Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2013, Article ID 764095, 7 pages
http://dx.doi.org/10.1155/2013/764095

Review Article

The Mutual Beneficial Effect between Medical Imaging and Nanomedicine

Huiting Qiao,[1] Libin Wang,[1] Jintao Han,[2] Yingmao Chen,[3] Daifa Wang,[1] and Deyu Li[1]

[1] *Key Laboratory for Biomechanics and Mechanobiology of Ministry of Education, School of Biological Science and Medical Engineering, Beihang University, Beijing 100191, China*
[2] *Department of Interventional Radiology and Vascular Surgery, Peking University Third Hospital, Beijing, China*
[3] *Department of Nuclear Medicine, General Hospital of PLA, Beijing 100853, China*

Correspondence should be addressed to Deyu Li; deyuli@buaa.edu.cn

Received 13 June 2013; Accepted 15 July 2013

Academic Editor: Xiaoming Li

The reports on medical imaging and nanomedicine are getting more and more prevalent. Many nanoparticles entering into the body act as contrast agents, or probes in medical imaging, which are parts of nanomedicines. The application extent and the quality of imaging have been improved by nanotechnique. On one hand, nanomedicines advance the sensitivity and specificity of molecular imaging. On the other hand, the biodistribution of nanomedicine can also be studied *in vivo* by medical imaging, which is necessary in the toxicological research. The toxicity of nanomedicine is a concern which may slow down the application of nanomedical. The quantitative description of the kinetic process is significant. Based on metabolic study on radioactivity tracer, a scheme of pharmacokinetic research of nanomedicine is proposed. In this review, we will discuss the potential advantage of medical imaging in toxicology of nanomedicine, as well as the advancement of medical imaging prompted by nanomedicine.

1. Introduction

Medical imaging is an important technology in clinical and medical research, which enables the observation of human and animals *in vivo*. The development of medical imaging contributes a lot to diagnosis and therapy. However, researchers are not satisfied with single anatomical image. To detect physiological function and biological process, functional imaging, molecular imaging, and multimodality imaging are invented and have developed prosperously [1–3]. Most molecular imaging today depends on synthesized probe with special property [4]. For nuclear medicine, for example, the probe is also expressed as radioactive tracer or tracer [5, 6] for positron emission tomography (PET). For fluorescence molecular tomography the probe is a fluorescence agent [7]. In terms of traditional imaging, some agents are used to increase the contrast of images [8, 9]. Contrast agent can enhance their applications and even upgrade them to cellular and molecular level.

Nanotechnology has a remarkable great contribution to the development of medical imaging. Nanomedicine is a scientific specialty of nanotechnology, which has great potentials to develop the diagnostic and therapeutic approaches [10–12]. Nanomedicine has drawn broad interests in medical imaging, as well as the targeted therapy [13]. Modified by nanotechnique, some probes and contrast agents become more efficient [14], and then they can be called nanomedicine [15]. Some kinds of nanoparticle, just as metal nanoparticles, become nanomedicine used as contrast agent of medical imaging [16, 17]. With the application of nanomedicine, medical imaging will have a broader prospect in application.

Nevertheless, the nanomedicine, used in medical imaging, must eliminate the potential risks in safety issues. Most nanomaterials have been discovered to affect cell behavior [18, 19] and even to damage the physiological system [20, 21]. The discussion of the biocompatibility and toxicity of nanomaterial is of a great importance in biological and medical research. The toxicology of nanomaterials is usually studied on cellular scale or smaller size, while the pharmacokinetics is also necessary to understand its potential toxicity [22]. As pharmacokinetics of tracer is studied by

means of nuclear medicine [23, 24], the dynamic distribution of nanomedicine could also be studied by medical imaging [25]. Thus, medical imaging could advance the research of nanomedicine, especially in the field of toxicology.

This paper aims at discussing the interaction between medical imaging and nanomedicine. Nanomedicine extents the application of medical imaging, and medical imaging enhances toxicological research at system scale. In this review, we will first discuss some imaging techniques, which are commonly used in clinic, and the imaging agents, including traditional agent and nanomedicine. Then a discussion will be shared about the toxicological research of nanomedicine. In the end, a feasible means combined with medical imaging and nanomedicine will be proposed for the quantificational study of nanomedicine toxicity.

2. The Development of Imaging Affected by Nanomedicine

The development of medical imaging is built on multiple techniques. In the past decade, it has been promoted especially by nanotechnique [15]. Every imaging technique has its limitation as well as the superiority, nanomedicine is used as probe, or contrast agent, to extend the application of imaging and to improve the quality of images [26–28].

CT, which is based on X-ray attenuation, can recognize inner structure by the different attenuation coefficients of tissues. Though CT is a high-resolution imaging, it is limited in soft-tissue imaging. To increase the contrast of images, metal salts, metal particles, and some iodinated compounds have been used as contrast agents in X-ray-based imaging [29]. High osmolality, short circulation time, and toxicity of heavy metal bulk may lead to some adverse reactions at the same time. Nanotechnique overcomes some of these problems. Conjugated with nanoparticle, iodinated compounds prolong the circulation time [30], and nonionic water-soluble iodinated contrast agents have lower osmolality [31]. Heavy metal nanoparticle has shown its efficiency as contrast agent in CT imaging [32–34].

