



MEDICAL APPLICATION OF NANOTECHNOLOGY IN NANOMEDICINE

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ABSTRACT

Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future. The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical that may include advanced drug delivery systems, new therapies, and in vivo 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. Therefore, this review focused on nanomaterials can be useful for both in vivo and in vitro biomedical research and applications.

Keywords: Nanomedicine, Nanotechnology, Applications.

INTRODUCTION

Nanomedicine is the medical application of nano technology [1]. Nanomedicine ranges from the medical applications of nano materials, to nano 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. One nanometer is one millionth of a millimeter.

Nanomedicine research is receiving funding from the US National Institutes of Health. Of note is the funding in 2005 of a five-year plan to set up four nanomedicine centers. In April 2006, the journal Nature Materials estimated that 130 nanotech-based drugs and delivery systems were being developed worldwide [2]. The biological and medical research communities have exploited the unique properties of nanomaterials for various applications (e.g., contrast agents for cell imaging and therapeutics for treating cancer). Terms such as *biomedical nanotechnology*, *nanobiotechnology*, and *nanomedicine* are used to describe this hybrid field. Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures.

The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles.

Nanomedicine is a large industry, with nanomedicine sales reaching \$6.8 billion in 2004, and with over 200 companies and 38 products worldwide, a minimum of \$3.8 billion in nanotechnology R&D is being invested every year. As the nanomedicine industry continues to grow, it is expected to have a significant impact on the economy.

Application of nanomedicine

Two forms of nanomedicine that have already been tested in mice and are awaiting human trials that will be using gold nanoshells to help diagnose and treat cancer, and using liposomes as vaccine adjuvants and as vehicles for drug transport. Similarly, drug detoxification is also another application for nanomedicine which has shown promising results in

rats. A benefit of using nanoscale for medical technologies is that smaller devices are less invasive and can possibly be implanted inside the body, plus biochemical reaction times are much shorter. These devices are faster and more sensitive than typical drug delivery.

Drug delivery

Nanotechnology has provided the possibility of delivering drugs to specific cells using nanoparticles. The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach would reduce costs and human suffering. An example can be found in dendrimers and nanoporous materials. Another example is to use block co-polymers, which form micelles for drug encapsulation. They could hold small drug molecules transporting them to the desired location. Another vision is based on small electromechanical systems; nanoelectromechanical systems are being investigated for the active release of drugs. Some potentially important applications include cancer treatment with iron nanoparticles or gold shells. A targeted or personalized medicine is intended to reduce the drug consumption and treatment expenses resulting in an overall societal benefit by reducing the costs to the public health system.

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. 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 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 [3].

Drug delivery systems, lipid- or polymer-based nanoparticles, can be designed to improve the pharmacological and therapeutic properties of drugs. 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 defense 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 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 [4].

It is greatly 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 [5].

Applications and reported research studies

- Abraxane, approved by the U.S. Food and Drug Administration (FDA) to treat breast cancer and non-small-cell lung cancer (NSCLC), is the nanoparticle albumin bound paclitaxel.
- In a mice study, scientists from Rice University and University of Texas MD Anderson Cancer Center reported enhanced effectiveness and reduced toxicity of an existing treatment for head and neck cancer when using the nanoparticles to deliver the drug. The hydrophilic carbonic clusters functionalized with polyethylene glycol or PEG-HCC are mixed with the chemotherapeutic drug paclitaxel (Taxol) and the epidermal growth factor receptor (EGFR) targeted Cetuximab and injected intravenously. They found the tumors were killed more effectively with radiation and the healthy tissue suffered less toxicity than without the nanotechnology drug delivery. The standard treatment contains Cremophor EL which allows the hydrophobic paclitaxel to be delivered intravenously. Replacing the toxic Cremophor with carbon nanoparticles eliminated its side effect and improved drug targeting which in turn required a lower dose of the toxic paclitaxel.
- Researchers at Case Western Reserve University reported using nanoparticle chain to deliver doxorubicin to breast cancer cells in a mice study. Three magnetic, iron-oxide nanospheres were chemically linked to one doxorubicin-loaded liposome and formed a 100 nm long nanoparticle chain. After the nanochains penetrated the tumor, radiofrequency field was generated that caused the magnetic nanoparticles to vibrate and rupture the liposome, dispersing the drug in its free form throughout the tumor. The result showed that the nano treatment was more effective in halting tumor growth than the standard treatment with doxorubicin. It is also less harmful to healthy cells since only 5% to 10% of the standard dose of doxorubicin were used.
- Nanoparticles made of polyethylene glycol (PEG) carrying payload of antibiotics at its core could swift charge thus allowing them to target bacterial infection more precisely inside the body, a group of MIT researchers reported. The nanoparticles, containing a sub-layer of pH sensitive chains of the amino acid histidine, carry a slightly negative charge when circulating in the blood stream, can evade detection and clearing by the immune system. When they encounter an infection site the particles gain a positive charge provoked by the slightly acidic environment at the infection sites, allowing them to bind to the negatively charged bacterial cell walls and release antibiotics at locally high concentration. This nano delivery system can potentially destroy bacteria even it has developed resistance to

