PREMIER JOURNAL OF SCIENCE REVIEW

Applications of Nanotechnology in Medicine with a Focus on Diagnostic Imaging

Mostafa Farghal[1,2]

[1]Faculty of Veterinary Medicine, University of Calgary, 3280 Hospital Drive NW, T2N 4Z6, Calgary, Alberta, Canada

[2]Faculty of Veterinary Medicine, Minia University, Minia, Egypt

Correspondence to: Mostafa Farghal, mostafa.farhgal@ucalgary.ca

Additional material is published online only. To view please visit the journal online.

Cite this as: Farghal M. Applications of Nanotechnology in Medicine with a Focus on Diagnostic Imaging. Premier Journal of Science 2025;4:100037

DOI: https://doi.org/10.70389/PJS.100037

Received: 22 October 2024

Revised: 19 November 2024

Accepted: 19 November 2024

Published: 10 December 2024

Ethical approval: N/a

Consent: N/a

Funding: No industry funding.

Conflicts of interest: N/a

Author contribution: Mostafa Farghal – Conceptualization, Writing – original draft, review and editing

Guarantor: Mostafa Farghal

Provenance and peer-review: Commissioned and externally peer-reviewed

Data availability statement: N/a

ABSTRACT

Nanotechnology has emerged as a transformative approach in medicine, with extensive applications in diagnostics and therapeutics. In diagnostic imaging, it has significantly enhanced accuracy, sensitivity, and specificity in disease detection, surpassing traditional imaging modalities. Nanoparticles, such as magnetic and gold nanoparticles, have contributed to improved resolution and contrast, enabling earlier and more precise diagnoses such as the use of superparamagnetic iron nanoparticles in detecting early-stage tumors. Despite its promise, the clinical application of nanotechnology faces significant challenges, including high costs, lack of standardized regulatory frameworks for its use (such as guidelines for follow-up evaluation), and concerns about the long-term safety of nanoparticles. For example, the accumulation of nanoparticles in the body affects the immune, respiratory, and cardiovascular systems. Addressing these issues requires further research to ensure its safe and effective integration into clinical settings. Although the existing literature provides valuable insights into nanotechnology applications, it often tends to be either too specialized or overly general, creating a gap in the comprehensive knowledge regarding its role in diagnostic imaging. This review aims to provide a comprehensive overview of the role of nanotechnology in diagnostic imaging, focusing on its applications in enhancing techniques such as magnetic resonance imaging, computed tomography, and ultrasound. It also explores current challenges and future directions, emphasizing the need for continued research to fully realize the potential of nanotechnology in clinical practice. Future research should focus on the development of nanoparticles with no adverse health effects, the creation of techniques to assess the long-term health impacts of existing nanoparticles, and the establishment of international standards for their clinical use.

Keywords: Nanotechnology, Diagnostic imaging, Nanoparticles, MRI, Biosensors

Introduction

Nanotechnology is a recent scientific approach that enables the manipulation of materials at the molecular level, profoundly altering their physical and chemical properties.[1] Over the last decades, the integration of nanotechnology into medicine, commonly referred to as nanomedicine, has revolutionized the field of health care. Nanoparticles have emerged as versatile tools in various medical applications, including advanced diagnostic instruments, targeted drug delivery, biomedical implants, and tissue engineering.[2] Nanoparticles, typically ranging from 1 to 100 nm in size, exhibit unique properties that differentiate them from bulk materials, offering unprecedented precision in medical interventions.[3] Due to their nanoscale dimensions, nanoparticles can interact with biological systems at a cellular and molecular level, providing innovative solutions for disease diagnosis and treatment.

One of the most important types of nanoparticles is gold nanoparticles (AuNPs), which have been widely used for medical and non-medical applications due to their unique properties. They are inert, biocompatible, and notably low in toxicity. They can be produced on a large scale by reducing the oxidation of gold Au^{+1} (aureus) or Au^{+3} (auric) to Au^{0} by a reducing agent through various physical, chemical, and biological methods under different circumstances.[4] Another important type of nanoparticles is magnetic nanoparticles, characterized by their unique finite-size and surface effects that dominate their magnetic behavior. These nanoparticles exhibit properties such as high field irreversibility, high-saturation magnetization, superparamagnetism, additional anisotropy contributions, and shifted hysteresis loops following field cooling.[5]

Recent advancements have shown that nanomedicine, particularly in vitro diagnostics, significantly enhances disease diagnosis through improving the capture of rare biological targets and amplifying signal transduction during target analyte recognition.[6] The development of nanodiagnostics platforms, including point-of-care devices, holds immense promise for early disease detection and molecular diagnostics, offering simple and rapid alternatives. However, despite the rapid progress in this field, challenges remain, particularly regarding the long-term safety of nanoparticles in clinical use.[6]

Despite the significant advancements in nanotechnology applications across medical fields, particularly in diagnostic applications, the existing literature often lacks a comprehensive, cohesive review that bridges the gap between highly specialized and overly general studies.

Many reviews focus narrowly on specific diseases or technologies, such as nanotechnology's role in diagnosing coronary artery disease or its applications in diabetes management.[7–9] Although these reviews provide valuable insights into niche applications, they may not offer a broader perspective on how nanotechnology is transforming diagnostic imaging. Conversely, broad reviews tend to overlook critical advancements in diagnostic imaging by providing generalized summaries that do not explore the full potential of nanotechnology in enhancing disease identification and imaging resolution.[10–12]

The objective of this review is to fill this gap via focusing specifically on the use of nanotechnology in diagnostic imaging, offering an in-depth exploration of current advancements and future potential in this area. By concentrating on the unique capabilities of nanoparticles such as quantum dots, AuNPs, and magnetic nanoparticles, to enhance imaging modalities like magnetic resonance imaging (MRI), ultrasound, and computed tomography (CT), this review seeks to provide a more targeted understanding of how nanotechnology is reshaping diagnostic applications.[13,14] This review highlights the emerging trends and challenges that remain in integrating nanotechnology into routine diagnostic imaging practices.

