gadolinium- (III) nanodiamond complex enhances its clinical applications (10).

Nanotubes and fullerene C80 are other agents that act as nanodiamonds and act as a stable barrier for gadolinium ions. These factors have more effects on images than nanodiamonds and increase magnetic imaging signals by 40 times.

In the first type, called the gadonanule compound, gadolinium metal atoms are trapped inside very short carbon nanotubes (11, 12, 13). Of course, many researchers have focused only on longer nanotubes,

while the advantage of short carbon nanotubes over their longer counterparts is that they are much better absorbed by cells. Thus, although gadolinium is toxic, when it is chelated or chemically bound to another compound, its toxicity is eliminated and it can be injected into the body. Invented in 2005 in the laboratory of Rice University professor of chemistry Professor Lon Wilson, the nanotubes encapsulate clusters of gadolinium ions. In this way, although these atoms cannot escape their carbon cage, they increase the resolution of MRI imaging. For this reason, these agents are harmless to the body and can be used to mark cells from within (14). See Figure 1.

Fullerene-based imaging factors remain in the tumor longer than gadolinium contrast agents, so the tumor growth range is better identified. Another advantage of fullerene is that it can be used to transport therapeutic metals. The method used to produce gadolinium agent can also be used to produce fullerenes that carry useful therapeutic metals such as lithium, terbium, or holmium. For example, fullerene containing the gadolinium-terbium compound can simultaneously image the tumor, delivering lethal doses of the radioactive material to tumor cells. As long as the metal atoms are firmly embedded in the fullerene, the medicinal properties of the various formulations may not change. This advantage accelerates the progress of treatment through Fullerin-based agents (15).

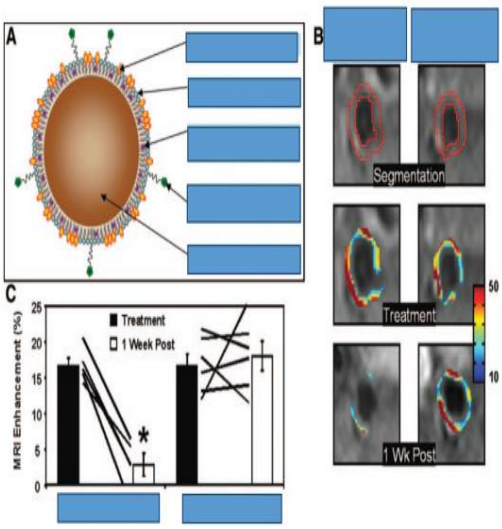

Figure 1. The contrast mass medium in injections steps [6].

In this regard, some international cooperation has been done. In a joint collaboration, a way has been found to manipulate the resolution factors within silicon particles. Thus, the efficiency of these factors in MRI imaging increased 50 times, which shows a higher resolution of the images than the mentioned factors. Here, a nanometer slice of silicon in the form of a hockey disc is used as a means of conveying the resolution factors. These plates, called silicon microparticles or [4] SiMPs, have cavities. Resolution factors were drawn into these cavities. In MRI, hydrogen atoms in water are manipulated to interact with and be aligned with the magnetic field applied by the device. These hydrogen atoms are then allowed to return to their original magnetic state, a process called relaxation. In the presence of the element gadolinium, which is paramagnetic, the rest time is shorter and these areas become brighter than their background. Silicon microparticles are small, about one micrometer wide, but when trapped by water molecules and clusters of gadolinium-containing nanotubes, the brightness of the protons is greatly increased in MRI imaging. Because decomposition of SiMPs into harmless silicic acid takes about 24 hours, there is plenty of time to image the molecules (16, 17).

