

CLINICAL APPLICATIONS OF NANOMEDICINES: A REVIEW

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ABSTRACT: Molecular nanotechnology has been defined as the three-dimensional positional control of molecular structure to create materials and devices to molecular precision. The human body is comprised of molecules; hence the availability of molecular nanotechnology will permit dramatic progress in human medical services. More than just an extension of "molecular medicine," nanomedicine will employ molecular machine systems to address medical problems, and will use molecular knowledge to maintain and improve human health at the molecular scale. Nanomedicine will have extraordinary and far-reaching implications for the medical profession, for the definition of disease, for the diagnosis and treatment of medical conditions including aging, and ultimately for the improvement and extension of natural human biological structure and function. Nanomedicine is the preservation and improvement of human health using molecular tools and molecular knowledge of the human body. Nanomedicines are an emerging group of therapeutics that take advantage of our understanding of phenomena on the nanometer scale. Nanomedicines research requires expertise in a range of diverse fields and thus requires multidisciplinary teams. This article presents a brief review of Nanomedicines with an emphasis on its various aspects associated i.e. introduction, definition, medical and clinical uses, especially role of nanomedicines in treatment of dreadful disease like cancer in current scenario. The article also reveals the concept of nanorobots as well as implications for nanotoxicology from nanomedicines.

Key words: Nanomedicine, nanotechnology, nanoparticles, nanostructured materials, nanomachines, nanorobots, nanoscience.

INTRODUCTION

Nanosized materials have been investigated as potential medicines for several decades. Consequently, a great deal of work has been conducted on how to exploit constructs of this size range in a beneficial way. Similarly, a number of the consequences from the use of these materials have already been considered. Nanosized materials do behave differently to low-molecular-weight drugs, the biological properties of nanomaterials being mainly dependent on relevant physiology and anatomy. Bio distribution, movement of materials through tissues, phagocytosis, opsonization and endocytosis of nanosized materials are all likely to have an impact on potential toxicity. In turn these processes are most likely to depend on the nanoparticle surface.

Evidence from the literature is considered which suggests that our understanding of these areas is incomplete, and that bio distribution to specific sites can occur for nano-particles with particular characteristics. However, our current knowledge does indicate which areas are of concern and deserve further investigation to understand how individual nanoparticles behave and what toxicity may be expected from them.

Nanomedicine is a subfield of nano-technology. It is often defined as the repair, construction and control of human biological systems using devices built upon nanotechnology standards. Basically, nanomedicine is the medical application of nanotechnology. Nanostructured materials, engineered enzymes and many other products of biotechnology will be very useful in the future. Of course, the full potential of nanomedicine is unlikely to arrive until after complex, high-sophisticated, medically programmable nanomachines and nanorobots are developed. When that happens, every medical doctor's dream will become reality. We all know that the mankind is still fighting against many complex illnesses like cancer, multiple sclerosis, cardiovascular diseases, Alzheimer's and Parkinson's diseases, diabetes as well as some inflammatory or infectious diseases (i.e. HIV). Nanotechnology raises hopes and expectations for millions of patients that suffer from those diseases. For example, it is expected that doctors will be able to destroy the very first cancer cells and so stop the disease from growing.

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials, to electronic biosensors, and even possible future applications of molecular nanotechnology. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials (Wagner, V, et al, 2006). Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future (Jasmer, RM, et al, 2002). The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry that may include advanced drug delivery systems, new therapies, and in imaging. Neuro-electronic interfaces and other nanoelectronics-based sensors are another active goal of research. Further down the line, the speculative field of molecular nanotechnology believes that cell repair machines could revolutionize medicine and the medical field. Nanomedicine is a large industry, with nanomedicine sales reaching 6.8 billion dollars in 2004, and with over 200 companies and 38 products worldwide, a minimum of 3.8 billion dollars in nanotechnology R&D is being invested every year. As the nano-medicine industry continues to grow, it is expected to have a significant impact on the economy. Nanotechnology has a very broad definition based on scale, and nanomedicines are likewise based not only on the type of medicine or their function but also on a nanosized range. While most nanotechnology is expected to have an upper size limit of 100 nm, in the drug delivery field this is more generally accepted as medicines in the size range from a few nanometres to <1000 nm in diameter. In practice, the useful range of nanomedicines more normally falls within the range of 5–250 nm as these tend to have a similar range of properties based on physiological and anatomical consequences.

The term 'nanomedicine' can cover a wide variety of materials and structures. In general, they have been around for considerably longer than they have been known as nanomedicines, and some have been investigated for the last three or more decades. The sort of materials that could be called nanomedicines can include proteins, polymers, dendrimers, micelles, liposomes, emulsions, nanoparticles and nanocapsules. Nanomaterials are also used in diagnostics, e.g. colloids for radio pharmacy and as contrast agents in magnetic resonance imaging. New developments in nanomaterials are now producing small and ultra-small paramagnetic iron oxide particles (USPIOs) and investigating quantum dots for this field. In general, nanomaterials of this size are not able to penetrate membranes readily, and consequently are mostly dependent on the anatomy and physiology of the body to determine their distribution.