MRI is based on nuclear magnetic resonance and the relaxation of proton spins in a magnetic field. It has a high resolution for soft tissue and is highly functional for brain and nervous system scan. While For the tiny difference between lesion and normal tissue, MRI is not as sensitive or specific as ideal molecular imaging. Nanocontrast agents can help MRI become a more efficient molecular imaging [27]. Gadolinium chelates are commonly used contrast agents to enhance the signal of MRI [35]. Gadolinium-loaded single-walled carbon nanotubes are super paramagnetic, 40 times more than traditional agent [36]. Iron oxide nanoparticles (hundreds of nanometers) are super paramagnetic, which have been used to diagnose liver diseases [37, 38]. Ultrasmall iron oxide nanoparticles (less than 50 nanometers) are applied to detect macrophage [39]. The application of MRI becomes more and more extensive with the progressive research on magnetic nanomedicine [40, 41].

Nuclear medicine molecular imaging, as PET and SPECT, relies on radiotracers, which are also called probes. Fluorodeoxyglucose (^{18}FDG) is the most commonly used radiopharmaceutical in PET imaging [42]. As the analog of glucose, FDG can be used to detect cancer, which has a high glucose metabolic rate [43, 44]. FDG is not always sensitive to all lesions. ^{11}C-acetate is more suitable for the detection of liver cancer [45]. For specific diagnosis, the probe of proper target is the key of medical imaging [46, 47]. Combined with nanoparticles, the radiotracers become more and more multiform; for example, radionuclides can be labeled on proteins, antibodies, and peptides. The radiolabeled single-walled carbon nanotubes can be used in PET imaging, and the efficiency can be increased by peptide coating [48]. The sensitivity and specificity of nuclear medicine imaging will increase with the application of nanomedicine.

Besides upper imaging technique, nanotechniques advance other medical imaging. The combination of nanoparticle and fluorescent probe greatly enhances imaging [49]. Quantum dot, which is referred to as semiconductor nanocrystals, can be used in fluorescence image, even to image the vasculature near tumor probe [50, 51]. To visualize microvascular, nano/microcapsules have been designed as a contrast agent for ultrasonic imaging [52].

Nanomedicine may be the most suitable probe or contrast agent for multimodality imaging because of the convenience of integrating multiple properties [53, 54]. In PET/MRI imaging, radiolabeled iron oxide nanoparticles are not only the tracers for PET but also the contrast agents for MRI [55]. With the ability of multifunction load [56], nanomedicine may boost the fusion of multiple imaging techniques and even the combination of the process of diagnosis, therapy, evaluation, and disease prevention [57]. There are so many mechanisms for creating imaging agent in nanoscale, which will progressively develop the sensitive and specific imaging technique.

3. The Study on Toxicity of Nanomedicine Could Be Supported by Imaging

Many nanomedicines are not only for imaging but also for therapy [58–60]. Nanomedicine can deliver therapeutic agents into targeted specific tissues and cells [61]. For example, gold nanoparticles are the potential for the therapy of various diseases such as cancer and Alzheimer [34, 62, 63]. Unlike the nanobiomaterials applied *in vitro* [64, 65], nanomedicines face more risks along with the opportunities. Biocompatibility and toxicological research are significant for the materials which will be applied in human body [66, 67]. It has been reported that some nanoparticles produce inflammation and tissue damages and other adverse health effects in body [68–70]. Toxicology study is the essential safety assessment of nanomedicine [71].

In the study of toxicity, *in vivo* experiments are absolutely necessary for the understanding of nanotoxicity in the physiological system. The examination of serum biochemical parameters, urine parameters, and histopathology can reveal the injury of viscera and have been used as methods to

