# THE POTENTIAL APPLICATIONS OF NANOTECHNOLOGY IN MEDICAL DIAGNOSTIC IMAGING TECHNIQUES

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## ABSTRACT

According to Freitas, nanomedicine is: "...the comprehensive monitoring, control, construction, repair, defense, and improvement of all human biological systems, working from the molecular level, using engineered nanodevices and nanostructures..." [1] Nanomedicine is a field that has the potential to revolutionise the way we look at medical treatment and diagnostics, and it is the diagnostic side of nanomedicine that we will be focusing on in this paper.

Though medical diagnostics it becoming ever more accurate, the applications of nanotechnology, for example buckyballs, quantum dots and iron oxide particles could both reduce clinical risk and enhance imaging, enabling greater sensitivity and specificity in the field of medical diagnostics. By examining current techniques and comparing them to possible future ones in both scientific and ethical contexts we can see that despite some drawbacks, they have the potential to offer vast improvements in the field of diagnostic imaging.

## INTRODUCTION

Nanotechnology refers to working with matter on an extremely small scale, in order to build machines on a sub-atomic level. In the last few years many exciting discoveries have been made, and lots of research conducted in order to gain an insight into the potential benefits this field could bring. One area of nanotechnology that has been focused on is nanomedicine. With a potential to revolutionise anything from cancer treatment to healing burns, it is a field that is attracting a lot of interest.

The application of nanotechnology in diagnostic imaging is especially interesting due to the size and properties of the materials concerned. Many problems encountered today (e.g. the toxicity of some radiological contrast agents) could be solved by nanotechnology, and the quality of imaging could be greatly improved. It offers the best of both worlds, with reduced risk for the patient and an enhanced diagnostic capability for the doctor.

In this paper we will be focusing on three possible applications of nanotechnology in diagnostic imaging: the use of buckyballs, quantum dots and iron oxide particles. We will examine their effectiveness when compared to current imaging techniques and also look at any possible drawbacks.

Magnetic resonance imaging (MRI) currently uses the contrast agent gadolinium. It is a paramagnetic ion, meaning that it moves differently in a magnetic field, making it useful as a contrast agent for MRI. It can also be used in chelated form (the metal is part of a ring structure that includes large organic molecules) which reduces its ability to aggregate in body tissues, thereby reducing toxicity. It is then eliminated via the kidneys. [2] The chemical properties of the agent cause an increase in the T1 relaxation time (the time taken for the protons to go from an excited state to a ground state) in a MRI scan, this releases a radiofrequency signal that can be translated into an image. The use of gadolinium based contrast agents allows better differentiation between tissues in certain scans.

However, the use of gadolinium is not without its disadvantages. When using gadolinium, there is a danger that some of the metal can remain in the body and cause damage. Patients with existing kidney disease are at an increased risk of developing an incurable condition called Nephrogenic Systemic Fibrosis (NSF), with symptoms including hardening of the skin and stiffening of the joints. [3]

Radioactive elements are also used in diagnostic imaging. Ninety percent of all isotopes used in healthcare are used for this purpose and of these, technetium-$99^m$ is the most common. [4] In the case imaging using radioactive tracers this can take two main forms. In the first form the tracer is injected, inhaled or taken orally depending on the organ or function being studied in the patient. A number of isotopes are used, bound to specific compounds that allow processes in the body to be studied. The isotopes used have relatively short half lives and emit gamma radiation, thereby reducing potential damage to body tissue. A gamma camera is used to detect single photons that are emitted, and can be used to provide planar images of an organ/area of the body. From the points that the emissions are emitted from, a picture can be built up about the functioning of the organ, which is then enhanced by a computer.

