

A review of the uses of Nanoscience in Medicine

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PASS

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Abstract

Many scientists regard nanoscience as the next technological revolution with potential applications in every field from communications to medicine, and sports equipment to sunscreens. The greater chemical reactivity, interesting physical properties and ability to cross biological membranes makes these tiny particles extremely useful but also potentially very toxic and dangerous to human health. This review takes a broad look at how nanotechnology is being applied in medical research and healthcare. The development of new medicines, their role as therapeutic carriers, target probes and imaging agents are all considered as well as some of the problems associated with this rapidly emerging technology.

Introduction

Nanotechnology is one of the most exciting areas of research in science. In 2006 alone, £6 billion was invested in new and inventive applications of nanoparticles. Market forecasts indicate that total sales of nanotechnology in 2015 will be £1.2 trillion¹. A convergence of physics, chemistry, biology, materials science and electronics, nanotechnology looks set to influence all aspects of everyday life, with applications that include running shoes, mp3 players, drug delivery systems, solar cells, mobile phones, digital cameras and even paints so slick they can clean themselves when it rains.

The use of nanotechnology in medicine understandably offers some very exciting opportunities. This is because the relatively small size nanoparticles in comparison to, for example, the size of a cell makes them very useful indeed as they can manipulate matter at an atomic level. With cells, this may be the passage of molecules across the phospholipid membrane² for example.

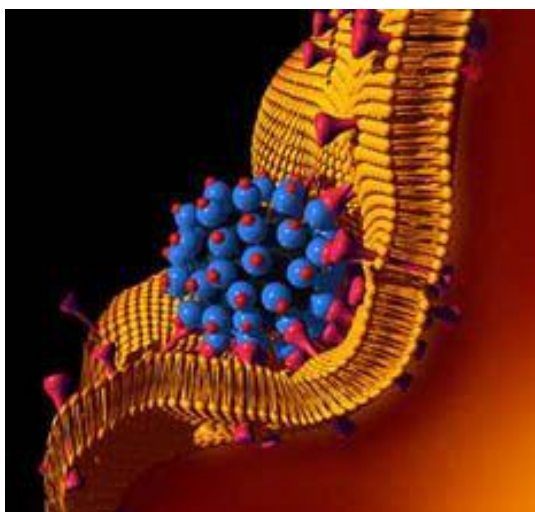


Figure 1 – a nanoparticle binds to the phospholipid bilayer.

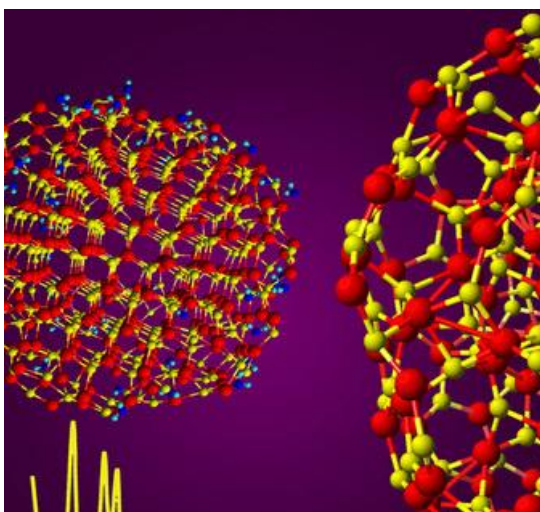


Figure 2 – 3D representation of complex nanoparticles which could be used in drug delivery systems.

Nanoparticles are defined as “small objects that behave as a whole unit in terms of their transport and properties” they are normally between 1 and 100 nanometers in diameter and their huge surface area to volume ratio make them highly chemically reactive. Obeying

the laws of quantum mechanics, as opposed to the laws of classical physics, nanoparticles are endowed with electrical, optical and magnetic properties that make them very useful and interesting.