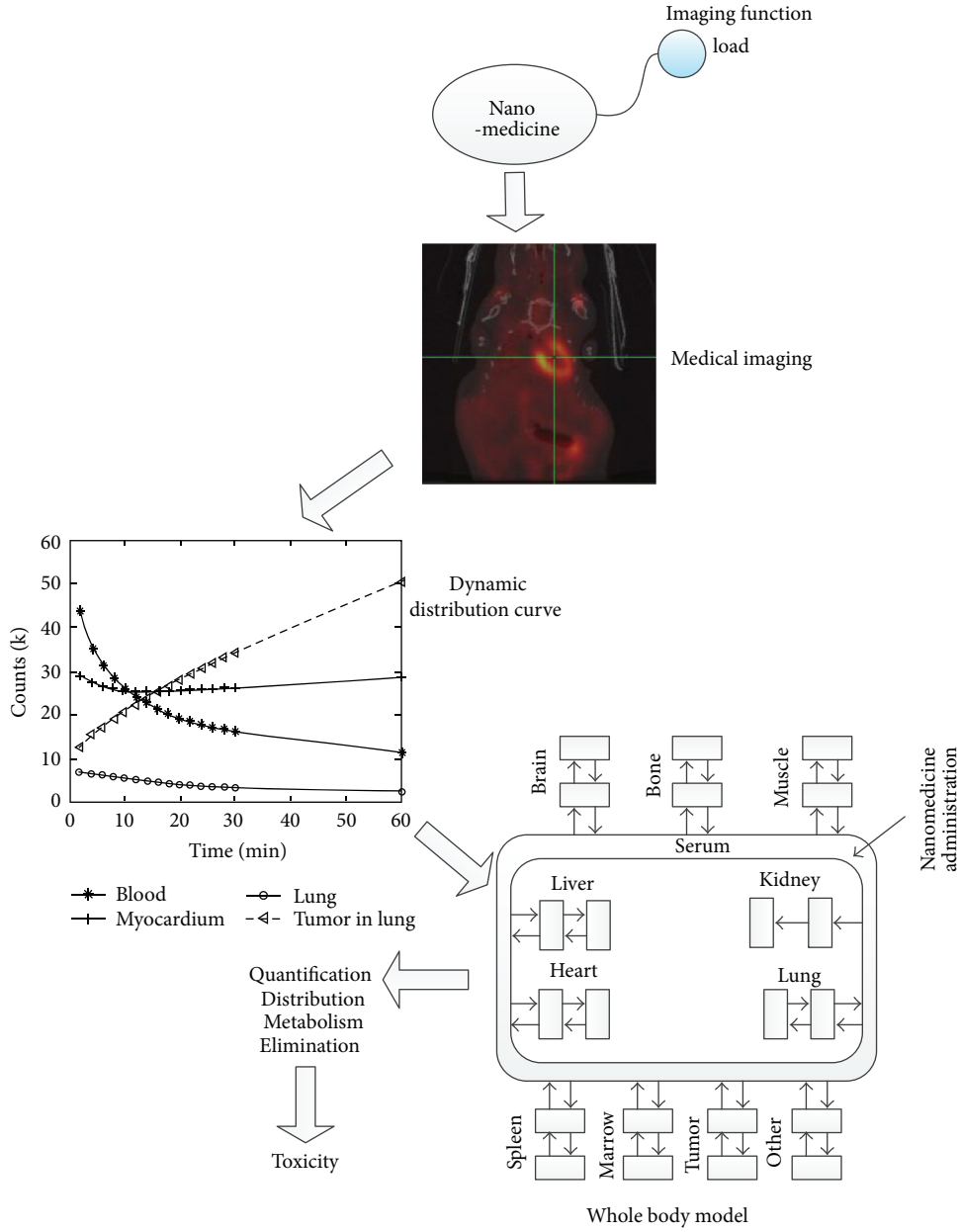

Figure 1: The scheme of *in vivo* toxicity study by medical imaging.

study toxicity of nanomaterials [72–74]. In the study of the nanotoxicity, biodistribution and elimination are of a great importance [61]. Nanoparticles can translocate in human body, even if they are inhaled, and the position where they settle down may decide the level of damage [75]. Central nervous system is the potential susceptible target for some nanoparticles, in which the potential lesion induced by nanoparticles will be hazardous [69, 76]. In traditional biodistribution experiments, small animals were sacrificed after administration, and the organs, liver, spleen, lung, heart, and kidney, were excised to detect the biodistribution of nanoparticles [77, 78]. In the biodistribution experiment of Fe_2O_3 nanoparticles [79], isotope was labeled to be detected by high purity germanium detector after organs excised. The radiolabeled nanoparticle can also be detected by whole body gamma camera image [25]. In other words, medical imaging can be used as a tool to study toxicity of nanomedicines. PET/CT has been used to study the tissue biodistribution and pharmacokinetics of DOTA-functionalized single-walled carbon nanotubes [80] and nano graphene [81]. MRI has been used to track mesoporous silica nanomedicine for three months [82]. The distribution of nanomedicine in various organs could be derived by medical imaging.

Pharmacokinetic model is a quantificational method to describe the dynamic fate of a drug after administration, which is usually required for new drug design. Though

the dynamic distributions of nanomedicine have been discussed in some literatures [25, 81, 82], yet few pharmacokinetic models have been established. Zhu et al. used one-compartment model to describe the kinetic of ferric oxide nanoparticles in human body quantificationally [79]. In this model, the rate of absorption and elimination was included, but the different distribution of nanomedicine cannot be represented. In another application of molecular imaging, kinetic models of tracer are established to describe the metabolism of glucose [83]. By dynamic PET imaging, the kinetic models were established separately for some tissues [84, 85] and then formed a whole body model [86, 87]. The distribution metabolism and elimination are all involved, which are parts of toxicity study.