antibiotics because of the targeted high dose and prolonged release of the drug. Although a lot of work is still needed, the researchers believe that it points to a new direction of using nanotechnology to treat infectious disease.

- Using the biomimetic strategy, researchers in the Harvard University Wyss Institute demonstrated in a mouse model that the drug coated nanoparticles can dissolve blood clots by selectively binding to the narrowed regions in the blood vessels – just like the platelets do. Aggregates of biodegradable nanoparticles coated with tissue plasminogen activator (tPA), each about the size of a platelet, were injected intravenously. In the region of vessel narrowing, shear stresses dissociate the aggregates and release the tPA-coated nanoparticles which bind and degrade the blood clots. By precise targeting and concentrating drug at the location of obstruction, the dose used is less than 1/50th of the normal dose. The nanotherapeutics will greatly reduce the severe side effect of bleeding, commonly found in standard treatment of thrombosis [6].
- The X-shaped RNA nanoparticles capable of carrying four functional modules were created by researchers in the University of Kentucky. These RNA molecules are chemically and thermodynamically stable, able to remain intact in the mouse body for more than 8 hours and to resist degradation by RNase in the blood stream. With its four arms attached with a combination of different active agents, for example, iRNA (for gene silencing) microRNA (for gene expression regulation), aptamer (for targeting) and ribozyme (as catalyst), the X-shaped RNA can achieve therapeutic and diagnostic functions by regulating gene expression and cellular function, and binding to cancer cells with precision, enhanced by its polyvalent nature and synergistic effects by design.
- An early phase clinical trial using the platform of ‘Minicell’ nanoparticle for drug delivery have been tested on patients with advanced and untreatable cancer. Built from the membranes of mutant bacteria, the minicells were loaded with paclitaxel and coated with cetuximab, antibodies that bind the epidermal growth factor receptor (EGFR) which is often overexpressed in a number of cancers, as a ‘homing’ device to the tumor cells. The tumor cells recognize the bacteria from which the minicells have been derived, regard it as invading microorganism and engulf it. Once inside, the payload of anti-cancer drug kills the tumor cells. Measured at 400 nanometers, the minicell is bigger than synthetic particles developed for drug delivery. The researchers indicated that this larger size give the minicells a better profile in side-effects because the minicells will preferentially leak out of the porous blood vessels around the tumor cells and do not reach the liver, digestive system and skin. This Phase 1 clinical trial demonstrated that this treatment is well tolerated by the patients. As a platform technology, the minicell drug

delivery system can be used to treat a number of different cancers with different anti-cancer drugs with the benefit of lower dose and less side-effects [7].

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 bio pharmaceuticals using nano materials like nano particles and Dendrimers is an emerging field called nano biopharmaceutics, and these products are called nano biopharmaceuticals.

