A Brief Review on Role of Nanotechnology in Medical Sciences

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Abstract Medical nanotechnology or *nanomedicine* is the medical aspect or application of nanotechnology using different approaches such as nanoelectronic biosensors, nanomaterials, and a very futuristic but underdeveloped molecular nanotechnology that includes molecular manufacturing. Medical nanotechnology aims to provide cheaper yet quality health and medical equipment, facilities, and treatment strategies through continuous researches and studies. A number of pharmaceutical and medical companies all over the world have already adhered to medical nanotechnology because of its numerous benefits and practical uses. Current modalities of diagnosis and treatment of various diseases, especially cancer, have major limitations such as poor sensitivity or specificity and drug toxicities respectively. Newer and improved methods of cancer detection based on nanoparticles are being developed. They are used as contrast agents, fluorescent materials, molecular research tools, and drugs with targeting antibodies. Paramagnetic nanoparticles, quantum dots (qdots), nanoshells, and nanosomes are few of the nanoparticles used for diagnostic purposes. Drugs with high toxic potential like cancer chemotherapeutic drugs can be given with a better safety profile with the utility of nanotechnology. These can be made to act specifically at the target tissue by active as well as passive means. Other modalities of therapy such as heat-induced ablation of cancer cells by nanoshells and gene therapy are also being developed. This review discusses the various platforms of nanotechnology being used in different aspects of medicine. The safety of nanomedicine is not yet fully

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defined. However, it is possible that nanomedicine in future would play a crucial role in the treatment of human diseases and also in enhancement of normal human physiology.

Keywords Diagnostics · Drugs · Nanomedicine · Nanotechnology · Therapeutics · Quantum dot

Introduction

"Nano" means very small, and it comes from the Greek word "nanos", meaning dwarf. It is also used as a prefix to indicate size in the series kilo-, milli-, micro-, nano-meter. A nanometer is one thousand millionth of a metre, 10^{-9} m.

Nanoscale is generally considered to be at a size below 0.1 μm or 100 nm. Nanoscience can be defined as the study of phenomena and manipulation of materials at atomic, molecular, and macromolecular scales where properties differ significantly from those at a larger particulate scale. Nanotechnology is then the design, characterization, production and application of structures, devices, and systems by controlling the shape and size at the nanometer scale.

Nanotechnology is considered an emerging technology with enormous potential in a range of applications. In addition to various industrial uses, great innovations are foreseen in metrology, electronics, biotechnology, medicine, and medical technology. It is anticipated that nanotechnology can have an enormous positive impact on human health. The potential medical applications are predominantly in diagnostics, monitoring, the availability of more durable and better prosthetics, and new drug delivery systems for potentially harmful drugs.

Nanoparticles and Nanostructures

Nanoparticles and nanostructures can be prepared either by the "top down" technique starting with large particles and making things smaller by grinding or pulverizing, or the "bottom up" technique making things larger by building atom by atom or molecule by molecule. The limit to making things smaller seems to be reached, while making nanostructures by synthesis has just started. In the latter case, avoiding random reactions and thus the control of the process is critical for the production of nanostructures. The development of enhanced microscopy techniques such as, Scanning Tunneling Microscopy and Atomic Force Microscopy, has facilitated the use of the bottom-up process. Some uses of nanotechnology include: Nanomaterials used in nanostructured materials, coatings, electronics, and active surfaces. Most of the time such nanoparticles will be fixed within or on the surface of materials.

Bionanotechnology and nanomedicine are rather promising areas for nanotechnology. Applications will probably include diagnostics, imaging techniques, materials for prosthetics, and drug delivery. Other applications may be as supporting structures in biomaterials and medical devices including the use in scaffolds for tissue engineering. Micro- and nano-grooves present on material surfaces may direct cellular growth; however, cell behavior is also influenced by chemical coating.

Private and public research efforts worldwide are developing nanoproducts aimed at improving health care and advancing medical research. Some of these products have entered the marketplace, more are on the verge of doing so, and others remain more a vision than a reality. The potential for these innovations is enormous, but questions remain about their long-term safety and the risk–benefit characteristics of their usage. Since 2000, when former President Bill Clinton announced the founding of the U.S. National Nanotechnology Initiative (NNI), governments in Europe, Japan, and other Asian nations have responded with competitive investments in national nano programs. The European Commission, a body of the European Union (EU) that funds about 24 % of the publicly financed research in the EU, and the Union's 15 member nations will spend about $180 million on nanotechnology in 2002. The NNI budget for fiscal year (FY) 2002 is $604 million, including $40.8 million for the National Institutes of Health (NIH). For FY 2003, proposed budgets amount to $710.2 million in the United States, and between $270 and $315 million in the EU.