Diagnostic Applications of Nanotechnology in Medicine

Visible symptoms of diseases are commonly used by medical professionals to identify diseases. In the last decades, nanotechnology has emerged as a new tool for diagnosing diseases with high efficiency and sensitivity.[1] Nanodevices are utilized for early and fast disease diagnosis for further medical procedural recommendations. These devices utilize nanotechnology for disease predisposition at the molecular and cellular level.[15] Nanotechnology applications in the medical field have revolutionized the sector of healthcare diagnostics through improving the accuracy, sensitivity, and speed of medical diagnostic tests.[16]

There are multiple applications of nanotechnology in the diagnostic medical sector, such as nanoparticle-based diagnostic imaging, whereas nanoparticles are annexed to specific biomarkers to improve imaging modalities. MRI, CT scans, and ultrasound scans are examples of nanoparticle-based diagnostic imaging.[17] Biosensors represent another application of nanotechnology, whereas nanotechnology has been employed for the creation of sensitive biosensors able to estimate low levels of biomolecules in bodily fluids including urine and blood, facilitating early disease detection.[18]

One of the primary innovations is the use of nanoparticles, such as quantum dots and AuNPs, in imaging modalities like MRI, CT, positron emission tomography, and ultrasound. These nanoparticles enhance contrast, allowing for a more detailed visualization of tissues at the molecular level, thus enabling earlier detection of diseases, such as cancer.[19] Quantum dots have demonstrated superior photostability and tunable fluorescence properties, making them ideal for tracking molecular changes in real time.[20] In addition, AuNPs improve the efficacy of optical imaging via scattering and absorbing light at specific wavelengths, improving the resolution of the imaging techniques.[21] This progress in nanotechnology is crucial for identifying diseases at earlier stages, enabling timely interventions and eventually improving patient outcomes.[21]

Moreover, the integration of nanotechnology into biosensor development has enabled rapid and precise detection of biomarkers for several diseases. Nanoscale biosensors, often incorporating nanoparticles or nanowires, can detect extremely low concentrations of biomarkers in bodily fluids such as blood, saliva, or urine, facilitating early diagnosis of conditions such as diabetes, cancer, and gastrointestinal and cardiovascular diseases.[22] The sensitivity of these devices is due to the high surface-to-volume ratio of nanoparticles, which increases binding efficiency to target molecules.[6] Nanotechnology-based diagnostics hold the potential to transform personalized medicine, enabling medical professionals to identify diseases before clinical symptoms appear and tailor treatment plans based on the molecular profile of the patient.[6,9]

Nanotechnology in Diagnostic Imaging

Due to the unique optical, magnetic, and electrical properties of nanoparticles at the nanoscale, they have been utilized in imaging applications. The advancement in the engineering field has resulted in multimodal imaging methods combining information from two modalities to provide in-depth clinical information.[23] Nanoparticles are considered the front drivers of such next-generation multimodal technologies because they provide an abundance of surface area for the functionalization of various reporters; for example, surface ligands to facilitate stimuli-responsive behavior and site-specific localization. Moreover, the majority of imaging agents used in the past have been organic or organo-metallic compounds that suffered from inherent limitations, such as poor contrast generation or photobleaching.[21,23]

In the case of imaging, the association of a contrast agent with tumors through bonding of the surface ligands of nanoparticles to the cancer biomarker has significant use in tracking the diagnosis. However, identification of appropriate ligands that bind to the cancer biomarker is still a key challenge.[23] Contrast agents are often used to track a particular physiological process during imaging, and nanoparticles have a significant role in the future of medical diagnostics because of their advantages over the conventional contrast agents (Figure 1).[23] Examples include controlled biological clearance pathways, specific molecular targeting capabilities,[24] and the prolonged blood circulation time, which provide a longer time for imaging. This offers an advantage over contrast agents made from particles larger than 1 μm, which are rapidly cleared by the body's reticuloendothelial system following injection into the bloodstream.[24]

Magnetic Resonance Imaging

MRI is a commonly used non-invasive clinical imaging tool, which works on the principle of nuclear magnetic resonance.[25] Gd(III)-based T_1 contrast agents have dominated the clinical imaging domain for a long time while iron oxide nanoparticle-based T_2 contrast agents, previously approved for clinical use, have been withdrawn due to poor clinical performance (Figure 2).[26] However, the incidence of nephrotoxicity caused by Gd(III)-based contrast agents has been reported, while iron oxide nanoparticles have been widely biocompatible.[27] On the other hand, size control of the iron oxide nanoparticles in the 1–100 nm range resulted in controlled magnetic properties ranging from paramagnetic to ferrimagnetic, which significantly improves their application and clinical performance as a T_1 or T_2 contrast agent.[28]