Applications and reported research studies

- Nanoparticles delivering the myelin antigens were found to induce immune tolerance in a mouse model with relapsing multiple sclerosis. Biodegradable polystyrene microparticles coated with the myelin sheath peptides reset the mouse's immune system and prevent the disease from recurring or reduce the symptoms by halting the attack of the immune system to the protective myelin sheath coating the nerve fibers of the central nervous system. Team of researchers in Northwestern University indicated that this treatment method can potentially be used in other autoimmune diseases [8].

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 tumor 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 [9].

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 tumor cells. Additionally, the small size of nanoparticles (10 to 100 nanometers), allows them to preferentially accumulate at tumor sites (because tumors 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 tumor? This question is under vigorous investigation; the answer to which could shape the future of cancer treatment. A

promising new cancer treatment that may one day replace radiation and chemotherapy is edging closer to human trials. Kanzius RF therapy attaches microscopic nanoparticles to cancer cells and then "cooks" tumors inside the body with radio waves that heat only the nanoparticles and the adjacent (cancerous) cells.

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.

The basic point to use drug delivery is based upon three facts: a) efficient encapsulation of the drugs, b) successful delivery of said drugs to the targeted region of the body, and c) successful release of that drug there.

Researchers at Rice University under Prof. Jennifer West, have demonstrated the use of 120 nm diameter nanoshells coated with gold to kill cancer tumors in mice. The nanoshells can be targeted to bond to cancerous cells by conjugating antibodies or peptides to the nanoshell surface. By irradiating the area of the tumor with an infrared laser, which passes through flesh without heating it, the gold is heated sufficiently to cause death to the cancer cells.

Nanoparticles of cadmium selenide (quantum dots) glow when exposed to ultraviolet light. When injected, they seep into cancer tumors. The surgeon can see the glowing tumor, and use it as a guide for more accurate tumor removal.

In photodynamic therapy, a particle is placed within the body and is illuminated with light from the outside. The light gets absorbed by the particle and if the particle is metal, energy from the light will heat the particle and surrounding tissue. Light may also be used to produce high energy oxygen molecules which will chemically react with and destroy most organic molecules that are next to them (like tumors). This therapy is appealing for many reasons. It does not leave a "toxic trail" of reactive molecules throughout the body (chemotherapy) because it is directed where only the light is shined and the particles exist. Photodynamic therapy has potential for a noninvasive procedure for dealing with diseases, growth and tumors [10].

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. 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.

Visualization

Tracking movement can help 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 used to dye the cells. These dyes needed to be excited by light of a certain wavelength in order for them to light up. While different color dyes absorb different frequencies of light, there was a need for as many light sources as cells. A way around this problem is with luminescent tags. These tags are quantum dots 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 quantum dots 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 [11].

Tissue engineering

Nanotechnology may be able to help reproduce or repair damaged tissue. "Tissue engineering" makes use of artificially stimulated cell proliferation by using suitable nanomaterial-based scaffolds and growth factors. For example, bones could be regrown on carbon nanotube scaffolds. Tissue engineering might replace today's conventional treatments like organ transplants or artificial implants. Advanced forms of tissue engineering may lead to life extension.

Antibiotic resistance

Nanoparticles can be used in combination therapy for decreasing antibiotic resistance. It has been shown that Zinc Oxide nanoparticles can decrease the antibiotic resistance and enhance the antibacterial activity of Ciprofloxacin against microorganism in Vitro. Nanoparticles can interfere with the different proteins which are interacting in the antibiotic resistance or pharmacologic mechanisms of drugs [12].

Immune response

Buckyballs have been investigated for the ability to "interrupt" the allergy/immune response by preventing mast cells (which cause allergic response) from releasing histamine into the blood and tissues, by binding to free radicals dramatically better than any anti-oxidant currently available, such as vitamin E.

Diagnostic and medical devices

Nanotechnology-on-a-chip is one more dimension of lab-on-a-chip technology. Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms. Gold nanoparticles tagged with short segments of DNA can be used for detection of genetic sequence in a

sample. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots into polymeric microbeads. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures.

Nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferable to the use of injectable drugs, because the latter frequently display first-order kinetics (the blood concentration goes up rapidly, but drops exponentially over time). This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range [13].