One of the earliest applications of nanotechnology in medicine was the use of nanocrystals of silver⁴ to treat wounds. Nanoparticles containing nitric oxide gas⁵ have been shown to reduce infection by killing bacteria and burn dressings coated with nanocapsules containing antibiotics have allowed much quicker treatment of infection while reducing the number of changes of dressing required. In trauma patients, nanosized aluminosilicate particles have been shown to absorb water and thus cause blood clots to form more quickly and therefore reduce bleeding⁶.

However it was the laboratory preparation of fullerenes (by Nobel prize winners Kroto Curl and Smalley, 1985)⁷ that lead to some of the most interesting applications in nanomedicine. Fullerenes are molecules made entirely of carbon atoms that form a hollow sphere or tube. The spherical fullerenes, which look like a football, are commonly referred to as buckyballs (fig 3) and the cylindrical types are referred to as carbon nanotubes (fig 4) shown below. Fullerenes have since been found to occur in nature and have also been detected in outer space!

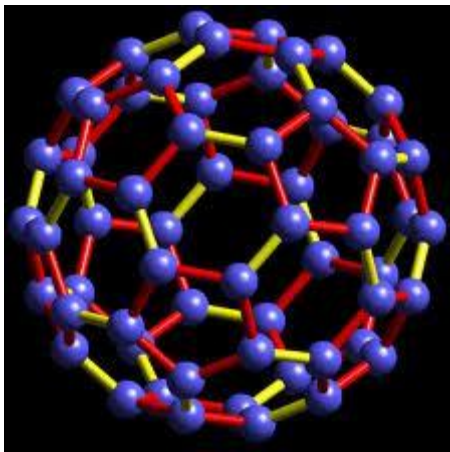


Fig 3 Buckyballs

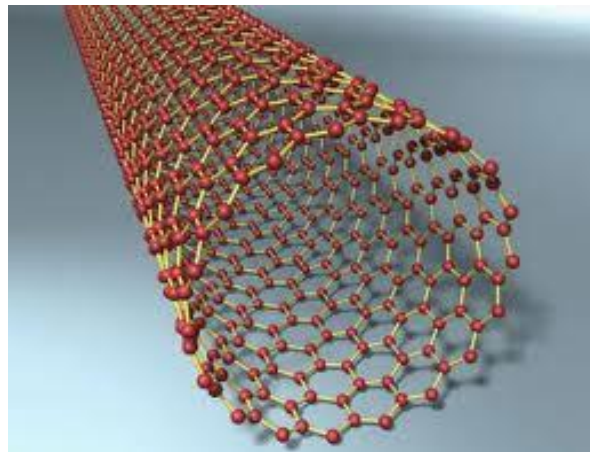


Fig 4 Carbon nanotubes

Some of the challenges in modern medicine are related to the bioavailability of drugs. Low availability limits the usefulness of new treatments which look really promising in the laboratory. Because many molecules are broken down in the process of digestion or as they are carried in the blood stream, only a small proportion (sometimes as little as 1%) get to the cells where they are required. Consequently high doses are used which can have adverse effects.

Normal antibiotics are also unable to cross the blood brain barrier, unlike in other areas of the body where they can diffuse between the gaps of the cells of the capillaries. Scientists

hope that antibiotics encapsulated in nanoparticles might provide a vital breakthrough in dealing with infection in the brain, as they could diffuse across the blood brain barrier.

The unique structure, inert nature and stability of fullerene molecules are what give them enormous potential in the diagnosis and treatment of disease. They can be used to encapsulate medicines or other molecules, providing a protective barrier and stealth characteristics which enables the delivery of drugs, heat, light or radioactive substances to specific cells. They are engineered to target diseased cells, by ligand binding, allowing direct treatment without the traumatic side effects like nausea or hair loss. The crucial property of fullerenes that makes them so useful is that they are permeable with the phospholipid bilayer – allowing encapsulated substances to be delivered to the cells where they are needed more quickly and efficiently than ever before.

Scientists are currently working on the development of novel nanomaterials which can be used as new drugs for treating Cancer, Parkinson's and Cardiovascular disease (to name a few) as well as the development of artificial tissues to replace diseased kidneys or livers and even repair nerve damage.