As mentioned earlier, iron oxide is another widely used magnetic particle that acts as an MRI signal amplifier, like gadolinium. Coating or combining iron oxide with nanostructures has increased the signaling. Coating the particle with compounds such as peptide (18), silica (19), micelles (20) and dextran (21) showed an increase in the resolution of MRI images. Especially when placed inside a silica coating, it shows a versatile combination with the ability to image, target and treat tumors, which is an advantage over other factors (19). Dextran-coated iron oxide interacts only with the acidic environment of tumors. Therefore, nanoparticles are not absorbed by the body and do not cause disease in the individual. In addition, it is possible to remove particles from the patient's body after imaging. Dextran, on the other hand, eliminates the possibility of targeting tumors or other tissues. Scientists have tried to solve this problem by coating nanoparticles with proteins that bind to tumor surface receptors, but not all tumors are the same. In fact, one of the problems with receptor-based methods is that not all types of tumors can be assured. When the receptor is present in only 30% of tumors, it cannot be used to examine the whole body. But this method can target many tumors. Almost all tumors have a different acidic environment than healthy tissues. A work called the Warburg effect, which is one of the metabolic features of tumors, can be used to overcome the problem of targeting. Many cells in the body are aerobic and receive their main energy from oxygen. However, even when oxygen is high, tumor cells use an anaerobic process to provide energy. These cells, like tired muscles, convert glucose to lactic acid, but unlike muscles, tumors disrupt the blood flow around them and can not easily get rid of

this acid. For this reason, tumors almost always have a lower pH than the surrounding healthy tissues. Using chitosan glycol has made it possible for nanoscale carriers to remain neutral around healthy tissues, but ionized in an acidic environment and thus absorbed by tumors (21). See Figure(2).

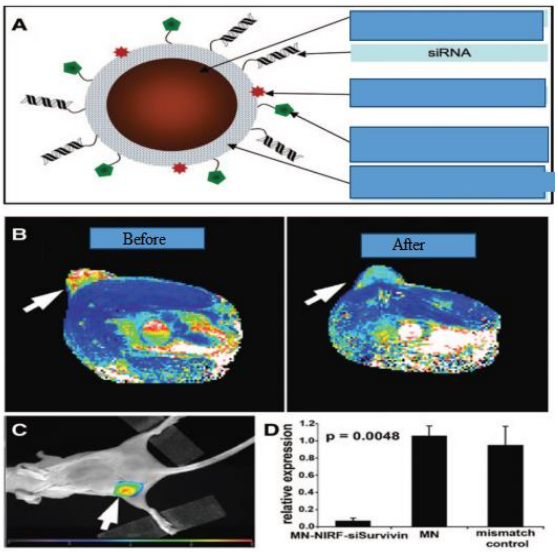

Figure 2. SiRNA iron oxides in the treatment of cancer [7].

B) Design methods of contrast nanoparticles

One of the issues that researchers have considered is the instability of iron oxide nanoparticles in aqueous medium. In fact, the main challenge in using these nanoparticles as a contrast agent is to stabilize them in the aqueous environment. Iron oxide nanoparticles can accumulate in the target tissue, reduce the signal intensity and darken the image in that area. Therefore, this problem has been solved by producing a stable magnetic nanofluid that stabilizes iron oxide nanoparticles in aqueous medium with poly (N-vinylpyrrolidone) and with the help of chemical bonds. In this regard, first iron oxide nanoparticles are prepared using a conventional and more economical all-sediment method in aqueous medium. The surface of the nanoparticles prepared using silane A is then functionalized and through this the reactive vinyl functional group enters the surface of the nanoparticles. Then, by radical polymerization method, N-vinyl pyrrolidone monomer can be polymerized on the surface of functionalized nanoparticles. Therefore, the prepared nanoparticles have a high magneticity and after coating with a biocompatible poly (N-vinyl pyrrolidone), they have a very high stability for a long time (22). Surfactant cysteine is another agent that is used as an iron oxide stabilizer. This combination also improves magnetic properties, increases saturation magnetism, and ultimately improves the contrast of MRI images. The use of synthesized particles in the clinical and human phases can be useful in the early and easier detection of cancerous lesions and tissues using MRI images. In diagnostic and therapeutic applications in humans (23).