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 (ALS and multiple sclerosis). 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 nonrefuelable strategies. A refuelable strategy implies energy is refilled continuously or periodically with external sonic, chemical, tethered, magnetic, or electrical sources. A nonrefuelable strategy implies that all power is drawn from internal energy storage which would stop when all energy is drained [14].

One limitation to this innovation is the fact that electrical interference is a possibility. Electric fields, electromagnetic pulses (EMP), and stray fields from other *in vivo* electrical devices can all cause interference. Also, thick insulators are required to prevent electron leakage, and if high conductivity of the *in vivo* medium occurs there is a risk of sudden power loss and "shorting out." Finally, thick wires are also needed to conduct substantial power levels without overheating. Little practical progress has been made even though research is happening. The wiring of the structure is extremely difficult because they must be positioned precisely in the nervous system so that it is able to monitor and respond to nervous signals. The structures that will provide the interface must also be compatible with the body's immune system so that they will remain unaffected in the body for a long time. In addition, the

structures must also sense ionic currents and be able to cause currents to flow backward. While the potential for these structures is amazing, there is no timetable for when they will be available [15].

Medical applications of Molecular 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 [16].

Nanorobots

The somewhat speculative claims about the possibility of using nanorobots 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 bloodborne 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 tumor mass, etc.) so that he or she can be sure that the procedure was successful [17].

Cell repair machines

Using drugs and surgery, doctors can only encourage tissues to repair themselves. With molecular machines, there will be more direct repairs. Cell repair will utilize the same tasks that living systems already prove possible. Access to cells is possible because biologists can insert needles into cells without killing them. Thus, molecular machines are capable of entering

the cell. Also, all specific biochemical interactions show that molecular systems can recognize other molecules by touch, build or rebuild every molecule in a cell, and can disassemble damaged molecules. Finally, cells that replicate prove that molecular systems can assemble every system found in a cell. Therefore, since nature has demonstrated the basic operations needed to perform molecular-level cell repair, in the future, nanomachine based systems will be built that are able to enter cells, sense differences from healthy ones and make modifications to the structure.

The healthcare possibilities of these cell repair machines are impressive. Comparable to the size of viruses or bacteria, their compact parts would allow them to be more complex. The early machines will be specialized. As they open and close cell membranes or travel through tissue and enter cells and viruses, machines will only be able to correct a single molecular disorder like DNA damage or enzyme deficiency. Later, cell repair machines will be programmed with more abilities with the help of advanced AI systems [18].

Nanocomputers will be needed to guide these machines. These computers will direct machines to examine, take apart, and rebuild damaged molecular structures. Repair machines will be able to repair whole cells by working structure by structure. Then by working cell by cell and tissue by tissue, whole organs can be repaired. Finally, by working organ by organ, health is restored to the body. Cells damaged to the point of inactivity can be repaired because of the ability of molecular machines to build cells from scratch. Therefore, cell repair machines will free medicine from reliance on self-repair alone.

Nanonephrology

Nanonephrology is a branch of nanomedicine and nanotechnology that seeks to use nano-materials and nano-devices for the diagnosis, therapy, and management of renal diseases. It includes the following goals:

1. the study of kidney protein structures at the atomic level
2. nano-imaging approaches to study cellular processes in kidney cells
3. nano medical treatments that utilize nanoparticles to treat various kidney diseases

Advances in Nanonephrology are expected to be based on discoveries in the above areas that can provide nano-scale information on the cellular molecular machinery involved in normal kidney processes and in pathological states. By understanding the physical and chemical properties of proteins and other macromolecules at the atomic level in various cells in the kidney, novel therapeutic approaches can be designed to combat major renal diseases [19]. The nano-scale artificial kidney is a goal that many physicians dream of. Nano-scale engineering advances will permit programmable and

controllable nano-scale robots to execute curative and reconstructive procedures in the human kidney at the cellular and molecular levels. Designing nanostructures compatible with the kidney cells and that can safely

operate in vivo is also a future goal. The ability to direct events in a controlled fashion at the cellular nano-level has the potential of significantly improving the lives of patients with kidney diseases.

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