Discussion

Diagnosis and Imaging

The successful treatment of diseases like cancer hinges upon early diagnosis which requires the detection and characterization of very small quantities of biomarker. The use of nanoparticles in detection techniques are being developed extensively. For example gold particles can be used to detect nucleic acids⁸ and magnetic nanoparticles can be used to identify samples containing specific proteins, nucleic acid sequences and other interesting biochemical compounds associated with neoplasia⁹.

Similarly, Iron Oxide nanoparticles are used to improve magnetic resonance imaging (MRI) images of tumours¹⁰. Peptides that bind to the tumour are used to coat the nanoparticles so that they accumulate around the tumour and it is the magnetic property of iron that helps to improve the images obtained by the scan.

Nanoscale light emitting particles or quantum dots (q-dots) are under intense development due to their programmable qualities¹¹. Made from semiconductor materials such as cadmium selenide or zinc sulphide, their unique optical and electronic properties make them far more sensitive and better suited than current probes in imaging and diagnostic techniques. Only 2-10nm wide (about 50 atoms) they are believed to be one of the most important and relevant medical applications in the short term.

Oncology

One of the problems of the treatment of cancer is that the various drugs/therapies cannot distinguish between healthy and diseased cells, killing them indiscriminately so that the patient's quality of life is compromised by the side effects of the many treatments available. As mentioned in the introduction, nanotechnology is being applied to the many different methods of therapy currently used in cancer care. For example q-dot nanoparticles can concentrate the heat from Infra red light¹² which is then used to kill cancer cells without damaging the healthy cells that surround the tumour. Targeted heat therapy is being developed to destroy breast cancer tumours¹³. Here antibodies that are specific to the tumour are attached to nanotubes causing them to accumulate around the tumour and burrow inside. The nanotubes absorb the Infrared light, producing heat which kills the tumour.

In a similar way, radiation therapy can be improved by activating nanoparticles with x-rays to generate electrons which destroy the cancer cells they are attached to.

Nanoparticles can also be used to deliver drugs more efficiently to tumours by making the drug target the tumour specifically by coating the nano-polymer with ligands¹¹ normally in the form of peptides. Two classes of nanoparticles are currently dominating this area of research, polymer drug conjugates and liposomes.

Conjugates are small-molecule therapeutic agents which have two unfavourable properties – they have a short in-vivo circulation time, and are non-site-specific. Fortunately these small-molecule drugs can be conjugated into polymeric nano-carriers like the microbubble shown in Fig 5 below. This increases the in-vivo circulation time from several minutes to several hours, thus reducing the number of times the drug has to be administered. Furthermore, the route of cellular uptake is reduced, enhancing the passive delivery of the drug to its target tissue.

Liposomes are spherical vesicles with a bilayered membrane structure composed of lipid molecules. These are used as pharmaceutical carriers because:-

- They can encapsulate both hydrophobic and hydrophilic drugs.
- They provide a barrier against the undesired effects of the external conditions where the drug is being delivered.
- They can target specific cells, tissues or organs when they work with specific ligands.
- They can be coated with polymers such as Polyethylene glycol (PEG) to increase their half-life in-vivo.
- They can be modified to meet specific needs of size, surface charge and other properties.