"Price" is one of the factors that play a decisive role in the use of nanostructures as contrast agents. Because many foreign samples are expensive, some researchers, especially Iranian researchers, have based their research on it. These researchers are looking to produce more contrast-enhancing contrast-enhancing nanoparticles and cheaper production methods than those on the market and abroad. For example, iron oxide nanoparticles were synthesized using the reverse ion fermentation salt deposition method. The synthesis of these nanoparticles by this method is very simple and cheap (24). Also, cobalt ferrite nanoparticles with dextran coating have been synthesized and investigated by chemical deposition method. Similar particles that are commercially available worldwide today are very expensive and difficult to obtain. These nanoparticles have been successful in animal model experiments and, due to their small size, will allow early detection of cancers and small metastases. Therefore, the possibility of manufacturing and availability of these particles in the country is possible at a lower cost. In addition, by binding gadobutrol to the surface of the dendrimer, a stronger contrast material is produced with the ability to have a higher and more efficient image resolution. In other words, by synthesizing a biodegradable and biocompatible nanometer polymer and placing the drug on it, the extracellular contrast material is transformed into an intracellular material. The dendrimer used in this method is also very cheap and simple to produce and is a suitable and ideal option due to its non-toxicity (25).

Some of the most commonly used agents and nanostructures are referred to as contrast enhancers. Other factors have also been used by researchers, each of which has enhanced the quality of MRI images due to their specific characteristics. Some of these factors and their important characteristics are mentioned in Table(1).

In addition to the many studies that have been done on nanostructures as contrast enhancers, some individuals and companies have sought to make and supply magnetic signal amplifying particles. Usually, nanoparticle products available in the market are such that only a part of the particles in a product is in the dimensions desired by the consumer. In this regard, some companies have sought to produce magnetic nanoparticles with suitable sizes and more accurate

than previous models and market them. We can mention the two companies of Manhattan Scientific and Manano Azote Biotech, which jointly started the supply of iron oxide nanoparticles to the market. The two companies have launched special nanoparticles under the brand name "NanoMRX" that can be used to increase the contrast of MRI images. These nanoparticles are manufactured by Senior Scientific, a subsidiary of Manhattan Scientific. The uniformity and dimensional accuracy of NanoMRX nanoparticles are different from other iron oxide nanoparticles on the market; For this reason, it can improve test results. NanoMRX nanoparticles have dimensions of 5 to 30 nanometers and its dimension uncertainty is only 0.5 nanometers. The market for precision-sized nanoparticles is still young, but there are many people in the same market who want to buy this product. This is a sign of the high potential in this area (26).See Figure (3).

As mentioned earlier, nanotechnology, in addition to increasing the resolution of MRI images by nanostructures, has had a significant effect on MRI imaging by building new MRI devices with more capabilities.

With the help of a magnetic field, it is possible to identify the single electron and the nucleus of an atom. Doing so makes it possible to produce three-dimensional images of molecules. In fact, it is possible to build a nanoscale MRI machine. A very small force called an electron spin, which has a sensitivity of about 400 electrons, was identified.

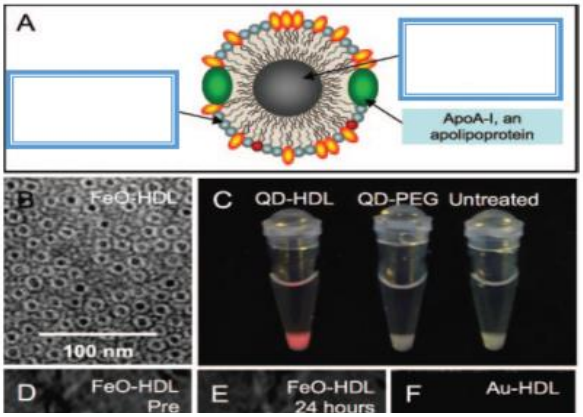

Figure 3. Particles in vitro in MRI atherosclerosis [8].

This force is directed to one side in the presence of a very strong magnetic field. Now, by applying a radio frequency field, the spins can be changed, which is called the deflection axis. In MRI machines, the voltage created by the deflection of the axis is detected and recorded by a coil, while researchers are trying to make a device that can do exactly that, except that the force to be detected here is the force of a single electron or The nucleus is a molecule (27).