Positron Emission Topography (PET) also uses radioactive elements but in a slightly different way. A positron emitting radionuclide is injected and its distribution within the body detected. When the radionuclide starts to decay, it emits a positron which reacts with an electron next to it, and this send out two gamma waves in opposite directions to each other. Using this, PET can give an extremely accurate picture of the location of a problem, and even the effect it is having. The radionuclide fluorine – 18 has proved useful in the detection of many cancers. [4]

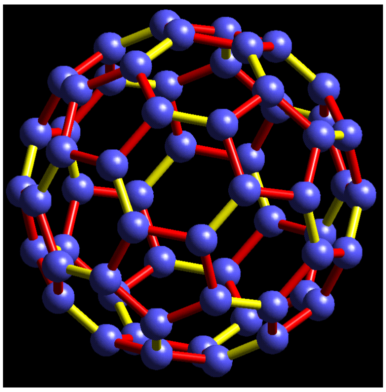
Despite the advantages of using radioactive isotopes in the field of diagnostic imaging, there are also several disadvantages. Firstly, the tracers used are radioactive, which always carries a small but important health risk. Furthermore, nanotechnology has the potential to greatly improve the quality of imaging produced and thus enable greater accuracy when making a diagnosis.

By examining some of the techniques that offer solutions to the problems already mentioned, or those that improve the quality of diagnostic imaging, we can come to a conclusion about the suitability of nanotechnology in diagnostic imaging.

## DISCUSSION

### Buckyballs

A Buckyball is a fullerene. Fullerenes, by definition, contain only pentagonal and hexagonal faces, which form a cage structure. Every fullerene contains twelve pentagonal faces. Fullerenes have a high strength to weight ratio, due to their hollow structure. They have the ability to absorb light and release it as heat or transfer it to another molecule. Due to their spherical shape, they do not fit together simply; therefore they create many gaps between molecules which make it difficult for them to move against each other. These gaps can be filled with group one or two metals, which give them the additional property of being superconducting at low temperatures. [7]



A buckyball (short for buckminsterfullerene) is a spherical molecule with sixty carbon atoms, and hence has the formula $C_{60.}$ Each atom is bonded to three other carbon atoms, forming a molecule which is about 1nm in diameter [5]. (Left [12])

Richard Smalley first produced buckyballs by vaporising carbon with a laser and allowing it to condense. However, this only produced a small number of buckyballs; not enough for commercial use. It wasn't until researchers at the Max Planck Institute in Germany and the University of Arizona found out how to make larger quantities of buckyballs. They vaporised carbon by placing two carbon electrodes together and generating a reaction arc between them in a chamber filled with low pressure of neon or helium. Although the products had to be separated using solvents like benzene, this method produced enough buckyballs to analyse [5]. To produce buckyballs on a commercial scale, a technology school, Massachusetts Institute of Technology (MIT), developed a process called combustion synthesis, which produces a large number of buckyballs. Combustion synthesis involves a self-sustained reaction in a solution of different oxidisers in same state (e.g., metal nitrates) and fuels (e.g. urea, glycine, hydrazides). [6] This is then either reacted layer by layer or as an entire volume, depending on the conditions and reactors used in the process. [6]

When producing buckyballs, if you vaporise a metal alongside the carbon, buckyballs form around the metal atoms. The metal gadolinium, as mentioned above, can cause damage if it remains inside the body for an extended period of time. By containing these potentially harmful atoms in a buckyball, known as a metallofullerine when combined, researchers hope to be able to flush the gadolinium enclosed in a buckyball completely out of the body, rather than leaving it to be absorbed into the tissues, and thus reduce toxic side effects. [5]

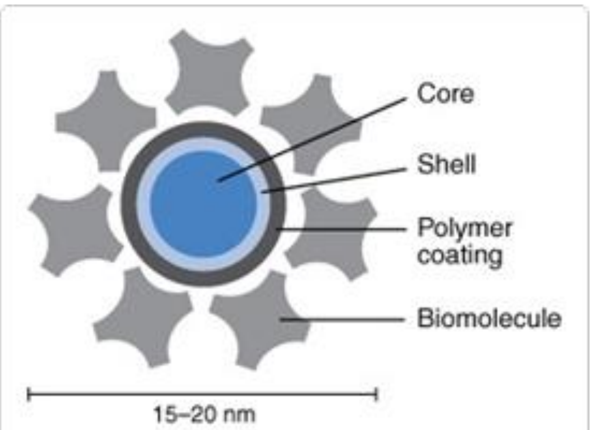
The materials could be used as a more effective contrast agent in magnetic-resonance imaging (MRI). Metal-nitride fullerenes give forty times better contrast than contrast agents currently, such as gadolinium, although the exact mechanism behind that is not yet understood.