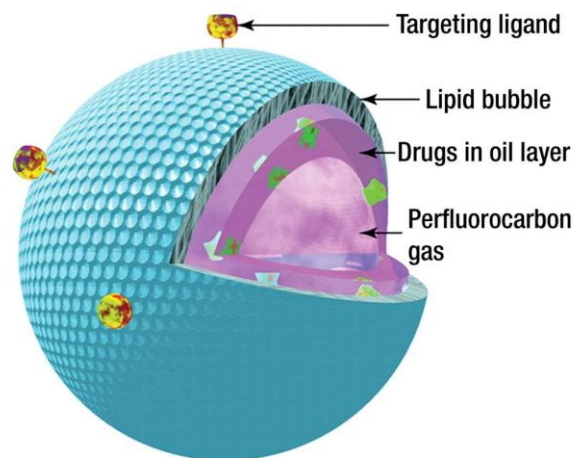


Fig 5 Microbubble constructed for drug delivery

The main focus of future developments is designing nanoparticles that have two, three or even multiple functions¹⁴ - for example, a nanoparticle that can contain two or more drugs, or target two or more areas of the body by having two or more ligands. This could then be developed into hugely complex nanoparticles that can deliver multiple drugs to metastases that could be spread in different organs of the body. An interesting example of this uses gold nanorods to accumulate at the tumour, concentrate heat from Infra red light which increases the level of stress proteins on the tumour's surface. A drug carrying liposome with

appropriate targeting ligands then binds to the protein and because of the increased levels of protein so the process of drug accumulation speeds up¹².

Heart Disease

Heart and vascular disease is the number one killer in the western world and so there is significant interest in how nanotechnology could be applied to detect and treat defective valves and plaques which build up in the arteries and cause heart attacks. Researchers at the University of Santa Barbara have developed a technique where a peptide is bound to a nanoparticle that can bind to the plaque. The next step would be to attach imaging agents to examine the plaque or drugs to break down the fatty material and dissolve it¹⁵.

Following on from their work to seek and destroy tumors, researchers at Harvard Medical school (Langer 2010) have developed particles they refer to as “nanoburrs” which have potential in the treatment of heart disease. (fig6).¹⁶

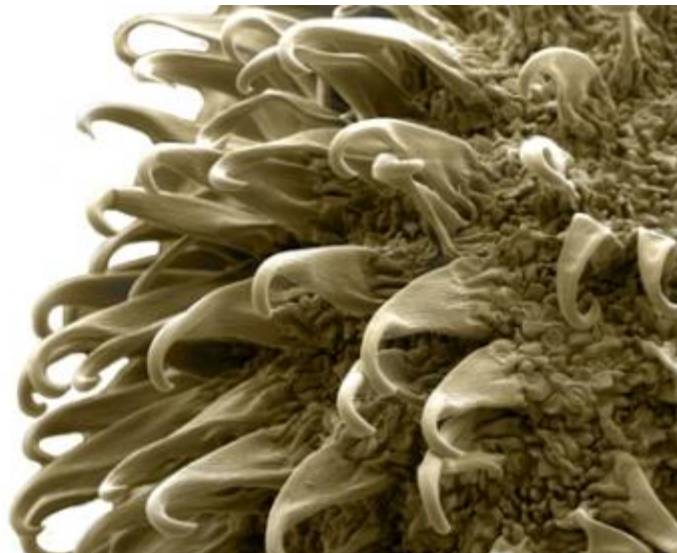


Fig 6 - Nanoburrs

Once again, these nanoburrs are targeted spherical particles only 60 nm in diameter that attach themselves to arterial cell walls where they can slowly release the drug they are carrying. The burrs are made up of tiny protein fragments that stick to proteins in the basement membrane that are only exposed in damaged cells. The cell division inhibiting drug Paclitaxel, used in tests, was released slowly as it breaks off from the polymer chain it is attached to. The speed of release is determined by the length of the polymer chain and so the timing of the drug can be altered by changing the polymer chain length. In laboratory tests, twelve days of drug release is the maximum achieved. Tests in rats revealed that the nanoburrs can reach their target cells even when they are injected into the tail. These exciting findings demonstrate potential usefulness for clearing and repairing clogged or damaged arteries in areas where stents are not suitable such as at around the junctions of arteries.

At the Royal Free hospital in London, Professor Hamilton and his colleagues have designed and made artificial arteries from a polymer developed through nanotechnology¹⁷. These arteries have been shown to pulse with the movements of the body and could help repair damaged arteries that might otherwise lead to the amputation of limbs or myocardial infarction. The polymer has other molecules embedded in it that aid circulation, prevent clotting and encourage stem cells to coat its walls thus allowing the artificial tissue to avoid rejection and promote long term health. Breakthroughs like this hold great promise for the building of new organs and other body parts.