On the other hand, single electrons can be placed on a diamond crystal to realize a nanoscale magnetic imaging device. There are many challenges ahead to build such a device. For example, how can a magnetic field be measured using the resonance of single electrons inside a diamond crystal? Resonance is a phenomenon in which an object tends to oscillate at a frequency higher than its original oscillation frequency. This phenomenon happens around us many times. For example, this phenomenon is used in various instruments and pendulum clocks. In magnetic imaging, this means that imaging is possible only in a small distance from the field. This makes imaging difficult. Despite all these difficulties, imaging is currently being done, but complex processes must be used to draw the right image. It is also necessary to use software to overcome hardware limitations. This leads to a longer and more difficult interpretation process. Therefore, a trick based on quantum computing can be used to overcome hardware limitations and see the entire magnetic field. This improved the ratio between the maximum visible field strength and field accuracy by a factor of 10 compared to previous standard methods. Therefore, a step was taken towards the construction of a nanoscale MRI device that can be used to study the properties of molecules (28).

Using nano-MRI microscopes, IBM scientists have observed molecular structures 60,000 times better than what modern MRI technology allows. This technology is the first to upgrade MRI capabilities to the nanoscale and represents a major breakthrough in the construction of microscopes capable of detecting single atoms in three dimensions. This technology uses force-assisted identification to remove current MRI limitations in imaging very small objects. They designed special magnetic tips for this microscope that can detect the very weak magnetic properties of the nuclei of atoms. By accurately identifying the location of atoms in very small nanoelectronic structures, it is possible to fabricate accurately and increase the efficiency of products (29).

There is also another type of MRI machine with high magnetic power and no need for a liquid helium cooling system. This device, made by the Swedish company Mediso, is equipped with a nano-scanning system that captures living tissues with high resolution. Since 2012, Mediso has successfully installed and commissioned several different MRI machines. But this new instrument has a high superconductivity system and is equipped with a very powerful magnetic field. In fact, the secret of integrating Tesla 3 and 7 systems in this new device is related to its nanoscan capability. Mediso recently signed a memorandum of understanding with

Superconducting System. The company is one of the leading manufacturers of field-effect cooling MRI magnets. The purpose of this memorandum was to build 3 and 7 Tesla magnets. The patented refrigerant-free superconducting magnet technology allows the production of lightweight, portable magnets, eliminating the need to use liquid helium for cooling. Tesla Magnet 3 is one of the most common magnets used in clinics. With this magnet, you can create high and low fields in MRI and perform high contrast imaging and high resolution images of different parts of the body, such as the brain and cancer cells. This device can be upgraded to Tesla 7 system to meet the needs of the research department. Madiso nano-scan MRI machine is capable of imaging the living environment of the body. This device is designed, manufactured and distributed by Mediso (30).

Discussion and conclusion

Nanotechnology has so far had a significant impact on medical imaging techniques, especially MRI. The introduction of various nanostructures to enhance image quality, the fabrication of magnetic nanoparticles required for accurate and appropriate imaging, and the construction of new MRI devices with greater capabilities have been brought about by nanotechnology in recent decades. It seems that in the field of improving the contrast of images with the help of nanoparticles coated with various factors, many studies have been done and promising solutions have been proposed that can increase the quality of the resulting images many times and thus recognition the disease in early stages.

Many researches have been done in the universities and research institutes of the country to increase the resolution of MRI images with the help of nanostructures such as dextran (31), dendrimer (32) and iron oxide (17) and many scientific articles have been published by researchers. In some of these studies, cellular and animal experiments on nanostructures are currently underway to obtain licenses to commercialize these nanocarriers.

In addition to producing nanostructures, some companies are looking to build MRI machines with more and newer capabilities. Such a device is now being built by an in-house company. This device can reduce the temperature up to 40 degrees Kelvin (33). International collaborations have also taken place between Iranian and foreign researchers to build a magnetic nanoscope to identify prostate cancer cells (34) as well as to formulate and commercialize nanoparticles synthesized with different coatings for MRI use (17).

However, few products have reached the stage of commercialization and marketing. Work on producing MRI machines with more and newer capabilities has been limited, and many contrast-enhancing factors have been the result of scientific and laboratory findings. In addition, many of the magnetic nanoparticles used in imaging are not of the desired size and accuracy, resulting in unexpected results. This is a good opportunity for domestic researchers to move towards producing higher quality devices and better image resolution, and as a result turn their scientific products into technology.