Thus the development of nanomedicine could be prompted by medical imaging, especially in the aspect of toxicology. According to the application of medical imaging in metabolism research, there is a feasible research scheme for toxicological study, as shown in Figure 1. Loaded with imaging-functionalized particles, the nanomedicines could be detected by medical imaging. Radioactivity label is preferred for PET or SPECT, magnetic nanoparticles could be attached for MRI, and quantum dots will be suitable for fluorescence image. Nanotechniques may show their advantage in designing probe for multimodality imaging. Then the dynamic distribution curve of nanomedicine in different tissues can be received from images, which can be used to establish the pharmacokinetic model. In the pharmacokinetic model, the processes of absorb, distribution, metabolism, and elimination are described quantificationally. These processes are also called biodistribution, an important aspect of toxicology. This scheme, using mathematic model to describe the biodistribution of nanomedicine, is a potential application of medical imaging in nanotoxicity research.

4. Conclusions

The rapid development of medical imaging and nanomedicine gives us a promising prospect of diagnosis and therapy. Sensitive, specific, and *in vivo* diagnosis and personal therapy benefit from the combination of medical imaging and nanomedicine. Nanomedicines, used as imaging contrasts, tracers, or probes can improve the sensitivity of imaging detection; thus, the sparsely expressed targets would be discovered. With the well-designed nanomedicine, medical imaging could also be used for tumor imaging [88], physiological mechanism study [89], and even DNA detection [90]. It is beneficial not only to imaging but also to the development of nanomedicine. The potential toxicity is the biggest barrier to the clinical application of nanomedicine. Quantificational dynamic systemic researches on the distribution of nanomedicines *in vivo* are necessary to toxicology. Medical imaging is the most convenient method to analyze the biodistribution of nanomedicine and to assess the nanomedical treatment [91]. Nanomedicines can be detected *in vivo* by medical imaging, after they are loaded with imaging-functionalized particles or radioactive labeled. Therefore, imaging will allow the risk stratification and monitoring of therapy effects. With reference to metabolic studies of radioactivity tracer, the pharmacokinetic model of nanomedicine could also be established by means of dynamic medical imaging, which will contribute to the advancement of nanomedical toxicology. In summary, medical imaging and nanomedicine advance each other and will play an important role towards more advanced medicine. Attention should be focused not only on the success of nanomedicine application in medical imaging but also on the potential advantages of imaging for nanomedical toxicology research.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant no. 81101123, no. 61108084, no. 61227902, and no. 11002016), 111 project, and the Fundamental Research Funds for the Central Universities of China.

References

[1] M. Rudin and R. Weissleder, "Molecular imaging in drug discovery and development," *Nature Reviews Drug Discovery*, vol. 2, no. 2, pp. 123–131, 2003.

[2] S.-K. Woo, K. M. Kim, T. S. Lee et al., "Registration method for the detection of tumors in lung and liver using multimodal small animal imaging," *IEEE Transactions on Nuclear Science*, vol. 56, no. 3, pp. 1454–1458, 2009.

[3] L. Fass, "Imaging and cancer: a review," *Molecular Oncology*, vol. 2, no. 2, pp. 115–152, 2008.

[4] R. Weissleder, "Molecular imaging: exploring the next frontier," *Radiology*, vol. 212, no. 3, pp. 609–614, 1999.

[5] G. Komar, M. Seppänen, O. Eskola et al., "18F-EF5: a new PET tracer for imaging hypoxia in head and neck cancer," *Journal of Nuclear Medicine*, vol. 49, no. 12, pp. 1944–1951, 2008.

[6] J. Höglund, A. Shirvan, G. Antoni et al., "18FML-10, a PET tracer for apoptosis: first human study," *Journal of Nuclear Medicine*, vol. 52, no. 5, pp. 720–725, 2011.

[7] S. Kossodo, M. Pickarski, S.-A. Lin et al., "Dual *in vivo* quantification of integrin-targeted and protease-activated agents in cancer using fluorescence molecular tomography (FMT)," *Molecular Imaging and Biology*, vol. 12, no. 5, pp. 488–499, 2010.

[8] F. Hallouard, N. Anton, P. Choquet, A. Constantinesco, and T. Vandamme, "Iodinated blood pool contrast media for preclinical X-ray imaging applications—a review," *Biomaterials*, vol. 31, no. 24, pp. 6249–6268, 2010.

[9] N. J. J. Johnson, W. Oakden, G. J. Stanisz, R. Scott Prosser, and F. C. J. M. van Veggel, "Size-tunable, ultrasmall NaGdF4 nanoparticles: insights into their T1 MRI contrast enhancement," *Chemistry of Materials*, vol. 23, no. 16, pp. 3714–3722, 2011.

[10] R. Wang, P. S. Billone, and W. M. Mullett, "Nanomedicine in action: an overview of cancer nanomedicine on the market and in clinical trials," *Journal of Nanomaterials*, vol. 2013, Article ID 629681, 12 pages, 2013.