Three applications of nanotechnology are particularly suited to biomedicine: diagnostic techniques, drugs, and prostheses and implants. Interest is booming in biomedical applications for use outside the body, such as diagnostic sensors and "labon- a-chip" techniques, which are suitable for analyzing blood and other samples, and for inclusion in analytical instruments for R&D on new drugs. For inside the body, many companies are developing nanotechnology applications for anticancer drugs, implanted insulin pumps, and gene therapy. Other researchers are working on prostheses and implants that include nanostructured materials.

Nanotechnology in Medicine: Application

The use of nanotechnology in medicine offers some exciting possibilities. Some techniques are only imagined, while others are at various stages of testing, or actually being used today. Nanotechnology in medicine involves applications of nanoparticles currently under development, as well as longer range researches that involve the use of manufactured nanorobots to make repairs at the cellular level.

Drug Delivery

One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light, or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allows direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. The basic point to use drug delivery is based upon three facts: (a) efficient encapsulation of the drugs, (b) successful delivery of the said drugs to the targeted region of the body, and (c) successful release of that drug there.

Nanomedical approaches to drug delivery enter 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 [1, 2]. 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. 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 favorable distribution and improved contrast. The new methods of nano-engineered materials that are being developed might be effective in treating illnesses and diseases such as cancer. What nano-scientists 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.

Drug delivery systems, lipid- or polymer-based nanoparticles can be designed to improve the pharmacological and therapeutic properties of drugs [3, 4]. The strength of drug delivery systems is their ability to alter the pharmacokinetics and biodistribution of the drug. When designed to avoid the body's defence mechanisms, nanoparticles have beneficial 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 biodistribution 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 nano drugs 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.

Diagnostic and Imaging Techniques

Carbon nanotubes and gold nanoparticles are being used in a sensor that detects proteins indicative of oral cancer. Tests have shown this sensor to be accurate in detecting oral cancer and provide results in less than an hour. Silver nanorods in a diagnostic system are being used to separate viruses, bacteria, and other microscopic components of blood samples, allowing clearer Raman spectroscopy signals of the components. This method has been demonstrated to allow identification of viruses and bacteria in less than an hour.

Iron oxide nanoparticles can be used to improve MRI images of cancer tumors. The nanoparticle is coated with a peptide that binds to a cancer tumor; once the nanoparticles are attached to the tumor the magnetic property of their oxide enhances the images from the Magnetic Resonance Imagining scan. Nanoparticles can attach to proteins or other molecules, allowing detection of disease indicators in a lab sample at a very early stage. There are several efforts to develop nanoparticle disease detection systems underway. One system being developed by Nanosphere, Inc. uses gold nanoparticles, nanosphere has clinical study results with their Verigene system involving its ability to detect four different nucleic acids, while another system being developed by T2 Biosystems uses magnetic nanoparticles to identify specimens, including proteins, nucleic acids, and other materials.

Gold nanoparticles that have antibodies attached can provide quick diagnosis of flu virus. When light is directed on a sample containing virus particles and nanoparticles the amount of light reflected back increases because the nanoparticles cluster around virus particles, allowing a much faster test than those currently used.

Quantum Dots (qdots) may be used in the future for locating cancer tumors in patients and in the near term for performing diagnostic tests in samples. Invitrogen's website provides information about qdots that are available for both uses, although at this time the use "in vivo" is limited to experiments with lab animals. Concerns about the toxicity of the material that qdots are made from are one of the reasons for restricting the use of qdots in human patients. However, work is being done with qdots composed of silicon, which is believed to be less toxic than the cadmium contained in many qdots.

Antimicrobial Techniques

One of the earliest nanomedicine applications was the use of nanocrystalline silver which is as an antimicrobial agent for the treatment of wounds. A nanoparticle cream has been shown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection.

Burn dressing that is coated with nanocapsules containing antibiotics. If an infection starts, the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibiotics. This allows much quicker treatment of an infection and reduces the number of times a dressing has to be changed.

Cell Repair

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes [5].

Protein and Peptide Delivery

Protein and peptides exert multiple biological actions in the 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 nano-biopharmaceutics, and these products are called nanobiopharmaceuticals.