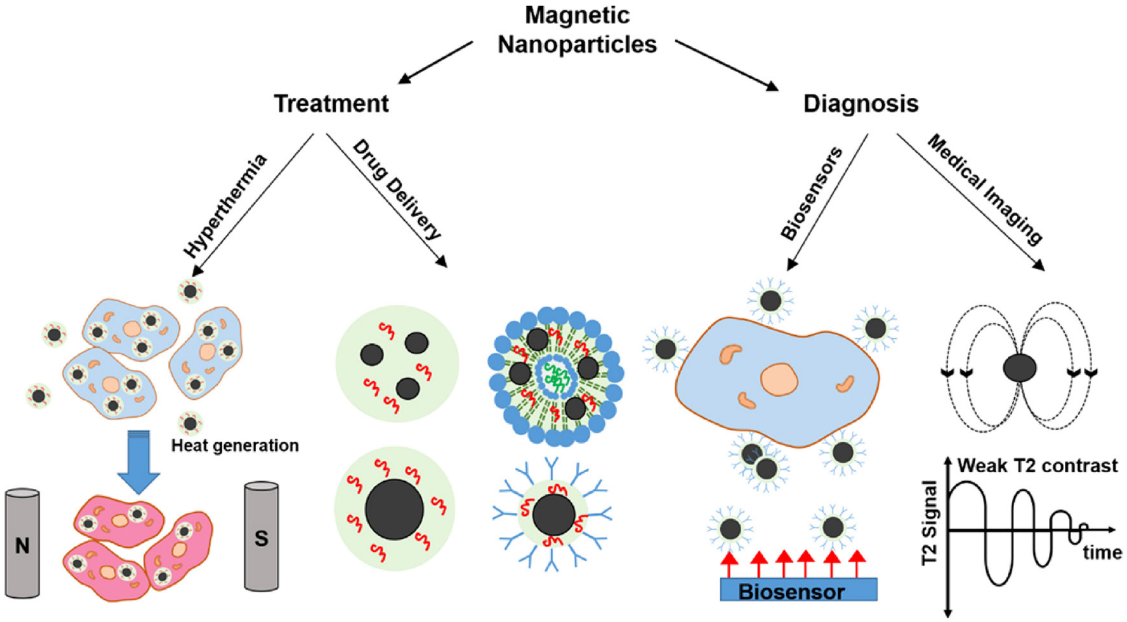

Fig 1 | Different forms of the magnetic nanoparticles with diagnostic and therapeutic applications of cancer[63]

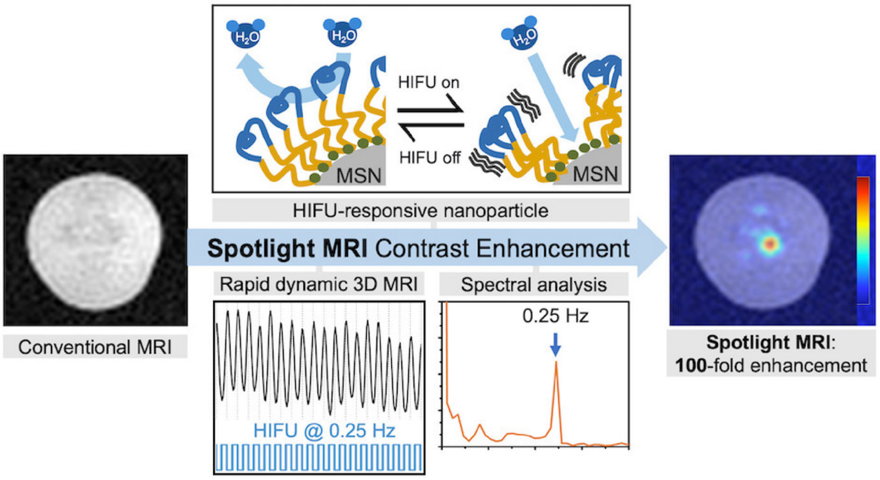

Fig 2 | Illustration of using nanoparticles for magnetic resonance imaging[66]

Nanotechnology implementation in the medical imaging sector has several advantages. Iron-based nanoparticles cause a change in the magnetic field, but gold-based nanoparticles are non-paramagnetic and do not affect the contrast of the tissues or blood.[28,29] MRI contrast agents require alteration of the proton relaxation and must be able to perturb the local magnetic field around the proton. The perturbing field in the MRI generated by superparamagnetic particles can extend up to 50 times its diameter, impacting water protons in several surrounding cell layers.[24] However, the use of AuNPs is less common due to their lack of magnetic properties.

Despite this, Faradaic AuNPs, which gain their magnetic properties through oxidation or reduction reaction, hold potential for MRI applications.[30] Superparamagnetic nanoparticles, with iron oxides and a carbohydrate or polymer coat, play a key role in various MRI systems, including cardiovascular molecular imaging.[30] The size, physical properties, and pharmacokinetics of magnetic nanoparticles make them appropriate for molecular and cellular imaging of atherosclerotic plaques and myocardial injury. Targeted imaging with magnetic nanoparticles is being actively investigated, and improvements in contrast-enhanced MRI have been of great interest.[31]

Ultrasound

Ultrasound is characterized by frequencies exceeding 20 kHz, which is the upper audible threshold in healthy adults. The ultrasound technology was initially employed for submarine detection, and then its application has expanded from the military to medical fields.[32] This expansion is due to its non-invasive, real-time, and portable characteristics, combined with high safety and low cost. Ultrasound has been extensively developed as a versatile tool for biomedical applications, adopting different parameters.[33] Currently, diagnostic imaging and therapeutic interventions are considered the two main domains of ultrasound applications. Ultrasound imaging provides detailed anatomical information into targeted areas or tissues, leveraging the principle that backscattered signals from acoustic waves vary with ultrasound contrast agents and tissue composition.[34] Ultrasound plays an essential role in disease diagnosis, facilitates the controlled release of therapeutics, opens the blood–brain barrier, and induces elevated temperatures.[35]