Autoimmune diseases and Inflammation

There is much potential for nanotechnology in the treatment of many other diseases such as arthritis. Rheumatoid arthritis is a debilitating and painful autoimmune disease which results in chronic inflammation around the joints and eventual joint destruction. This inflammation is caused by the body's immune system attacking the tissues surrounding the joints¹⁸. Many of the drugs that are currently used to treat rheumatoid arthritis while powerful, are expensive, have only temporary benefits and problematic side effects such as gastric irritation, osteoporosis, hypertension and weight gain so protecting the drug by encapsulating it in nanoparticles and targeting them specifically to the affected tissues could be hugely beneficial. A number of studies are already in the clinical trial stages of research.

Damaged cartilage which causes joint pain and loss of function can eventually lead to osteoarthritis. A novel biologically active nanomaterial has recently been demonstrated (Stupp, Shah & Shah 2010) to promote the growth of new cartilage something not possible using conventional methods and very interesting as cartilage, unlike bone, does not grow back once damaged. This new therapy uses bone marrow stem cells to generate natural cartilage.¹⁹

Another autoimmune disease, Multiple Sclerosis is where the immune system attacks the central nervous system, damaging the protective myelin sheath a fatty layer which is wrapped around the axons of neurones in the brain and spinal cord²⁰. When the myelin is damaged, the ability of the axon to conduct electrical signals is lost and so the nerve cells are no longer able to communicate, resulting in physical and cognitive disability. Treatments are available that are reasonably effective in slowing the progression of the disease although none are a cure and they have several adverse effects. Recently, iron oxide nanoparticles have been shown to improve therapeutic efficacy of MS drugs and reduce side effects²¹. Nanocarriers could be used to target drugs to the damaged cells whose job it is to maintain and repair the myelin sheath. The ability to repair the myelin sheath has been described by Simon Gillespie Chief Executive of the MS Society as "one of the most exciting developments in recent years. It's hard to put into words how revolutionary this discovery could be."

The inflammation of the uveal tract in the eye (Uveitis) is also very difficult to treat due to the eye's unique and effective defence mechanisms to prevent foreign substances from entering it. With topical treatments only about 5% of the active ingredient actually reaches its target. Drug-loaded liposomes could be injected directly into the eye thus reducing the dosing required to treat the inflammation²¹.

Molecules like buckyballs have been shown to act as antioxidants as they are able to trap the damaging free radicals formed in an allergic response (Ryan 2007) and thus block the inflammation that arises in an allergic reaction²². Free radicals are pathological markers of many conditions such as Cancer, Asthma, Schizophrenia, Parkinson's and Alzheimer's disease causing much damage to all cell components including lipids, proteins and DNA through oxidative stress; so the ability of buckyballs to mop up excess free radicals could have potential in many areas of medicine. Dosing would be an important issue however as reactive oxygen species can be beneficial as they are used as part of the body's defence system to attack and kill pathogens.

Oral administration of Drugs

In the future, drugs that are delivered by injection could become a thing of the past as the drug could be encapsulated in a nanoparticle that helps it avoid degradation as it passes through the digestive system and persist in the blood stream unharmed. One such drug for the treatment of systemic fungal diseases uses a nanoparticle called a cochleate^{2,23} is in the early stages of clinical trials. If a similar method could be used to administer insulin, the benefits for diabetics who have to self-inject before every meal are huge.

Food modification and Obesity

Nanoscience is having a widespread impact in food technology and there are lots of interesting examples of their applications in this field with many beneficial health effects. For example, enzymes are often added to food to hydrolyze components that are not nutritious and so increase the bio-availability of essential vitamins and minerals. To increase the activity and life of these enzymes, nanomaterials can be used to provide better enzyme-support systems due to their large surface-to-volume ratios.

