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Case Study

NANOTECHNOLOGY: TRENDS AND FUTURE PROSPECTIVE

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ABSTRACT
Nanotechnology ("nanotech") is the manipulation of matter on an atomic, molecular and supramolecular scale. It is based on the characterization, fabrication and manipulation of structures or materials smaller than 100 nm (approximately 1–100 nm in length) (Cushen *et al*., 2012). Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science and engineering. Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules. The microscopes needed to see things at the nanoscale are scanning tunneling microscope (STM) and the atomic force microscope (AFM). Nanomaterials can be useful for both *in vivo* and *in vitro* biomedical research and applications. 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 (Abeer, 2012). A variety of nanomaterials are used for diagnosis and treatment include metallic nanoparticle, quantum dots, carbon nanotubes, magnetic nanoparticles, liposomes, dendrimers and engineered hybrid nanoparticles (Dilbaghi *et al.,* 2013). Materials at the nanoscale have enhanced properties such as higher strength, lighter weight, increased control of light spectrum, and greater chemical reactivity than their larger-scale counterparts. With the advancement in technology, we can expect to generate capability to perform surgery at cellular level, thereby removing individual diseased cells and even repairing defective portions of the individual cells.

KEYWORDS: Nanotechnology ("nanotech"), Liposome, Nanomaterials, STM, AFM.

INTRODUCTION

Nanotechnology ("nanotech") is the manipulation of matter on an atomic, molecular and supramolecular scale. Nanotechnology is based on the characterization, fabrication and manipulation of structures or materials smaller than 100 nm (approximately 1–100 nm in length) (*Cushen et al*., 2012). A nanometer (nm) is a unit of length in the metric system, equal to one billionth of a meter or 10^{-9} of a meter. Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science and engineering. Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules. But something as small as an atom is impossible to see with the naked eye. In fact, it's impossible to see with the microscopes typically used. The microscopes needed to see things at the nanoscale were invented relatively recently, about 30 years ago, such as the scanning tunneling microscope (STM) and the atomic force microscope (AFM). 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, bionanotechnology andnanomedicine are used to describe this hybrid field. Nanomaterials can be useful for both *in vivo* and *in vitro* biomedical research and applications. 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 (Abeer, 2012). A variety of nanomaterials are used for diagnosis and treatment include metallic nanoparticle, quantum dots, carbon nanotubes, magnetic nanoparticles, fullerenes, liposomes, dendrimers and engineered hybrid nanoparticles (Dilbaghi *et al.,* 2013).

Today's scientists and engineers are finding a wide variety of ways to deliberately make materials at the nanoscale to take advantage of their enhanced properties such as higher strength, lighter weight, increased control of light spectrum, and greater chemical reactivity than their larger-scale counterparts.

Past development in nanotechnology

Although modern nanoscience and nanotechnology are quite new, nanoscale materials were used for centuries. Alternate-sized gold and silver particles created colors in the stained glass windows of medieval churches hundreds of years ago.

The ideas and concepts behind nanoscience and nanotechnology started with a talk entitled "There's Plenty of Room at the Bottom" by physicist Richard Feynman (father of nanotechnology) at an American Physical Society meeting at the California Institute of Technology (CalTech) on December 29, 1959, long before the term nanotechnology was used. In his talk, Feynman described a process in which scientists would be able to manipulate and control individual atoms and molecules. Over a decade later, in his explorations of ultra precision machining, Professor Norio Taniguchi in the 1974 coined the term 'nanotechnology'. It wasn't until 1981, with the development of the scanning tunneling microscope (STM) that could "see" individual atoms that modern nanotechnology began.

RECENT TRENDS OF NANOTECHNOLOGY

In Drugs and Medicine

Nanotechnology can deliver medicine or drugs into specific parts of the human body, thereby making them more effective and less harmful to the other parts of the body. Anti-cancer gold nanoparticles have been found very effective. Gold "nanoshells" are useful to fight cancer because of their ability to absorb radiation at certain wavelengths. Once the nanoshells enter tumor cells and radiation treatment is applied, they absorb the energy and heat up enough to kill the cancer cells. Not only gold but other elements can also be used (Abeer, 2012).

In Disease diagnosis

Nanosensors

Principles of nanotechnology have been exploited in biosensing that detects analytes of very small amounts at very low concentrations **(**Dixon, 2008). Nanosensors are miniature devices that can diagnose samples which use biological material or tissue based on biorecognition element which is immobilized on the surface of physicochemical transducer. Nanosensors are envisioned from the integration of chemical, physical and biological devices which work together as a sensor at nanoscale. Majorly, nanosensors are based on two detection principles - catalytic and affinity sensing. Catalytic sensors utilize enzymes, cells, tissues/organelles and microorganisms as the recognition agent. Affinity sensors are those which utilize whole antibodies, antibody fragments, nucleic acid/ aptamers, receptors, lectins, phages, novel engineered scaffold derived bonding proteins, molecular imprinted polymers, plastic antibodies and synthetic protein binding agents as the recognition agent (Kodadek and Bachhawat- sikder, 2006). Nanosensors have major role in veterinary sciences, they use very small amount of a chemical contaminant, virus or bacteria which is helpful for agriculture and food systems that in return improves the feedstock (Scott, 2005). For online detection of veterinary drug residues in milk, porcine bile and bovine urine, a commercially handled robot was designed with the help of Surface Plasmon Resonance (SPR) technique.