Nanomedicine has not only significantly enhanced the diagnosis and treatment of diseases but also stimulated the development of related medical devices and new biomaterials.[36] The synergy of ultrasound and nanotechnology has stimulated ultrasound-based medicine, evidenced by the increasing number of articles on ultrasound and nanomedicine.[37] Rapid innovations and progress in research on ultrasound biomedicine, employed in disease diagnosis, treatment, and theranostics, have occurred in the last decade.[38] This progress resulted in a mass of multifunctional nanosystems such as polymers, liposomes, micelles, dendrimers, inorganic nanoparticles, and microbubbles, which have been used in ultrasound-mediated diagnosis, treatment, and theranostics for various diseases (Figure 3). Ultrasound-mediated biomedical imaging, ultrasound-enhanced drug release and gene transfection, ultrasound-triggered therapy, ultrasound-based synergistic therapy, and ultrasound-based theranostics are examples of these applications.[39,40]

The engineering of ultrasound-responsive nanostructures requires careful consideration of their size, composition, and morphology to ensure appropriate acoustic properties and biological interactions.[41] Surface functionalization strategies play a pivotal role in refining these ultrasound-based nanosystems. Techniques such as polyethylene glycol modification, or PEGylation, are employed to enhance the blood circulation longevity of these systems.[41] In addition, the modification of targeting ligands on the surface of these systems is crucial for enhancing their accumulation in targeted lesion tissues, thereby improving the efficacy and specificity of diagnostic applications.[40,41] Moreover, the intrinsic physicochemical properties and unique biological effects of ultrasound and ultrasound-triggered nanoplatforms are leveraged to achieve effective and safe theranostic applications. The interaction of nanosystems with ultrasound waves could induce various biological effects, such as localized hyperthermia or enhanced permeability in targeted tissues, which can be exploited for therapeutic purposes such as drug delivery or gene transfection.[39,41]

In the field of ultrasound-based biomedicine, organic nanosystems primarily comprise lipid-based, polymer-based, and microporous organic polymer-based nanomaterials, which are characterized by exceptional biocompatibility, superior biodegradability, and facile fabrication processes.[41] On the other hand, inorganic nanomaterials are distinguished by their superior physiological and chemical stability and multifunctional capabilities.[35] The recent progress in the development of inorganic nanomaterials enhanced their applications as novel agents for ultrasound-induced theranostic applications, specifically targeting a range of diseases, including noble metal-based, titanium-based, metal oxide-based, silica-based, and carbon-based nanomaterials.[37,41] Other nanomaterials such as Hollow Prussian blue nanoparticles with porous shells have been synthesized for light-responsive ultrasound imaging.[42] Solid nanoparticles can improve ultrasonic grayscale images in both tissue phantoms and live mouse livers. For instance, silica nanospheres (100 nm) dispersed in agarose at a mass concentration of 1–2.5% have been imaged using a high-resolution ultrasound system with a transducer center frequency of 30 MHz. Additionally, this study investigated polystyrene particles of various sizes (500–3000 nm) and concentrations (0.13–0.75% mass), which were dispersed in agarose and imaged under similar conditions.[43]

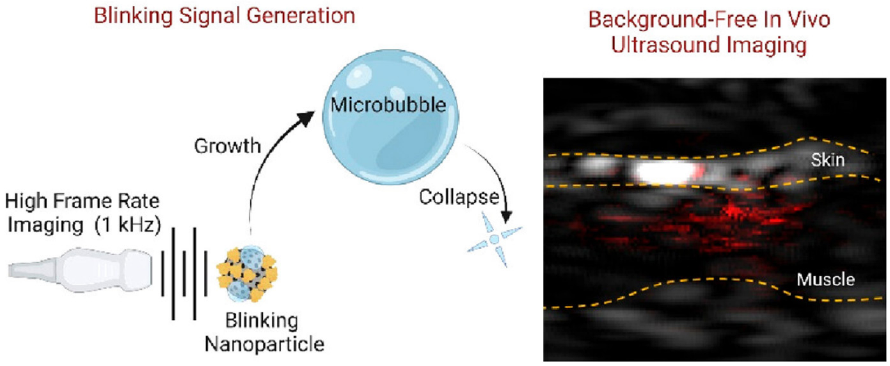

Fig 3 | Illustration of ultrasound imaging using blinking nanoparticles[67]

Jawaid et al.[44] explored the potential use of platinum nanoparticles, as a superoxide dismutase/catalase mimetic antioxidant. The platinum nanoparticles combined with ultrasound of 1 MHz have promoted apoptosis in human myelomonocytic lymphoma cells. As a result, the issues of the mechanisms of cell death following therapeutic ultrasound treatment in the presence or absence of platinum nanoparticles have been addressed.[44] Also, the platinum nanoparticles interfered with apoptosis and blocked ultrasound-induced autophagy. The authors concluded that autophagy induced after ultrasound mechanical effects operates the "pro-survival pathway" and its blockade by platinum nanoparticles causes enhancement of cell killing.[45]

Computed Tomography

Currently, X-ray-based CT is considered one of the most convenient imaging or diagnostic tools in hospitals due to its efficiency, availability, and cost.[13,24] In contrast to MRI and certain nuclear medicine imaging techniques, CT is not classified as a molecular imaging modality because specific contrast agents have not yet been developed for it.[46] Present CT contrast agents are predominantly based on iodine-containing molecules, proven effective in absorbing X-rays; however, they are non-specifically targeted because they cannot be conjugated to most biological components or cancer markers. In addition, they allow only very short imaging times due to rapid clearance by the kidneys.[46]

Recent progress toward nanotechnology-based CT imaging has been achieved. Hainfeld et al.[47] demonstrated that AuNPs can provide in vivo vascular contrast enhancement in CT imaging, though these AuNPs were not targeted as they were not conjugated to specific biomarkers. More recently, vascular CT contrast agents have been developed, including hybrid nanoparticles such as gadolinium-coated AuNPs, antibiofouling polymer-coated AuNPs, polymer-coated Bi_2S_3 nanoparticles, and polyethylene glycol-coated nanoparticles.[48–51] Interestingly, Popovtzer et al.[46] reported the possibility of the identification of squamous cell carcinoma in the head and neck using CT scans. In this study, AuNPs accumulated only on the targeted cancer cells, producing a strong and distinct X-ray attenuation that could be distinguished from the attenuation produced by untargeted, yet identical, cancer cells or normal cells.