Obesity is a preventable but major cause of death in the west and fast becoming one of the most serious health problems. There is no doubt of the connection between cheap, highly processed foods and poor health and the best solution to the problem of increasing obesity is of course a healthy balanced diet of fresh natural foods. However if nanotechnology can help to make processed foods less unhealthy it would be a positive step.

Biologists at Utah State University have developed the 'invisible diet'²⁴ where nanoparticles made from fat cells are introduced into the gut. These then bind to fat receptors which then tell the brain that they are full although the eater has in fact only consumed a very small low-calorie meal. Another similar idea involves coating food with nanoparticles²⁵ so that the

digestion of fat happens at a very specific point in the digestive process so that the fat receptors are bound up quickly and thoroughly once again tricking the body to feel full.

Size and shape of Nanoparticles

Very recently, extensive studies carried out at the University of Texas (Tao et al 2011)²⁶ have shown that the size and shape of nanoparticles are important factors that contribute to their effectiveness in medical applications. For example cylindrical shaped particles can persist in the blood stream for far longer than their spherical counterparts and disc shaped particles show much higher specificity in targeting biological sites in mice. The reasons for this are unclear and computer modelling could be used to further our understanding of the mechanisms of action and learn more about the unique biological properties of the different shaped particles.

Nanorobots

Looking forward, scientists are talking about the development of nanorobots which could be programmed and placed within the body to maintain health by repairing cells or even playing a part in surgical procedures.^{27, 28} While we might be suspicious of the idea it is important to remember that our bodies already contain all sorts of naturally occurring mobile nanoparticles. Our immune system is comprised of many different types of cells and antibodies that work together and function in much the same way nanorobots would, travelling in the blood stream repairing tissues, and killing off any bacteria or other invading microorganisms.

DNA replication and ribosomal involvement in protein synthesis are more examples of naturally occurring processes that could be mimicked by nanorobots. The race is now on for these tiny wonders to be developed, built and tested.

Challenges, Risks and Ethics

As with any new and emerging technology there are always problems and challenges which need to be overcome. Because nanosized particles have unique properties and behave differently than they do in their larger form there is much concern that they could be extremely toxic. For example nanoparticles of titanium dioxide which have been widely used in air and water cleaning systems have been shown to induce lung damage in mice. They have also been shown to convert benign mouse tumours into aggressive cancer cells.²⁹ Similarly carbon nanotubes which resemble particles of asbestos fibre have been shown to induce scarring and lung cancer in studies on mice.³⁰

There are concerns that since the particles are so small and could cross the blood-brain barrier, a membrane which protects the brain from harmful chemicals in the bloodstream; it is important that if we are going to use nanotechnology we must make sure that we are not poisoned in the process.³¹

New technologies are also expensive and if in the future nanomedicine is used for physical enhancements to make ourselves fitter, stronger and healthier with special abilities like rapid healing there would be many ethical questions concerning the emergence of a wealthy enhanced group of people and a poorer population who cannot afford such enhancements.

Conclusion

To conclude, it is clear that the potential of nanotechnology in medicine is enormous. This review has briefly described how the use of nanoparticles can be applied to the diagnosis and treatment of many life threatening conditions and diseases through drug delivery, drug targeting, removal of damaging free radicals and the eventual repair and maintenance of cells.

However there is also accumulating evidence that the powerful nature of these tiny species means they are also potentially very dangerous. This highlights the need to thoroughly understand the properties and mechanisms of action of these apparently wonder-particles. The need for a “strategic approach to research into potential risks to ensure the development of safe, publicly acceptable nanotechnology products” has been highlighted by experts and must be a priority for all current and future developments.³²

At the same time many ethical issues such as the appropriate use of animals in experiments and the impact of new developments on society are continually raised. As the exploration of nanoscience advances there will be much catching up to keep the legal aspects of research in line with all the exciting discoveries that scientists are making.

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Diagrams

Fig 1 & 2
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Buckyballs fig 3
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Carbon nanotubes fig 4
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Microbubble fig 5
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Nanoburrs fig 6
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