[11] P. Prabhu and V. Patravale, "The upcoming field of theranostic nanomedicine: an overview," *Journal of Biomedical Nanotechnology*, vol. 8, no. 6, pp. 859–882, 2012.

[12] X. Li, Y. Yang, Y. Fan, Q. Feng, F. Z. Cui, and F. Watari, "Biocomposites reinforced by fibers or tubes, as scaffolds for tissue engineering or regenerative medicine," *Journal of Biomedical Materials Research A*, 2013.

[13] Y. Liu, H. Miyoshi, and M. Nakamura, "Nanomedicine for drug delivery and imaging: a promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles," *International Journal of Cancer*, vol. 120, no. 12, pp. 2527–2537, 2007.

[14] A. Nazemi, F. Martínez, T. J. Scholl, and E. R. Gillies, "Biodegradable dendritic polymersomes as modular, high-relaxivity MRI contrast agents," *RSC Advances*, vol. 2, no. 21, pp. 7971–7973, 2012.

[15] D. P. Cormode, T. Skajaa, Z. A. Fayad, and W. J. M. Mulder, "Nanotechnology in medical imaging: probe design and applications," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 7, pp. 992–1000, 2009.

[16] A. J. Mieszawska, W. J. M. Mulder, Z. A. Fayad, and D. P. Cormode, "Multifunctional gold nanoparticles for diagnosis and therapy of disease," *Molecular Pharmaceutics*, vol. 10, no. 3, pp. 831–847, 2013.

[17] M. A. Hahn, A. K. Singh, P. Sharma, S. C. Brown, and B. M. Moudgil, "Nanoparticles as contrast agents for *in-vivo* bioimaging: current status and future perspectives," *Analytical and Bioanalytical Chemistry*, vol. 399, no. 1, pp. 3–27, 2011.

[18] X. Li, H. Gao, M. Uo et al., "Effect of carbon nanotubes on cellular functions *in vitro*," *Journal of Biomedical Materials Research A*, vol. 91, no. 1, pp. 132–139, 2009.

[19] X. Li, Y. Huang, L. Zheng et al., "Effect of substrate stiffness on the functions of rat bone marrow and adipose tissue derived mesenchymal stem cells *in vitro*," *Journal of Biomedical Materials Research A*, 2013.

[20] K. Takeda, K.-I. Suzuki, A. Ishihara et al., "Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems," *Journal of Health Science*, vol. 55, no. 1, pp. 95–102, 2009.

[21] A. Nel, T. Xia, L. Mädler, and N. Li, "Toxic potential of materials at the nanolevel," *Science*, vol. 311, no. 5761, pp. 622–627, 2006.

[22] S. Sharifi, S. Behzadi, S. Laurent, M. Laird Forrest, P. Stroeve, and M. Mahmoudi, "Toxicity of nanomaterials," *Chemical Society Reviews*, vol. 41, no. 6, pp. 2323–2343, 2012.

[23] C. Cobelli, D. Foster, and G. Toffolo, *Tracer Kinetics in Biomedical Research: From Data to Model*, Kluwer Academic/Plenum, New York, NY, USA, 2000.

[24] Y. Cui, J. Bai, Y. Chen, and J. Tian, "Parameter estimation for whole-body kinetic model of FDG metabolism," *Progress in Natural Science*, vol. 16, no. 11, pp. 1164–1170, 2006.

[25] A. Nemmar, P. H. M. Hoet, B. Vanquickenborne et al., "Passage of inhaled particles into the blood circulation in humans," *Circulation*, vol. 105, no. 4, pp. 411–414, 2002.

[26] R. P. Choudhary, V. Fuster, and Z. A. Fayad, "Molecular, cellular and functional imaging of atherothrombosis," *Nature Reviews Drug Discovery*, vol. 3, no. 11, pp. 913–925, 2004.

[27] M. F. Kircher and J. K. Willmann, "Molecular body imaging: MR imaging, CT, and US. Part I. Principles," *Radiology*, vol. 263, no. 3, pp. 633–643, 2012.

[28] C. J. Meledandri and D. F. Brougham, "Low field magnetic resonance techniques in the development of nanomaterials for biomedical applications," *Analytical Methods*, vol. 4, no. 2, pp. 331–341, 2012.

[29] S.-B. Yu and A. D. Watson, "Metal-based X-ray contrast media," *Chemical Reviews*, vol. 99, no. 9, pp. 2353–2377, 1999.

[30] Y. Liu, K. Ai, and L. Lu, "Nanoparticulate X-ray computed tomography contrast agents: from design validation to *in vivo* applications," *Accounts of Chemical Research*, vol. 45, pp. 1817–1827, 2012.

[31] N. Lee, S. H. Choi, and T. Hyeon, "Nano-sized CT contrast agents," *Advanced Materials*, vol. 25, no. 19, pp. 2641–2660, 2013.

[32] J. F. Hainfeld, D. N. Slatkin, T. M. Focella, and H. M. Smilowitz, "Gold nanoparticles: a new X-ray contrast agent," *British Journal of Radiology*, vol. 79, no. 939, pp. 248–253, 2006.