Considerable research is focusing on the development of nanoparticle CT contrast agents for molecular imaging of blood.[13] Each imaging modality uses different physical principles to obtain the image and requires the physical properties of the contrast agent to be compatible with the physics of the specific imaging system.[49,51] Most CT contrast agents lack this amplification ability and force, and since CT imaging requires millimolar contrast agent concentrations to induce sufficient contrast in the desired organ, a much larger amount is needed.[52] However, nanoparticle contrast agents can enhance image contrast, enabling a reduction in the high radiation exposure of CT. These new-generation CT contrast agents, made from materials of high atomic numbers (e.g., bismuth and gold), hold significant potential not only due to the production of higher contrast than conventional iodine-based contrast agents but more importantly for reducing the overall radiation exposure to patients.[49,53] Hainfeld et al.[54] investigated the molecular imaging of cancer with actively targeted CT contrast agents. It was revealed that AuNPs enhanced the visibility of xenografted human breast tumors in mice, and active tumor targeting is 1.6-fold more efficient than passive targeting. They also demonstrated that the specific uptake of the targeted AuNPs in the tumor periphery was 22-fold higher than that in the surrounding muscle. Chanda et al.[55] reported enhanced CT attenuation of bombesin-functionalized AuNPs, which selectively targeted cancer receptor sites that are overexpressed in prostate, breast, and small-cell lung carcinomas. Motiei et al.[52] recently investigated methods to differentiate between cancer and inflammation during functional CT since positron emission tomography scanning using ^{18}F glucose is unable to distinguish between an inflammatory lesion and a cancer lesion as both have increased glucose metabolism-associated uptake. They found that glucose AuNPs can act as a CT agent, which allows for the differentiation between cancer and an inflammatory process.

Potential Hazards of Nanoparticles

Nanoparticles, due to their microscopic dimension, pose various health hazards similar to particulate matter. Several studies have demonstrated that nanoparticles can cause pathologies of respiratory, cardiovascular, and gastrointestinal systems.[56] For example, carbon nanotubes can result in severe lung pathologies in mice, such as granulomas, inflammation, and necrosis, with more toxicity than carbon black and quartz.[57,58] Nanoparticles can enter the body through the lungs and other routes, potentially reaching vital organs through the bloodstream. They may even act as gene vectors or enter the central nervous system via the olfactory pathway, which raises concerns about their potential for brain inflammation.[59]

Research on rats and monkeys has revealed that nanoparticles, such as carbon and manganese particles, can accumulate in the olfactory bulb, raising concerns about their impact on the brain and other organs.[60] For example, nanotubes have been shown to promote platelet aggregation and accelerate vascular thrombosis in rats, whereas fullerenes did not demonstrate such effects, suggesting that they may be a safer option for drug delivery systems.[61] Ingestion of nanoparticles can lead to toxicity when they reach different organs and systems through the circulatory system.[62] The toxicity of nanoparticles may be associated with their ability to trigger pro-inflammatory mediators, leading to inflammatory response and potential organ damage. Nanoparticles also pose potential risks to the gastrointestinal system, possibly triggering inflammatory bowel diseases, and their full effects on humans are not yet well understood.[63]

Challenges for Nanobiotechnology Applications in Medicine

The main challenge for nanobiotechnology is developing instruments to evaluate the exposure to engineered nanomaterials in air and water.[5,64] Humans and animals' exposure to an environment potentially contaminated with nanomaterials may result in adverse consequences that should be monitored.[17,64] Another challenge is the development of reverse systems to assess the precise impact of engineered nanomaterials on health and the environment throughout the entire life, addressing the life cycle concern.[64] Also, developing applicable methods to assess the toxicity of engineered nanomaterials in the next years could be considered a challenging issue.[65] There are commercialization challenges of nanobiotechnology, including uncertainty of its effectiveness, scalability, funding, and scarce resources. In addition, the need for regulations for the use of nanotechnology represents another challenge in this field.[66] The efficiency of nanotechnology under clinical conditions remains unsatisfactory. Generally, each nanotherapeutic has its own challenges during clinical applications, but all nanotherapeutics face the shared challenges, including safety, scale-up, cost, and regulation and biological challenges.[64]

Conclusion

In conclusion, the integration of nanotechnology into the diagnostic field, particularly in diagnostic imaging, represents an advancement in medical diagnostics, improving the overall accuracy, sensitivity, and specificity for early disease diagnosis. As the potential of nanoparticles in imaging modalities has been proven, a comprehensive understanding of their applications and mechanisms in clinical settings is crucial. Despite the numerous advantages of nanotechnology in disease diagnosis, there are challenges for its application in clinical practice, including the long-term safety of these materials and their acceptance in clinical practice. Addressing these challenges is crucial for enhancing its applications in diagnostic imaging and advancing personalized medicine. Improving diagnostic accuracy using nanotechnology leads to innovative therapeutic strategies that can lead to better patient outcomes.