Acknowledgments

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

References

1- Corot C, Robert P, Idee JM, Port M. Recent advances in iron oxide nanocrystal technology for medical imaging. Adv Drug Deliv Rev. 2006;58: 1471-1504.

2- Mulder WJ, Griffioen AW, Strijkers GJ, Cormode DP, Nicolay K, Fayad ZA. Magnetic and fluorescent nanoparticles for multimodality imaging. Nanomedicine (Lond). 2007;2: 307- 324.

3- Mulder WJ, Strijkers GJ, Briley-Saboe KC, Frias JC, Aguinaldo JG, Vucic E, et al. Molecular imaging of macrophages in atherosclerotic plaques using bimodal PEG-micelles. MagnReson Med. 2007;58: 1164-1170.

4- Winter PM, Caruthers SD, Zhang H, Williams TA, Wickline SA, Lanza GM. Antiangiogenic synergism of integrin-targeted fumagillin nanoparticles and atorvastatin in atherosclerosis. JACC Cardiovasc Imaging 2008;1: 624-634.

5- Caldorera-Moore ME, Liechty WB, Peppas NA. Responsive theranostic systems: integration of diagnostic imaging agents and responsive controlled release drug delivery carriers. AccChem Res. 2011;44: 1061-1070.

6- Medarova Z, Pham W, Farrar C, Petkova V, Moore A. In vivo imaging of siRNA delivery and silencing in tumors. Nat Med. 2007;13: 372-377.

7- Amirbekian V, Lipinski MJ, Briley-Saebo KC, Amirbekian S, Aguinaldo JG, Weinreb DB, et al. Detecting and assessing macrophages in vivo to evaluate atherosclerosis noninvasively using molecular MRI. Proc Natl AcadSci U S A. 2007;104: 961-966.

8- Mulder WJ, Douma K, Koning GA, van Zandvoort MA, Lutgens E, Daemen MJ, et al. Liposome-enhanced MRI of neointimal lesions in the ApoE-KO mouse. MagnReson Med. 2006;55: 1170-1174.

9- Anderson EA, Isaacman S, Peabody DS, Wang EY, Canary JW, Kirshenbaum K. Viral nanoparticles donning a paramagnetic coat: conjugation of MRI contrast agents to the MS2 capsid. Nano Lett. 2006;6: 1160-1164.

10- Sitharaman B, Kissell KR, Hartman KB, Tran LA, Baikalov A, Rusakova I, et al. Superparamagnetic gadonanotubes are high-performance MRI contrast agents. ChemCommun (Camb). 2005;1: 3915-3917.

11- van Tilborg GA, Mulder WJ, Deckers N, Storm G, Reutelingsperger CP, Strijkers GJ, et al. Annexin A5- functionalized bimodal lipid-based contrast agents for the detection of apoptosis. Bioconjug Chem. 2006;17: 741-749.