[33] J. Della Rocca, D. Liu, and W. Lin, "Nanoscale metal-organic frameworks for biomedical imaging and drug delivery," *Accounts of Chemical Research*, vol. 44, no. 10, pp. 957–968, 2011.

[34] Y. Fang, C. Peng, R. Guo et al., "Dendrimer-stabilized bismuth sulfide nanoparticles: synthesis, characterization, and potential computed tomography imaging applications," *The Analyst*, vol. 138, no. 11, pp. 3172–3180, 2013.

[35] P. Caravan, J. J. Ellison, T. J. McMurry, and R. B. Lauffer, "Gadolinium(III) chelates as MRI contrast agents: structure, dynamics, and applications," *Chemical Reviews*, vol. 99, no. 9, pp. 2293–2352, 1999.

[36] B. Sitharaman, K. R. Kissell, K. B. Hartman et al., "Superparamagnetic gadonanotubes are high-performance MRI contrast agents," *Chemical Communications*, no. 31, pp. 3915–3917, 2005.

[37] H. B. Na, I. C. Song, and T. Hyeon, "Inorganic nanoparticles for MRI contrast agents," *Advanced Materials*, vol. 21, no. 21, pp. 2133–2148, 2009.

[38] C. Corot, P. Robert, J.-M. Idée, and M. Port, "Recent advances in iron oxide nanocrystal technology for medical imaging," *Advanced Drug Delivery Reviews*, vol. 58, no. 14, pp. 1471–1504, 2006.

[39] R. A. Trivedi, J.-M. U-King-Im, M. J. Graves et al., "*In vivo* detection of macrophages in human carotid atheroma: temporal dependence of ultrasmall superparamagnetic particles of iron oxide-enhanced MRI," *Stroke*, vol. 35, no. 7, pp. 1631–1635, 2004.

[40] K. Kattel, J. Y. Park, W. Xu et al., "Paramagnetic dysprosium oxide nanoparticles and dysprosium hydroxide nanorods as T2 MRI contrast agents," *Biomaterials*, vol. 33, no. 11, pp. 3254–3261, 2012.

[41] X. Liu, Z. Zhong, Y. Tang, and B. Liang, "Review on the synthesis and applications of Fe_3O_4 nanomaterials," *Journal of Nanomaterials*, vol. 2013, Article ID 902538, 7 pages, 2013.

[42] L. Kostakoglu, H. Agress Jr., and S. J. Goldsmith, "Clinical role of FDG PET in evaluation of cancer patients," *Radiographics*, vol. 23, no. 2, pp. 315–340, 2003.

[43] T. Kasai, K. Motoori, T. Horikoshi et al., "Dual-time point scanning of integrated FDG PET/CT for the evaluation of mediastinal and hilar lymph nodes in non-small cell lung cancer diagnosed as operable by contrast-enhanced CT," *European Journal of Radiology*, vol. 75, no. 2, pp. 143–146, 2010.

[44] E. M. Rohren, T. G. Turkington, and R. E. Coleman, "Clinical applications of PET in oncology," *Radiology*, vol. 231, no. 2, pp. 305–332, 2004.

[45] C.-L. Ho, S. C. H. Yu, and D. W. C. Yeung, "11C-acetate PET imaging in hepatocellular carcinoma and other liver masses," *Journal of Nuclear Medicine*, vol. 44, no. 2, pp. 213–221, 2003.

[46] M. J. Welch, C. J. Hawker, and K. L. Wooley, "The advantages of nanoparticles for PET," *Journal of Nuclear Medicine*, vol. 50, no. 11, pp. 1743–1746, 2009.

[47] E. Morales-Avila, G. Ferro-Flores, B. E. Ocampo-García, and F. de María Ramírez, "Radiolabeled nanoparticles for molecular imaging," in *Molecular Imaging*, pp. 15–38, 2012.

[48] Z. Liu, W. Cai, L. He et al., "*In vivo* biodistribution and highly efficient tumour targeting of carbon nanotubes in mice," *Nature Nanotechnology*, vol. 2, no. 1, pp. 47–52, 2007.

[49] S. D. Perrault and W. C. W. Chan, "*In vivo* assembly of nanoparticle components to improve targeted cancer imaging," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 25, pp. 11194–11199, 2010.

[50] T. L. Doane and C. Burda, "The unique role of nanoparticles in nanomedicine: imaging, drug delivery and therapy," *Chemical Society Reviews*, vol. 41, no. 7, pp. 2885–2911, 2012.

[51] C. Wang, X. Gao, and X. Su, "*In vitro* and *in vivo* imaging with quantum dots," *Analytical and Bioanalytical Chemistry*, vol. 397, no. 4, pp. 1397–1415, 2010.

[52] E. Pisani, N. Tsapis, J. Paris, V. Nicolas, L. Cattel, and E. Fattal, "Polymeric nano/microcapsules of liquid perfluorocarbons for ultrasonic imaging: physical characterization," *Langmuir*, vol. 22, no. 9, pp. 4397–4402, 2006.