References

1 Fakruddin M, Hossain Z, Afroz H. Prospects and applications of nanobiotechnology: a medical perspective. J Nanobiotechnol. 2012;10(1):31. Available from: https://doi.org/10.1186/1477-3155-10-31

2 Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of nanotechnology in medical field: a brief review. Glob Health J. 2023;7(2):70–7. Available from: https://www.sciencedirect.com/science/article/pii/S2414644723000337

3 Elmer W, White JC. The future of nanotechnology in plant pathology. Annu Rev Phytopathol. 2018;56(Volume 56, 2018):111–33. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-phyto- 080417-050108

4 Hammami I, Alabdallah NM, jomaa AA, kamoun M. Gold nanoparticles: synthesis properties and applications. J King Saud Univ-Sci. 2021;33(7):101560. Available from: https://www.sciencedirect.com/science/article/pii/S1018364721002214

5 Farzin DA, Etesami MSA, Quint MJ, Memic DA, Tamayol PA. Magnetic nanoparticles in cancer therapy and diagnosis. Adv Healthc Mater. 2020;9(9):e1901058. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7482193/

6 Dang Y, Guan J. Nanoparticle-based drug delivery systems for cancer therapy. Smart Mater Med. 2020;1:10–9.

7 Xu Y, Zhang L, Chen G, Chen P. Thinking on the application of nanotechnology in the mechanism research on the traditional Chinese medicine diagnosis and treatment of diabetes mellitus. J Phys Conf Ser. 2011;276(1):012050. Available from: https://dx.doi.org/10.1088/1742-6596/276/1/012050

8 Rhee JW, Wu JC. Advances in nanotechnology for the management of coronary artery disease. Trends Cardiovasc Med. 2013;23(2):39–45. Available from: https://www.sciencedirect.com/science/article/pii/S1050173812003015

9 Gonzalez L, Loza RJ, Han KY, Sunoqrot S, Cunningham C, Purta P, et al. Nanotechnology in corneal neovascularization therapy—A review. J Ocul Pharmacol Ther. 2013;29(2):124–34. Available from: https://www.liebertpub.com/doi/10.1089/jop.2012.0158

10 Moshed AMA, Sarkar MKI, Khaleque MdA. The application of nanotechnology in medical sciences: new horizon of treatment. Am J Biomed Sci. 2017;1–14. Available from: http://www.nwpii.com/ajbms/papers/AJBMS_2017_1_01.pdf

11 Roco MC. Nanotechnology: convergence with modern biology and medicine. Curr Opin Biotechnol. 2003;14(3):337–46. Available from: https://www.sciencedirect.com/science/article/pii/S0958166903000685

12 Surendiran A, Sandhiya S, Pradhan SC, Adithan C. Novel applications of nanotechnology in medicine. Indian J Med Res. 2009;130(6):689–701.

13 Wang W, Ye Z, Gao H, Ouyang D. Computational pharmaceutics - A new paradigm of drug delivery. J Controlled Release. 2021;338:119–36. Available from: https://www.sciencedirect.com/science/article/pii/S0168365921004363

14 Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. Molecules. 2023;28(18):6624. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10536529/

15 Dessale M, Mengistu G, Mengist HM. Nanotechnology: a promising approach for cancer diagnosis, therapeutics and theragnosis. Int J Nanomed. 2022;17:3735–49.

16 Zhang K, Mikos AG, Reis RL, Zhang X. Translation of biomaterials from bench to clinic. Bioact Mater. 2022;18:337–8. Available from: https://www.sciencedirect.com/science/article/pii/S2452199X22000706

17 Singh A, Amiji MM. Application of nanotechnology in medical diagnosis and imaging. Curr Opin Biotechnol. 2022;74:241–6.

18 Xu QY, Tan Z, Liao XW, Wang C. Recent advances in nanoscale metal-organic frameworks biosensors for detection of biomarkers. Chin Chem Lett. 2022;33(1):22–32. Available from: https://www.sciencedirect.com/science/article/pii/S1001841721004149

19 Yang Z, Gao M, Wu W, Yang X, Sun XW, Zhang J, et al. Recent advances in quantum dot- based light-emitting devices: challenges and possible solutions. Mater Today. 2019;24:69–93. Available from: https://www.sciencedirect.com/science/article/pii/S1369702118302335

20 Hassan M, Gomes VG, Dehghani A, Ardekani SM. Engineering carbon quantum dots for photomediated theranostics. Nano Res. 2018;11(1):1–41. Available from: https://doi.org/10.1007/s12274-017-1616-1

21 Krishnan S, Diagaradjane P, Cho SH. Nanoparticle-mediated thermal therapy: evolving strategies for prostate cancer therapy. Int J Hyperth Off J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2010;26(8):775–89.

22 Chung HU, Kim BH, Lee JY, Lee J, Xie Z, Ibler EM, et al. Binodal, wireless epidermal electronic systems with in-sensor analytics for neonatal intensive care. Science. 2019;363(6430):eaau0780.