12- Briley-Saebo KC, Mulder WJ, Mani V, Hyafil F, Amirbekian V, Aguinaldo JG, et al. Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. J MagnReson Imaging. 2007;26: 460-479.
13- Walczak P, Zhang J, Gilad AA, Kedziorek DA, Ruiz-Cabello J, Young RG, et al. Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. Stroke. 2008;39: 1569-1574.
14- Leatherdale CA, Woo WK, Mikulec FV, Bawendi MG. On the Absorption Cross Section of CdSe Nanocrystal Quantum Dots. The Journal of Physical Chemistry B. 2002;106: 7619- 7622.
15- Sosnovik D, Weissleder R. Magnetic resonance and fluorescence based molecular imaging technologies. Prog Drug Res. 2005;62: 83-115.
16- Hyafil F, Cornily JC, Feig JE, Gordon R, Vucic E, Amirbekian V, et al. Noninvasive detection of macrophages using a nanoparticulate contrast agent for computed tomography. Nat Med. 2007;13: 636-641.
17- Mukundan S, Jr., Ghaghada KB, Badea CT, Kao CY, Hedlund LW, Provenzale JM, et al. A liposomal nanoscale contrast agent for preclinical CT in mice. AJR Am J Roentgenol. 2006;186: 300-307.
18- Weissleder R, Mahmood U. Molecular imaging. Radiology. 2001;219: 316-333.
19- Klibanov AL. Microbubble contrast agents: targeted ultrasound imaging and ultrasound-assisted drug delivery applications. Invest Radiol. 2006;41: 354-362.
20- Schiffelers RM, Banciu M, Metselaar JM, Storm G. Therapeutic application of long-circulating liposomal glucocorticoids in auto-immune diseases and cancer. J Liposome Res. 2006;16: 185-194.
21- Slowing, II, Trewyn BG, Lin VS. Mesoporous silica nanoparticles for intracellular delivery of membraneimpermeable proteins. J Am Chem Soc. 2007;129: 8845 8849.
22- van Schooneveld MM, Vucic E, Koole R, Zhou Y, Stocks J, Cormode DP, et al. Improved biocompatibility and pharmacokinetics of silica nanoparticles by means of a lipid coating: a multimodality investigation. Nano Lett. 2008;8: 2517-2525.
23- Cormode DP, Skajaa T, van Schooneveld MM, Koole R, Jarzyna P, Lobatto ME, et al. Nanocrystal core high-density lipoproteins: a multimodality contrast agent platform. Nano Lett. 2008;8: 3715-3723.
24- Kwon GS, Kataoka K. Block copolymer micelles as longcirculating drug vehicles. Advanced Drug Delivery Reviews. 1995;16: 295-309.
25- Nahrendorf M, Jaffer FA, Kelly KA, Sosnovik DE, Aikawa E, Libby P, et al. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. Circulation. 2006;114: 1504-1511.
26- Weissleder R, Kelly K, Sun EY, Shtatland T, Josephson L. Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. Nat Biotechnol. 2005;23: 1418-1423.
27- Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4: 145- 160.
28- Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2005;26: 3995-4021.
29- Murray CB, Norris DJ, Bawendi MG. Synthesis and characterization of nearly monodisperse CdE (E = sulfur, selenium, tellurium) semiconductor nanocrystallites. Journal of the American Chemical Society. 1993;115: 8706-8715.
30- Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Itty Ipe B, et al. Renal clearance of quantum dots. Nat Biotechnol. 2007;25: 1165-1170.
31- Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, et al. Quantum dots for live cells, in vivo imaging, and diagnostics. Science. 2005;307: 538-544.
32- Gaumet M, Vargas A, Gurny R, Delie F. Nanoparticles for drug delivery: the need for precision in reporting particle size parameters. Eur J Pharm Biopharm. 2008;69: 1-9.
33- Veiseh O, Gunn JW, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. Advanced drug delivery reviews. 2010;62: 284- 304.
34- Montet X, Montet-Abou K, Reynolds F, Weissleder R, Josephson L. Nanoparticle imaging of integrins on tumor cells. Neoplasia. 2006;8: 214-222.
35- Hong S, Leroueil PR, Majoros IJ, Orr BG, Baker Jr JR, BanaszakHoll MM. The binding avidity of a nanoparticlebased multivalent targeted drug delivery platform. Chemistry & biology. 2007;14: 107-115.
36- Brust M, Walker M, Bethell D, Schiffrin DJ, Whyman R. Synthesis of thiol-derivatised gold nanoparticles in a twophase Liquid-Liquid system. Journal of the Chemical Society, Chemical Communications. 1994;1: 801-802.
37- Yu WW, Chang E, Falkner JC, Zhang J, Al-Somali AM, Sayes CM, et al. Forming biocompatible and nonaggregated nanocrystals in water using amphiphilic polymers. J Am Chem Soc. 2007;129: 2871-2879.
38- McCarthy JR, Kelly KA, Sun EY, Weissleder R. Targeted delivery of multifunctional magnetic nanoparticles. Nanomedicine (Lond). 2007;2: 153-167.
39- Shaw SY, Westly EC, Pittet MJ, Subramanian A, Schreiber SL, Weissleder R. Perturbational profiling of nanomaterial biologic activity. Proc Natl AcadSci U S A. 2008;105: 7387- 7392.
40- Mancini MC, Kairdolf BA, Smith AM, Nie S. Oxidative quenching and degradation of polymer-encapsulated quantum dots: new insights into the long-term fate and toxicity of nanocrystals in vivo. J Am Chem Soc. 2008;130: 10836-10837.