[53] X. Lin, J. Xie, G. Niu et al., "Chimeric ferritin nanocages for multiple function loading and multimodal imaging," *Nano Letters*, vol. 11, no. 2, pp. 814–819, 2011.

[54] M. Yang, K. Cheng, S. Qi et al., "Affibody modified and radiolabeled gold-Iron oxide hetero-nanostructures for tumor PET, optical and MR imaging," *Biomaterials*, vol. 34, no. 11, pp. 2796–2806, 2013.

[55] H.-Y. Lee, Z. Li, K. Chen et al., "PET/MRI dual-modality tumor imaging using arginine-glycine-aspartic (RGD)-conjugated radiolabeled iron oxide nanoparticles," *Journal of Nuclear Medicine*, vol. 49, no. 8, pp. 1371–1379, 2008.

[56] J. Gao, H. Gu, and B. Xu, "Multifunctional magnetic nanoparticles: design, synthesis, and biomedical applications," *Accounts of Chemical Research*, vol. 42, no. 8, pp. 1097–1107, 2009.

[57] M. Liong, J. Lu, M. Kovochich et al., "Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery," *ACS Nano*, vol. 2, no. 5, pp. 889–896, 2008.

[58] Z. Li, Q. Jin, C. Huang et al., "Trackable and targeted phage as positron emission tomography (PET) agent for cancer imaging," *Theranostics*, pp. 371–380, 2011.

[59] J. Kim, J. E. Lee, S. H. Lee et al., "Designed fabrication of a multifunctional polymer nanomedical platform for simultaneous cancer-targeted imaging and magnetically guided drug delivery," *Advanced Materials*, vol. 20, no. 3, pp. 478–483, 2008.

[60] X. Li, L. Wang, Y. Fan, Q. Feng, F.-Z. Cui, and F. Watari, "Nanostructured scaffolds for bone tissue engineering," *Journal of Biomedical Materials Research A*, 2013.

[61] J. Zhao and V. Castranova, "Toxicology of nanomaterials used in nanomedicine," *Journal of Toxicology and Environmental Health B: Critical Reviews*, vol. 14, no. 8, pp. 593–632, 2011.

[62] C. Boyer, M. R. Whittaker, V. Bulmus, J. Liu, and T. P. Davis, "The design and utility of polymer-stabilized iron-oxide nanoparticles for nanomedicine applications," *NPG Asia Materials*, vol. 2, no. 1, pp. 23–30, 2010.

[63] R. Singh and K. Kostarelos, "Designer adenoviruses for nanomedicine and nanodiagnostics," *Trends in Biotechnology*, vol. 27, no. 4, pp. 220–229, 2009.

[64] X. Li, H. Liu, X. Niu et al., "The use of carbon nanotubes to induce osteogenic differentiation of human adipose-derived MSCs in vitro and ectopic bone formation *in vivo*," *Biomaterials*, vol. 33, no. 19, pp. 4818–4827, 2012.

[65] X. Li, C. A. van Blitterswijk, Q. Feng, F. Cui, and F. Watari, "The effect of calcium phosphate microstructure on bone-related cells *in vitro*," *Biomaterials*, vol. 29, no. 23, pp. 3306–3316, 2008.

[66] S. T. Stern and S. E. McNeil, "Nanotechnology safety concerns revisited," *Toxicological Sciences*, vol. 101, no. 1, pp. 4–21, 2008.

[67] X. Li, Q. Feng, X. Liu, W. Dong, and F. Cui, "Collagen-based implants reinforced by chitin fibres in a goat shank bone defect model," *Biomaterials*, vol. 27, no. 9, pp. 1917–1923, 2006.

[68] K.-I. Inoue, H. Takano, R. Yanagisawa et al., "Effects of airway exposure to nanoparticles on lung inflammation induced by bacterial endotoxin in mice," *Environmental Health Perspectives*, vol. 114, no. 9, pp. 1325–1330, 2006.

[69] J. Wang, C. Chen, Y. Liu et al., "Potential neurological lesion after nasal instillation of TiO_2 nanoparticles in the anatase and rutile crystal phases," *Toxicology Letters*, vol. 183, no. 1–3, pp. 72–80, 2008.

[70] J. I. Phillips, F. Y. Green, J. C. A. Davies, and J. Murray, "Pulmonary and systemic toxicity following exposure to nickel nanoparticles," *American Journal of Industrial Medicine*, vol. 53, no. 8, pp. 763–767, 2010.

[71] H. Meng, T. Xia, S. George, and A. E. Nel, "A predictive toxicological paradigm for the safety assessment of nanomaterials," *ACS Nano*, vol. 3, no. 7, pp. 1620–1627, 2009.

[72] J. Wang, G. Zhou, C. Chen et al., "Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration," *Toxicology Letters*, vol. 168, no. 2, pp. 176–185, 2007.