This idea, however, is still in the theoretical stage and has not yet been tested. The main drawback for the availability of this technology in the near future is the rigorous testing which has to be performed. Like with any drug, it has to succeed Food and Drug Administration Approval [8], but they must also assess the benefits and drawbacks of this theory. What must be taken into consideration is how much of an improvement it will be to the existing gadolinium based contrast agent, at what cost. If the differences are only marginal, and hospitals must buy in new equipment and the buckyball-gadolinium complex is significantly more expensive, then the testing must address this. Another hindrance is the length of these trials. By the time it has been tested, approved and marketed, a newer and better contrast agent, at a lower price could have been developed. Scientists must consider trial length and the current development of imaging technology in order to address this issue.

## Quantum Dots

A nanoparticle is a particle with one or more dimensions of the order of about 100 nm or less. [9] Qdots are a type of nanoparticle known as fluorophores, which are substances that absorb photons of light, and then re-emit photons at a different wavelength. [14]

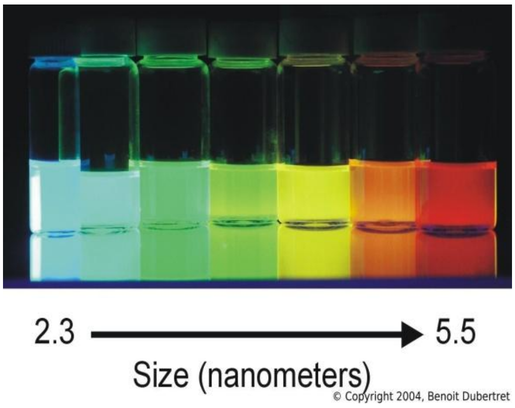
Quantum dots are roughly 5nm semiconducting nanocrystals composed of a few hundred to a few thousand semi conductor atoms made out of bio inert (non intrusive and non toxic) materials. Unlike modern day fluorescent dyes, which tend to decompose and lose their ability to fluoresce, quantum dots maintain their ability to withstand more cycles of excitation and light emission before beginning to fade.



Qdot structure (left [14]). The layers represent the distinct structural elements and are drawn roughly to scale. [14]

A.Paul Alivisatos and his company (Quantum Dot Production) have used these concepts in their Qdot product – a quantum dot surrounded by an inorganic shell that amplified its optical properties while protecting the Qdot from its environment. The

Qdot can have a variety of attachments to its shell; allowing it to attach to specific cell walls , or even penetrate a cell and light it up from the inside. [5] This is particularly useful among cancer detection, as it tags a cancerous tumour and lights it up, allowing it to be detected by diagnostic imaging equipment.



Changing their size or composition allows scientists to change their optical properties, which mean they can fluoresce in a variety of colours, when stimulated with light of a single wavelength. This is called quantum confinement; they have quantified discreet energy levels that are directly related to their size. [5] We can choose quantum dot sizes where the frequency of light required to make one group of dots fluoresce is an even multiple of the frequency required to make another group of dots fluoresce; both dots then fluoresce with the same wavelength of light. This allows for multiple tags to be tracked while using a single light source. [5]

Uniquely, quantum dots can be altered to emit any desired colours after excitation, solely depending on the size of the nanoparticle. The ability to control the emission from the Qdot by changing its core size is called size quantisation effect. [11] The smaller the particle, the closer it is to the blue end of the spectrum, and the larger is nearer the red end (shown above [13]). They can even tune Qdots beyond visible light into the infrared and ultraviolet spectrums for diagnostic purposes. [11]

Quantum dots focus on the contrast properties. With their long excitation and emission lifespan, they could hugely benefit radiologists if a patient has to have multiple scans, without having to re-inject and further expose the patient to the potentially toxic gadolinium. The unique fluorescing properties of the Qdots also prove a huge advantage in highlighting various areas of interest to doctors. However, although more promising, these are still undergoing medical developments and analysis for public use. For example, scientists have just developed a protein based coating which is not seen by live cells as toxic. [17] Although developments like these are slow, they are crucial to the future of medical imaging.