MEDICAL USE OF NANOMATERIALS

Drug delivery

Nanomedical approaches to drug delivery center on developing nanoscale particles or molecules to improve drug bioavailability. Bioavailability refers to the presence of drug molecules where they are needed in the body and where they will do the most good. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. This can potentially be achieved by molecular targeting by nanoengineered devices (LaVan, DA, et al, 2003). It is all about targeting the molecules and delivering drugs with cell precision. More than \$65 billion are wasted each year due to poor bioavailability. *In vivo* imaging is another area where tools and devices are being developed. Using nanoparticle contrast agents, images such as ultrasound and MRI have a favourable distribution and improved contrast. The new methods of nanoengineered materials that are being developed might be effective in treating illnesses and diseases such as cancer. What nanoscientists will be able to achieve in the future is beyond current imagination. This might be accomplished by self assembled biocompatible nanodevices that will detect, evaluate, treat and report to the clinical doctor automatically (Cavalcanti, A, et al, 2008).

Drug delivery systems, lipid- or polymer-based nanoparticles, can be designed to improve the pharmacological and therapeutic properties of drugs (Allen, TM, et al, 2004). The strength of drug delivery systems is their ability to alter the pharmacokinetics and bio distribution of the drug. Nanoparticles have unusual properties that can be used to improve drug delivery. Where larger particles would have been cleared from the body, cells take up these nanoparticles because of their size. Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm.

Efficiency is important because many diseases depend upon processes within the cell and can only be impeded by drugs that make their way into the cell. Triggered response is one way for drug molecules to be used more efficiently. Drugs are placed in the body and only activate on encountering a particular signal.

For example, a drug with poor solubility will be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Also, a drug may cause tissue damage, but with drug delivery, regulated drug release can eliminate the problem. If a drug is cleared too quickly from the body, this could force a patient to use high doses, but with drug delivery systems clearance can be reduced by altering the pharmacokinetics of the drug. Poor bio distribution is a problem that can affect normal tissues through widespread distribution, but the particulates from drug delivery systems lower the volume of distribution and reduce the effect on non-target tissue. Potential nanodrugs will work by very specific and well-understood mechanisms; one of the major impacts of nanotechnology and nanoscience will be in leading development of completely new drugs with more useful behavior and less side effects.

Protein and Peptide Delivery

Protein and peptides exert multiple biological actions in human body and they have been identified as showing great promise for treatment of various diseases and disorders. These macromolecules are called biopharmaceuticals. Targeted and/or controlled delivery of these biopharmaceuticals using nanomaterials like nanoparticles and Dendrimers is an emerging field called nanobiopharmaceutics, and these products are called nanobiopharmaceuticals.

Role in Treatment of Cancer

The small size of nanoparticles endows them with properties that can be very useful in oncology, particularly in imaging. Quantum dots (nanoparticles with quantum confinement properties, such as size-tunable light emission), when used in conjunction with MRI (magnetic resonance imaging), can produce exceptional images of tumour sites. These nanoparticles are much brighter than organic dyes and only need one light source for excitation. This means that the use of fluorescent quantum dots could produce a higher contrast image and at a lower cost than today's organic dyes used as contrast media. The downside, however, is that quantum dots are usually made of quite toxic elements.

Another nanoproperty, high surface area to volume ratio, allows many functional groups to be attached to a nanoparticle, which can seek out and bind to certain tumour cells. Additionally, the small size of nanoparticles (10 to 100 nanometers), allows them to preferentially accumulate at tumour sites (because tumours lack an effective lymphatic drainage system). A very exciting research question is how to make these imaging nanoparticles do more things for cancer. For instance, is it possible to manufacture multifunctional nanoparticles that would detect, image, and then proceed to treat a tumour? This question is under vigorous investigation; the answer to which could shape the future of cancer treatment (Nie, Shuming, et al, 2008).

Sensor test chips containing thousands of nanowires, able to detect proteins and other biomarkers left behind by cancer cells, could enable the detection and diagnosis of cancer in the early stages from a few drops of a patient's blood (Zheng, G, et al, 2005).