Molecular Imaging and Therapy

The small size of nanoparticles endows them with properties that can be very useful in oncology, particularly in imaging. Qdots, when used in conjunction with MRI (magnetic resonance imaging), can produce exceptional images of tumor sites. These nanoparticles are brighter than organic dyes and only need one light source for excitation. This means that the use of fluorescent qdots 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 qdots are usually made of quite toxic elements (Fig. 1).

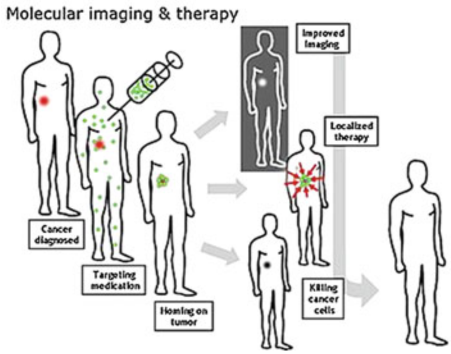

Fig. 1 A schematic illustration showing how nanoparticles or other cancer drugs might be used to treat cancer

Surgery

At Rice University, a flesh welder is used to fuse two pieces of chicken meat into a single piece. The two pieces of chicken are placed together touching each other. A greenish liquid containing gold-coated nanoshells is dribbled along the seam. An infrared laser is traced along the seam, causing the two sides to weld together. This could solve the difficulties and blood leaks caused when the surgeon tries to restitch the arteries that have been cut during a kidney or heart transplant. The flesh welder could weld the artery perfectly [6].

Visualization

Tracking movement can help to determine how well drugs are being distributed or how substances are metabolized. It is difficult to track a small group of cells throughout the body, so scientists dye the cells. These dyes need to be excited by light of a certain wavelength in order for them to light up. While different colored dyes absorb different frequencies of light, there is a need for as many light sources as cells. A way around this problem is with luminescent tags. These tags are qdots attached to proteins that penetrate cell membranes. The dots can be random in size, can be made of bio-inert material, and they demonstrate the nanoscale property that color is size-dependent. As a result, sizes are selected so that the frequency of light used to make a group of qdots fluoresce is an even multiple of the frequency required to make another group incandesce. Then both groups can be lit with a single light source.

Nanoparticle Targeting

It is increasingly observed that nanoparticles are promising tools for the advancement of drug delivery, medical imaging, and as diagnostic sensors. However, the biodistribution of these nanoparticles is still imperfect due to the complex host's reactions to nano- and micro-sized materials and the difficulty in targeting specific organs in the body. Nevertheless, a lot of work is still ongoing to optimize and better understand the potential and limitations of nanoparticulate systems. For example, current research in the excretory systems of mice 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 opsonization 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.

Neuro-Electronic Interfaces

Neuro-electronic interfacing is a visionary goal dealing with the construction of nanodevices that will permit computers to be joined and linked to the nervous system. This idea requires the building of a molecular structure that will permit control and detection of nerve impulses by an external computer. The computers will be able to interpret, register, and respond to signals the body gives off when it feels sensations. The demand for such structures is huge because many diseases involve the decay of the nervous system. Also, many injuries and accidents may impair the nervous system resulting in dysfunctional systems and paraplegia. If computers could control the nervous system through neuro-electronic interface, problems that impair the system could be controlled so that effects of diseases and injuries could be overcome. Two considerations must be made when selecting the power source for such applications. They are refuelable and non-refuelable strategies. A refuelable strategy implies energy is refilled continuously or periodically with external sonic, chemical, tethered, magnetic, or electrical sources. A non-refuelable strategy implies that all power is drawn from internal energy storage which would stop when all energy is drained.

Other Benefits of Medical Nanotechnology

Although some are still skeptical about the technology, scientists and researchers over continents have been practicing medicine using nanotechnology due to its numerous benefits. Some of these benefits to the medical field include the following:

- With nanotechnology, tools and equipment for surgery and diagnostic would be a lot cheaper yet remain to be effective and state of the art. Medical research and processes require highly advanced equipment that could be very expensive but once the equipment is fully developed, its manufacturing would be a lot easier and faster with the use of nanotechnology. The creation of complex tools that can diagnose serious diseases with a single laboratory test would minimize diagnostic costs and treatment. Using tiny nano-built sensors inserted into the human body for direct contact with the source of ailment would definitely make medical treatments easier and cheaper.
- With medical nanotechnology, treatment would be more efficient and precise. Instead of opening the whole body area for surgical purposes, a microscopic nanotool would spare the patient from bloody and risky surgical processes. With nanotechnology in the medical field, treatment would be precise, eliminating trial-and-error drug prescription. With a single laboratory test and highly technical computers, a detailed image of the body's system and processes can be automatically spotted including the cause of the disease and its possible treatment. With nanotechnology in the fields of medicine, medical malpractice would be eliminated and the side effects of taking medicines out of sheer guessing from the physicians would be avoided.
- With highly advanced medical equipment, potential diseases can easily be detected and prevented.
- Since diseases can be prevented, the quality of life for mankind would be improved and lifespan would be increased.
- With the application of nanotechnology in medicine, replacement of body organs using machines smaller than body cells can be possible. Because of advanced nanotechnology, candidates for organ replacement and augmentation will receive far better body organs enhanced by tiny machines introduced to the body for better organ performance and functions.
- Medical nanotechnology can largely contribute to genetic therapy and improvement. Diseases can be easily treated if approached at the genetic level. So instead of treating diseases based on the symptoms, nanotechnology will help medical practitioners treat the problem by looking at the root cause.

Nanotechnology and Nanomedicine in the Future

Medical diagnosis, proper and efficient delivery of pharmaceuticals, and development of artificial cells are the medical fields where nanosized materials have found practical implementations. As *suggested* by Freitas, the application of nanotechnology to medicine, nanomedicine, subsumes three mutually overlapping and progressively more powerful molecular technologies. First, nanoscale-structured materials and devices that can be fabricated today hold great promise for advanced diagnostics and biosensors, targeted drug delivery and smart drugs, and immunoisolation therapies. Second, biotechnology offers the benefits of molecular medicine via genomics, proteomics, and artificial engineered microbes. Third, in the longer term, molecular machine systems and medical nanorobots will allow instant pathogen diagnosis and extermination, chromosome replacement and individual cell surgery in vivo, and the efficient augmentation and improvement of natural physiological function. There are several other intriguing, still theoretical, proposals for practical applications of nanomechanical tools into the fields of medical research and clinical practice. One function of nanodevices in medical sciences could be the replacement of defective or incorrectly functioning cells, such as the respirocyte proposed by Freitas. It has also been postulated that nanomachines could distribute drugs within the patient's body. Such nanoconstructions could deliver medicines to particular sites, making more adequate and precise treatment possible. Such devices would have a small computer, several binding sites to determine the concentration of specific molecules, and a supply of some 'poison' that could be released selectively. Similar machines equipped with specific 'weapons' could be used to remove obstructions in the circulatory system or identify and kill cancer cells. It has been also proposed that nanorobots may be modified bacteria and viruses that already have most of the motorization and target delivery of genetic information. Moreover, nanorobots, operating in the human body could monitor levels of different compounds and store that information in internal memory. They could be used to rapidly examine a given tissue location, surveying its biochemistry, biomechanics, and histometric characteristics in greater detail. This would help in better disease diagnosing. The use of nanodevices would give the additional benefits of reduced intrusiveness, increased patient comfort, and greater fidelity of results, since the target tissue can be examined in its active state in the actual host environment.

Over the next couple of years it is widely anticipated that nanotechnology will continue to evolve and expand in many areas of life and science, and the achievements of nanotechnology will be applied in medical sciences, including diagnostics, drug delivery systems, and patient treatment. According to Dr Brazil from the Royal Society of Medicine (July 2003) opinion: "Nanotechnology provides the potential for significant advances over the next 50 years" with potential applications of:

1. biological nanosensors for diagnostics in the next 1–5 years,
2. generation of artificial muscles, development lab-on-a chip technology for more efficient drug discovery and targeted drug and gene delivery within the next 6–10 year, and
3. later on (after 10–50 years) introduction of nanomachines for in vivo treatment and nanopumps/vales for tissue engineering and generation of artificial organs, in health care and medicine.

Conclusion

Although the expectations from nanotechnology in medicine are high and the potential benefits are endlessly enlisted, the safety of nanomedicine is not yet fully defined. Use of nanotechnology in medical therapeutics needs adequate evaluation of its risk and safety factors. However, it is possible that nanomedicine in the future will play a crucial role in treatment of human diseases and also in enhancement of normal human physiology. With concurrent application of nanotechnology in other fields, its utility is likely to extend further into diagnostics, molecular research techniques, and tools.

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