23 Kim D, Kim J, Park YI, Lee N, Hyeon T. Recent development of inorganic nanoparticles for biomedical imaging. ACS Cent Sci. 2018;4(3):324–36. Available from: https://doi.org/10.1021/acscentsci.7b00574

24 Shilo M, Reuveni T, Motiei M, Popovtzer R. Nanoparticles as computed tomography contrast agents: current status and future perspectives. Nanomed. 2012;7(2):257–69. Available from: https://doi.org/10.2217/nnm.11.190

25 Berger A. Magnetic resonance imaging. BMJ. 2002;324(7328):35. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1121941/

26 Kiessling F, Mertens ME, Grimm J, Lammers T. Nanoparticles for imaging: Top or flop? Radiology. 2014;273(1):10–28. Available from: https://pubs.rsna.org/doi/10.1148/radiol.14131520

27 Kanal E, Tweedle MF. Residual or retained gadolinium: Practical implications for radiologists and our patients. Radiology. 2015;275(3):630–4. Available from: https://pubs.rsna.org/doi/10.1148/radiol.2015150805

28 Wei H, Bruns OT, Kaul MG, Hansen EC, Barch M, Wiśniowska A, et al. Exceedingly small iron oxide nanoparticles as positive MRI contrast agents. Proc Natl Acad Sci. 2017;114(9):2325–30. Available from: https://www.pnas.org/doi/full/10.1073/pnas.1620145114

29 Ghodasara P, Satake N, Sadowski P, Kopp S, Mills PC. Investigation of cattle plasma proteome in response to pain and inflammation using next generation proteomics technique, SWATH-MS. Mol Omics. 2022;18(2):133–42. Available from: https://pubs.rsc.org/en/content/articlelanding/2022/mo/d1mo00354b

30 Mohs AM, Provenzale JM. Applications of nanotechnology to imaging and therapy of brain tumors. Neuroimaging Clin N Am. 2010;20(3):283–92. Available from: https://www.sciencedirect.com/science/article/pii/S1052514910000286

31 Xing Y, Zhao J, Conti PS, Chen K. Radiolabeled nanoparticles for multimodality tumor imaging. Theranostics. 2014;4(3):290–306. Available from: https://www.thno.org/v04p0290.htm

32 Newman PG, Rozycki GS. The history of ultrasound. Surg Clin North Am. 1998;78(2):179–95. Available from: https://www.sciencedirect.com/science/article/pii/S003961090570308X

33 Deprez J, Lajoinie G, Engelen Y, De Smedt SC, Lentacker I. Opening doors with ultrasound and microbubbles: Beating biological barriers to promote drug delivery. Adv Drug Deliv Rev. 2021;172:9–36. Available from: https://www.sciencedirect.com/science/article/pii/S0169409X21000612

34 Kunjachan S, Ehling J, Storm G, Kiessling F, Lammers T. Noninvasive imaging of nanomedicines and nanotheranostics: principles, progress, and prospects. Chem Rev. 2015;115(19):10907–37. Available from: https://doi.org/10.1021/cr500314d

35 Son S, Kim JH, Wang X, Zhang C, Yoon SA, Shin J, et al. Multifunctional sonosensitizers in sonodynamic cancer therapy. Chem Soc Rev. 2020;49(11):3244–61. Available from: https://pubs.rsc.org/en/content/articlelanding/2020/cs/c9cs00648f

36 van der Meel R, Sulheim E, Shi Y, Kiessling F, Mulder WJM, Lammers T. Smart cancer nanomedicine. Nat Nanotechnol. 2019;14(11):1007–17. Available from: https://www.nature.com/articles/s41565-019-0567-y

37 Ouyang J, Tang Z, Farokhzad N, Kong N, Kim NY, Feng C, et al. Ultrasound mediated therapy: recent progress and challenges in nanoscience. Nano Today. 2020;35:100949. Available from: https://www.sciencedirect.com/science/article/pii/S1748013220301183

38 Zhang L, Du W, Kim JH, Yu CC, Dagdeviren C. An emerging era: conformable ultrasound electronics. Adv Mater. 2024;36(8):2307664. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/adma.202307664

39 Song X, Zhang Q, Chang M, Ding L, Huang H, Feng W, et al. Nanomedicine-enabled sonomechanical, sonopiezoelectric, sonodynamic, and sonothermal therapy. Adv Mater. 2023;35(31):2212259. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/adma.202212259

40 Zhang Q, Kuang G, Li W, Wang J, Ren H, Zhao Y. Stimuli-responsive gene delivery nanocarriers for cancer therapy. Nano-Micro Lett. 2023;15(1):44. Available from: https://doi.org/10.1007/s40820-023-01018-4

41 Huang H, Zheng Y, Chang M, Song J, Xia L, Wu C, et al. Ultrasound-based micro-/nanosystems for biomedical applications. Chem Rev. 2024;124(13):8307–472. Available from: https://doi.org/10.1021/acs.chemrev.4c00009

42 Jia X, Cai X, Chen Y, Wang S, Xu H, Zhang K, et al. Perfluoropentane-encapsulated hollow mesoporous Prussian blue nanocubes for activated ultrasound imaging and photothermal therapy of cancer. ACS Appl Mater Interfaces. 2015;7(8):4579–88. Available from: https://doi.org/10.1021/am507443p

43 Liu J, Levine AL, Mattoon JS, Yamaguchi M, Lee RJ, Pan X, et al. Nanoparticles as image enhancing agents for ultrasonography. Phys Med Biol. 2006;51(9):2179. Available from: https://dx.doi.org/10.1088/0031-9155/51/9/004

44 Jawaid P, Rehman MU, Hassan MA, Zhao QL, Li P, Miyamoto Y, et al. Effect of platinum nanoparticles on cell death induced by ultrasound in human lymphoma U937 cells. Ultrason Sonochem. 2016;31:206–15. Available from: https://www.sciencedirect.com/science/article/pii/S1350417715301061

45 Bayford R, Rademacher T, Roitt I, Wang SX. Emerging applications of nanotechnology for diagnosis and therapy of disease: a review. Physiol Meas. 2017;38(8):R183. Available from: https://dx.doi.org/10.1088/1361-6579/aa7182

46 Popovtzer R, Agrawal A, Kotov NA, Popovtzer A, Balter J, Carey Thomas E, et al. Targeted gold nanoparticles enable molecular CT imaging of cancer. Nano Lett. 2008;8(12):4593–6. Available from: https://doi.org/10.1021/nl8029114