[73] E. M. Kenyon, L. M. del Razo, and M. F. Hughes, "Tissue distribution and urinary excretion of inorganic arsenic and its methylated metabolites in mice following acute oral administration of arsenate," *Toxicological Sciences*, vol. 85, no. 1, pp. 468–475, 2005.

[74] G. Ciofani, S. Danti, G. G. Genchi et al., "Pilot *in vivo* toxicological investigation of boron nitride nanotubes," *International Journal of Nanomedicine*, vol. 7, pp. 19–24, 2012.

[75] E. Boisselier and D. Astruc, "Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity," *Chemical Society Reviews*, vol. 38, no. 6, pp. 1759–1782, 2009.

[76] C. Medina, M. J. Santos-Martinez, A. Radomski, O. I. Corrigan, and M. W. Radomski, "Nanoparticles: pharmacological and toxicological significance," *British Journal of Pharmacology*, vol. 150, no. 5, pp. 552–558, 2007.

[77] U. Gaur, S. K. Sahoo, T. K. De, P. C. Ghosh, A. Maitra, and P. K. Ghosh, "Biodistribution of fluoresceinated dextran using novel nanoparticles evading reticuloendothelial system," *International Journal of Pharmaceutics*, vol. 202, no. 1-2, pp. 1–10, 2000.

[78] E. Chambers and S. Mitragotri, "Long circulating nanoparticles via adhesion on red blood cells: mechanism and extended circulation," *Experimental Biology and Medicine*, vol. 232, no. 7, pp. 958–966, 2007.

[79] M.-T. Zhu, W.-Y. Feng, Y. Wang et al., "Particokinetics and extrapulmonary translocation of intratracheally instilled ferric oxide nanoparticles in rats and the potential health risk assessment," *Toxicological Sciences*, vol. 107, no. 2, pp. 342–351, 2009.

[80] M. R. McDevitt, D. Chattopadhyay, J. S. Jaggi et al., "PET imaging of soluble yttrium-86-labeled carbon nanotubes in mice," *PLoS ONE*, vol. 2, no. 9, article e907, 2007.

[81] H. Hong, Y. Zhang, J. W. Engle et al., "*In vivo* targeting and positron emission tomography imaging of tumor vasculature with66Ga-labeled nano-graphene," *Biomaterials*, vol. 33, no. 16, pp. 4147–4156, 2012.

[82] S.-H. Wu, Y.-S. Lin, Y. Hung et al., "Multifunctional mesoporous silica nanoparticles for intracellular labeling and animal magnetic resonance imaging studies," *ChemBioChem*, vol. 9, no. 1, pp. 53–57, 2008.

[83] A. Bertoldo, P. Vicini, G. Sambuceti, A. A. Lammertsma, O. Parodi, and C. Cobelli, "Evaluation of compartmental and spectral analysis models of [^{18}F]FDG kinetics for heart and brain studies with PET," *IEEE Transactions on Biomedical Engineering*, vol. 45, no. 12, pp. 1429–1448, 1998.

[84] Y. Cui, J. Bai, Y. Chen, and J. Tian, "Kinetic model parameter estimates of liver FDG metabolism," *Journal of Tsinghua University*, vol. 47, no. 3, pp. 420–423, 2007.

[85] H. Qiao, J. Bai, Y. Chen, and J. Tian, "Modeling the excretion of FDG in human kidneys using dynamic PET," *Computers in Biology and Medicine*, vol. 38, no. 11-12, pp. 1171–1176, 2008.

[86] M. T. Hays and G. M. Segall, "A mathematical model for the distribution of fluorodeoxyglucose in humans," *Journal of Nuclear Medicine*, vol. 40, no. 8, pp. 1358–1366, 1999.

[87] Y. Cui, J. Bai, Y. Chen, and J. Tian, "Parameter estimation for whole-body kinetic model of FDG metabolism," *Progress in Natural Science*, vol. 16, no. 11, pp. 1164–1170, 2006.

[88] M. K. Yu, J. Park, and S. Jon, "Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy," *Theranostics*, vol. 2, no. 1, pp. 3–44, 2012.

[89] L.-Y. Chien, J.-K. Hsiao, S.-C. Hsu et al., "*In vivo* magnetic resonance imaging of cell tropsim, trafficking mechanism, and therapeutic impact of human mesenchymal stem cells in a murine glioma model," *Biomaterials*, vol. 32, no. 12, pp. 3275–3284, 2011.

[90] H. Cho, D. Alcantara, H. Yuan et al., "Fluorochrome-functionalized nanoparticles for imaging DNA in biological systems," *ACS Nano*, vol. 7, no. 3, pp. 2032–2041, 2013.

[91] M. E. Lobatto, Z. A. Fayad, S. Silvera et al., "Multimodal clinical imaging to longitudinally assess a nanomedical anti-inflammatory treatment in experimental atherosclerosis," *Molecular Pharmaceutics*, vol. 7, no. 6, pp. 2020–2029, 2010.