## Iron Oxide Particles – MRI Contrast Agents

Superparamagnetic iron oxide nanoparticles (SPION) have become a topic of interest due to their tiny size (4-10nm) and excellent T2-type MRI contrast properties. The small size of SPIONs causes their unique magnetic properties that allow them to be manipulated by magnetic fields. [16] They are tumour-specific contrast agents which attach and highlight growing tumour cells. However uncoated (plain) SPION particles have a tendency to aggregate and are not physiologically stable. To reduce the toxicity, adding polymeric polyethylene glycol phosphatidyl ethanolamine (PEG-

PE) micelles, followed by coating the surface with anticancer anti-nucleosome antibody 2C5. (mAb 2C5) helps reduce the harmful effects within the body. In recent studies by NSTI Nanotech, they found that SPION-loaded mAb 2C5 immunomicelles were able to recognize and bind with human breast cancer MCF-7 cells in vitro. [15] Such passive tumour targeting is the result of the enhanced permeation and retention effect. Tumours result in leaky vasculature and poor drainage. Once SPION particles reach the tumour site, they enter through the porous endothelium and are retained by the tumour due to its compromised clearance mechanisms. [16]

In the first thirty minutes following intravenous injection of the product into mice, half of the dose injected remains in the blood, the other part being isolated mainly by the mononuclear phagocyte system (MPS).[15]

Many factors make iron oxide an excellent contrast agent in MRI scanning. They naturally occur in many animals and are the only inorganic particulate approved for in vivo human treatment. They are degradable and are of minimal toxicity, so they cause little harm, if any, to the patient. Supermagnetic iron oxide nanoparticles have exceptional magnetic properties, and so are able to generate sufficient contrast in low doses, compared to gadolinium, as mentioned previously. It is also insignificant compared to the huge amount of iron naturally occurring in various forms in the human body. The body has methods to metabolise the excess iron introduced by the particles. [16]

Although contrast agents based on strong magnetic materials, such as nickel and cobalt are attractive, these elements are highly toxic and when oxidised, are not degradable in the body. Pure iron nanoparticles are a possible alternative, but these are unstable and can often oxidise without protection. Often, they are so reactive they have been known to ignite in air.[16] So despite the greater properties in terms of the magnetic imaging, these products would, undoubtedly, cause damage to human health if put into practice as contrast agents. So iron oxide nanoparticles are the perfect balance between quality of imaging and patient health.

Iron oxide nanoparticles are being developed because they are the only inorganic compound which has passed tests for in vivo treatment. They’re safe to use as contrasts agents because the body can metabolise excess iron and they are given in tiny doses compared to gadolinium. As previously mentioned, iron oxide nanoparticles have good T2-type MRI contrast properties, due to their magnetic abilities. However, because CT scans and x-rays do not use magnetism for imaging, these nanoparticles are limited to use with MRI, this raises the issue of whether it’s worth hospitals investing a huge sum of money into only one imaging method. However, CT and X-ray utilise ionising radiation whereas MRI does not. Investing in a safer imaging modality may therefore prove worthwhile. Arguably, any improvement to a method is beneficial, but from the economic point of view the benefits both to the patients and the hospital must be weighed up against the disadvantages, in this way, one can assess whether it really is worth investing so much into something which will make a marginal difference.

## Ethics

Though nanotechnology has the potential to drastically change the way we look at medicine, will this, in the end, be for the better or the worse? Both in diagnostic imaging, and medicine in general, nanotechnology has much greater implications than is perhaps obvious at first glance.

Economically, the prospect of nanotechnology in general could be a problem for hospitals. Cutting edge treatments, though very effective, also tend to be very expensive. Hospitals will have to decide whether to offer better treatments to fewer patients, or carry on with existing, cheaper technology. For example, in 2006 Ann Marie Rogers was successful in her law case in which she fought for her right to be treated with the drug Herceptin, which at the time cost £26000 per course. However it was also ruled that in future decisions about the drug, cost was a factor that had to be taken into account. [10]

Following on from this, many of the applications of nanomedicine will not have the power to cure, merely prolong life, and this raises ethical issues in itself. Though we may have the ability to prolong life, what type of lives are we prolonging? Is it better to let a patient live longer even though their quality of life is greatly reduced? This is a very difficult decision for doctors and patients to make. Additionally, can our population afford to support this? Faced already with having to support an increasingly ageing population, the application of nanotechnology could have the potential to create more problems than it solves.