Nanoparticle targeting

It is greatly observed that nanoparticles are promising tools for the advancement of drug delivery, medical imaging, and as diagnostic sensors. However, the bio distribution of these nanoparticles is mostly unknown due to the difficulty in targeting specific organs in the body. Current research in the excretory systems of mice, however, shows the ability of gold composites to selectively target certain organs based on their size and charge. These composites are encapsulated by a dendrimer and assigned a specific charge and size. Positively-charged gold nanoparticles were found to enter the kidneys while negatively-charged gold nanoparticles remained in the liver and spleen. It is suggested that the positive surface charge of the nanoparticle decreases the rate of osponization of nanoparticles in the liver, thus affecting the excretory pathway. Even at a relatively small size of 5 nm, though, these particles can become compartmentalized in the peripheral tissues, and will therefore accumulate in the body over time. While advancement of research proves that targeting and distribution can be augmented by nanoparticles, the dangers of nanotoxicity become an important next step in further understanding of their medical uses (Minchin, Rod, et al, 2008).

Medical Applications of Nanotechnology

Molecular nanotechnology is a speculative subfield of nanotechnology regarding the possibility of engineering molecular assemblers, machines which could re-order matter at a molecular or atomic scale. Molecular nanotechnology is highly theoretical, seeking to anticipate what inventions nanotechnology might yield and to propose an agenda for future inquiry. The proposed elements of molecular nanotechnology, such as molecular assemblers and nanorobots are far beyond current capabilities.

Concept of Nanorobots

The somewhat speculative claims about the possibility of using nanorobots (Freitas, et al, 2005) in medicine, advocates say, would totally change the world of medicine once it is realized. Nanomedicine would make use of these nanorobots (e.g., Computational Genes), introduced into the body, to repair or detect damages and infections. According to Robert Freitas of the Institute for Molecular Manufacturing, a typical blood borne medical nanorobot would be between 0.5-3 micrometres in size, because that is the maximum size possible due to capillary passage requirement. Carbon could be the primary element used to build these nanorobots due to the inherent strength and other characteristics of some forms of carbon (diamond/fullerene composites), and nanorobots would be fabricated in desktop nanofactories specialized for this purpose.

Nanodevices could be observed at work inside the body using MRI, especially if their components were manufactured using mostly ^{13}C atoms rather than the natural ^{12}C isotope of carbon, since ^{13}C has a nonzero nuclear magnetic moment. Medical nanodevices would first be injected into a human body, and would then go to work in a specific organ or tissue mass. The doctor will monitor the progress, and make certain that the nanodevices have gotten to the correct target treatment region. The doctor will also be able to scan a section of the body, and actually see the nanodevices congregated neatly around their target (a tumour mass, etc.) so that he or she can be sure that the procedure was successful.

Implications for Nanotoxicology from nanomedicines

Nanoparticles could come from many sources. Those developed specifically as medicines have been under development for many years. As part of this development process, the materials and strategies developed for this work have been chosen to minimize the possibilities of causing adverse and toxic effects, in particular the choice of biodegradable, biocompatible materials and the development of surface coatings which avoid the accumulation of nanoparticles in the liver and spleen. Non-medical nanoparticles, which may be found in atmospheric pollution or produced in industrial processes, are unlikely to have these advantages, and their toxicology will be largely determined by the materials they are composed of and their surface characteristics. The latter will determine where they eventually accumulate. Many airborne nanoparticles are likely to have a hydrophobic surface and will therefore be prone to accumulation in the spleen and liver. However, a number of industrially produced nanomaterials do need to be treated to prevent aggregation, and such stabilized materials are likely to behave in a similar manner to the stabilized nanomedicines designed to circulate in the vasculature. Whichever path is followed, whether involving stabilized or unstabilized particles, there are potentially toxic consequences predictable from physiology and anatomy. Non-degradable nanoparticles which accumulate intracellularly are likely to have a number of effects. If taken up by macrophages, they would undoubtedly stimulate free radical release which may result in cell damage and inflammation. If the nanoparticles are taken up into the lysosomal compartment but are not biodegradable, they could potentially accumulate there and cause toxicity. This is clear by analogy with the variety of lysosomal storage diseases known, where lack of a degradative enzyme inevitably results in accumulation of material and toxic effects (Villodi, A, et al, 2004)

With any nanoparticle preparation, whether coated or not, a large proportion of administered dose finds its way to the liver, and so this is the organ most likely to be affected. In terms of other tissues, the endothelium is another tissue in direct contact with the nanoparticles. The endothelium is itself a mediator of a large number of physiological responses, so there are possibilities for toxicity here; however, its role in mediating uptake to particular tissues is now also seen to be of significance. Accumulation in spleen, gut, bone marrow, lymph nodes and brain is already known to be possible, but there are also possibilities not so far reported that other organs may also mediate uptake via the endothelium. In some cases such as the brain, only small proportions of circulating materials accumulate, so adverse effects are unlikely unless the materials are extremely toxic. However, in other tissues such as bone marrow or gut, the amount of accumulation could be substantial with more materials having a possibility of toxic effects.

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