47 Hainfeld JF, Slatkin DN, Focella TM, Smilowitz HM. Gold nanoparticles: A new X-ray contrast agent. Br J Radiol. 2006;79(939):248–53. Available from: https://doi.org/10.1259/bjr/13169882

48 Cai QY, Kim SH, Choi KS, Kim SY, Byun SJ, Kim KW, et al. Colloidal gold nanoparticles as a blood-pool contrast agent for x-ray computed tomography in mice. Invest Radiol. 2007;42(12):797. Available from: https://journals.lww.com/investigativeradiology/abstract/2007/12000/colloidal_gold_nanop articles_as_a_blood_pool.2.aspx

49 Alric C, Taleb J, Le Duc G, Mandon C, Billotey C, Le Meur-Herland A, et al. Gadolinium chelate coated gold nanoparticles as contrast agents for both x-ray computed tomography and magnetic resonance imaging. J Am Chem Soc. 2008;130(18):5908–15. Available from: https://doi.org/10.1021/ja078176p

50 Kattumuri V, Katti K, Bhaskaran S, Boote EJ, Casteel SW, Fent GM, et al. Gum Arabic as a phytochemical construct for the stabilization of gold nanoparticles: in vivo pharmacokinetics and x-ray-contrast-imaging studies. Small. 2007;3(2):333–41. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/smll.200600427

51 Rabin O, Manuel Perez J, Grimm J, Wojtkiewicz G, Weissleder R. An x-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. Nat Mater. 2006;5(2):118–22. Available from: https://www.nature.com/articles/nmat1571

52 Motiei M, Dreifuss T, Betzer O, Panet H, Popovtzer A, Santana J, et al. Differentiating between cancer and inflammation: a metabolic-based method for functional computed tomography imaging. ACS Nano. 2016;10(3):3469–77. Available from: https://doi.org/10.1021/acsnano.5b07576

53 Barajas-Montiel SE, Reyes-García CA. Fuzzy support vector machines for automatic infant cry recognition. In: DS Huang, K Li, GW Irwin, (eds). Intelligent Computing in Signal Processing and Pattern Recognition: international Conference on Intelligent Computing, ICIC 2006 Kunming, China, August 16–19, 2006. Berlin, Heidelberg: Springer. 2006. pp. 876–81. Available from: https://doi.org/10.1007/978-3-540-37258-5_107

54 Hainfeld JF, Slatkin DN, Smilowitz HM. The use of gold nanoparticles to enhance radiotherapy in mice. Phys Med Biol. 2004;49(18):N309. Available from: https://dx.doi.org/10.1088/0031-9155/49/18/N03

55 Chanda N, Kattumuri V, Shukla R, Zambre A, Katti K, Upendran A, et al. Bombesin functionalized gold nanoparticles show in vitro and in vivo cancer receptor specificity. Proc Natl Acad Sci. 2010;107(19):8760–5. Available from: https://www.pnas.org/doi/full/10.1073/pnas.1002143107

56 Li Z, Hulderman T, Salmen R, Chapman R, Leonard SS, Young SH, et al. Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes. Environ Health Perspect. 2007;115(3):377–82.

57 Nijhara R, Balakrishnan K. Bringing nanomedicines to market: Regulatory challenges, opportunities, and uncertainties. Nanomed Nanotechnol Biol Med. 2006;2(2). Available from: https://pubmed.ncbi.nlm.nih.gov/17292125/

58 Lam CW, James JT, McCluskey R, Hunter RL. Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. Toxicol Sci Off J Soc Toxicol. 2004;77(1):126–34.

59 Williams D. The risks of nanotechnology. Med Device Technol. 2005;16(9):6, 9–10.

60 Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, et al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect. 2006;114(8):1172–8.

61 Radomski A, Jurasz P, Alonso-Escolano D, Drews M, Morandi M, Malinski T, et al. Nanoparticle-induced platelet aggregation and vascular thrombosis. Br J Pharmacol. 2005;146(6):882–93.

62 Chen Z, Meng H, Xing G, Chen C, Zhao Y, Jia G, et al. Acute toxicological effects of copper nanoparticles in vivo. Toxicol Lett.

2006;163(2). Available from: https://pubmed.ncbi.nlm.nih.gov/16289865/

63 Medina C, Santos-Martinez MJ, Radomski A, Corrigan OI, Radomski MW. Nanoparticles: pharmacological and toxicological significance. Br J Pharmacol. 2007;150(5):552–8.

64 Zhang C, Yan L, Wang X, Zhu S, Chen C, Gu Z, et al. Progress, challenges, and future of nanomedicine. Nano Today. 2020;35:101008. Available from: https://www.sciencedirect.com/science/article/pii/S1748013220301778

65 Albalawi F, Hussein MZ, Fakurazi S, Masarudin MJ. Engineered nanomaterials: the challenges and opportunities for nanomedicines. Int J Nanomed. 2021;16:161–84. Available from: https://www.tandfonline.com/doi/abs/10.2147/IJN.S288236

66 Danchuk O, Levchenko A, da Silva Mesquita R, Danchuk V, Cengiz S, Cengiz M, et al. Meeting contemporary challenges: development of nanomaterials for veterinary medicine. Pharmaceutics. 2023;15(9):2326. Available from: https://www.mdpi.com/1999-4923/15/9/2326

67 Sabuncu S, Javier Ramirez R, Fischer JM, Civitci F, Yildirim A. Ultrafast background-free ultrasound imaging using blinking nanoparticles. Nano Lett. 20230000;23(2):659–66. Available from: https://doi.org/10.1021/acs.nanolett.2c04504