In medical diagnostics especially there are many factors to consider. Technology could become so accurate that we would have to redefine the way we look at health and disease.

For example, new diagnostic techniques could have the ability to detect the slightest deviation from what we perceive to be ‘healthy’. From minute changes in blood chemistry to the detection of cancerous cells – when does the amount of information become just too much information? If you detect a genetic defect in a cell that is known to sometimes lead to cancer, is that something that should be acted upon? Should you begin to treat cancer when there is one cancerous cell or five hundred?[1] It is also quite possible that the limiting factor in diagnostics will no longer be the technology but the people working with the information. Time constraints and budgeting may lead to inadequate time or resources to fully use the data provided. There is always the risk of human error, and such vast amounts of information may increase this risk. Furthermore, how are doctors meant to decide who to treat, when so many people potentially have something that could be perceived as disease? Especially when cost is considered, this is likely to be a significant problem.

The fact that so much data could be available could also create complications with privacy and confidentiality. Would it be feasible for computers to be able to process and store this much information, and as mentioned above, would it be feasible for doctors to be able to evaluate all this information? Even though many centres are shifting towards an electronic method of record storage and computer assisted diagnosis (CAD) it may be more difficult to safeguard these systems, and this raises many issues.

In addition, it is not yet clear if many potential treatments are completely safe. Patients need to be warned about the implications of taking these new drugs, and the side effects and long term consequences that may result from taking them. We do not currently have enough data to say that these treatments are non-harmful, and we don't know how nanoparticles may react inside the body. Many aspects such as toxicity have to be researched and taken into account. However, this is not something new in the field of diagnostic imaging. X-rays and other radiologic agents are known to carry risks, but are used when the advantages are thought to outweigh the disadvantages. One could argue that in principle these two situations are very similar.

Overall there are many factors to be considered when thinking about the applications of nanomedicine, especially with regard to diagnostic imaging. The decision will have to be made as to whether the advantages of nanomedicine outweigh the disadvantages. While it is possible that many of the problems posed may be able to be solved by modern technology (e.g. Data storage and CAD), others will have to be considered in a different way; with the greatest importance being placed on the benefits it will have for the patient and their family.

## CONCLUSION

Using nanotechnology, it may be possible to overcome some of the barriers which face us today in medicine, with regards to diagnostic imaging. Radiological imaging is a way to see inside a patient, without having to operate, and imaging can provide key, life-saving diagnoses. We are always developing technology to increase the resolving power of medical scanners, and nanotechnology can offer a way to hugely increase their efficiency, possibly without having to invest in new equipment and replace old scanners. By improving the contrast agent, we can offer benefits both in diagnostic terms and for the health and wellbeing of the patient.

However, nowadays, medicine is not only a service, but a business too. With limited funding, cost must be taken into account when considering treatment and research methods. If a new development is not economically viable then consideration must be given to whether hospitals can afford research, cost of treatment and the running cost of the treatment in the long term. This must be weighed up against the benefits of the new treatment compared to current technology. Obviously, whenever possible we want to use treatments which minimise risk to the patient, but when the risk is so small, economic factors must be taken into account.

Gadolinium, used today has the potential to cause disease if left to reabsorb into the tissues, by enclosing gadolinium in a buckyball, it may be more effective as it is not absorbed, remains detectable for longer, and is expelled without causing damage. Similarly quantum dots and iron oxide nanoparticles are ideas that are still in development, with rigorous training and standards to meet. Therefore it may be many years before we see these developments used every day in practise.

To conclude, the combination of imaging technology and nanotechnology could hugely improve the techniques currently used in diagnostic imaging, both in terms of patient safety and quality of imaging. With the new technologies proposed, harm to the patient is much reduced and the quality of the images produced can give doctors a much higher understanding of disease processes and assist the development of appropriate treatment, without the need for surgical intervention, with its associated clinical risks and costs. However, when proposing these measures, one must consider all aspects; from the ethical issues raised in this paper, to the financial impacts for Healthcare. Nanotechnology has the potential to vastly improve current techniques and influence the way in which we see and practise medicine.

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