Nanowires have been used for making extremely small, sensitive and electronic based nanosensors for the detection of biological species. In 2002, scientists reported carbon nanotube (CNT) based sensors that were implanted under skin for providing real time measurement of blood estradiol changes in animals. These implanted sensors have a major role in veterinary sciences as: once swallowed or implanted, these are capable of continuously sending data throughout the life of the animal and later to track animal products after slaughtering (Bruchez *et al.*, 1988).

NANOMATERIALS

Liopsomes

Liposomes are small artificial vesicles of spherical shape composed of single or multiple concentric bilayers, size ranging from 50-500 nm. Liposomes are formed in aqueous medium by self assembly of amphiphilic molecules such as phospholipids in which the polar head groups are located at the surface of the membranes when in contact with the aqueous medium, whereas the fatty acid chains form the hydrophobic core of the membranes, shielded from the water. Liposomes play a key role in diagnosis as they can be used as carriers for radioisotopes and contrast agents. They can also be used to detect hepatic metastases and blood perfusion imaging. Liposomes may also be applied in lymphatic imaging by subcutaneous administration (Oussernand Storm, 2001).

TABLE 1: Various nanoparticles used in diagnosing and treatment of wide variety of animals

Nanoparticles	Applications	Animals
Gold Nanoshells	Whole blood immunoassay	Mice
Iron-oxide nanoparticles	Enhanced MRI of atherosclerotic plaques	Rabbit
Quantum dots	Imaging of antigen specific T-cell receptor response	Macaques (Monkeys)
Selenium nanoparticles	Against hepatic injury	Mice
Liposomes	Anti-tumor activity against mammary tumor glands	Rats
Peptide conjugated gold nanoparticles	*in vitro* cytotoxic effects on mouse ovarian surface epithelial cell lines (MOSEC)	Mouse

Dendrimers

Dendrimers discovered in 1880 are macromolecules which are highly branched. The objective for synthesizing dendrimers, is to improve the pharmacokinetic behavior of currently available small-sized compounds from a broad extracellular to an intravascular distribution (Al - Jamal *et al.*, 2009). These are potential polymeric carriers, which are currently under investigation as contrast agents for magnetic resonance imaging (MRI), scintigraphy, X-ray techniques and computed tomography (CT). Major target studies of dendrimers include angiography, tissue perfusion determination, tumor detection and differentiation.

Quantum dots

Quantum dots are semiconductor nanocrystals having unique properties like high level of photostablility, tunable optical properties, single-wavelength excitation and size-tunable emission. The above discussed properties make quantum dots as one of the most capable therapeutic nanomaterial and highly acquiescent to biological and clinical applications. Due to their extremely small size (around 10 nm in diameter), they are used as fluorescent probes for biomolecular and cellular imaging (Bharali *et al.*, 2005). Diseases involving large number of genes and proteins can be detected by multicolour quantum dot probe that helps in imaging and tracking multiple molecular targets simultaneously. These applications lead quantum dots to be ideally used for biosensing.

Gold nanoparticles

Gold nanoparticles have proven to be the most flexible nanostructures, due to their ability to control size, shape, composition, structure, assembly, encapsulation thereby resulting in enhanced optical properties. They exhibit a unique phenomenon termed as surface plasmon resonance which is responsible for their large absorption and scattering cross-sections. Thus, gold nanoparticles are attractively used in biomedical applications (Mirkin *et al.*, 1996). Gold nanoparticles can be functionalized easily with biological molecules such as antibiotics and nucleic acid using various strategies and can be employed for diagnosis. The attractive features of gold nanoparticles such as ease of synthesis, non-cytotoxicity, high biocompatibility, broad optical properties make them fascinating for diagnosis.

Magnetic nanoparticles

Magnetic nanoparticles are finding increasing applications in the areas of medical diagnostic and therapeutic because of the advantageous properties associated with them such as lesser dipole dipole interactions, lower sedimentation rates, facilitation in tissue diffusion, high magnetization so as to be controlled by external magnetic fields and to reach the targeted pathologic tissue and their small size that make them available for circulation through the capillary systems of organs and tissues. They are often used for the development of biological sensors, immunoassays, cell separation, protein binding studies and biochips. Magnetic nanoparticles (MNPs) have various applications like contrasts for magnetic resonance image, magnetic hyperthermia, magnetic separation, drug delivery, fluorescence-modified superparamagnetism, intracellular uptake and use in cellular imaging. Magnetic nanoparticles have been widely used in the early diagnosis of diseases. They are especially important for some fatal diseases such as cancer. Some magnetic nanoparticles like iron oxide nanoparticles have been used in perfusion imaging for *in-vivo* characterization of tumors (Strijkers *et al.*, 2005).

IN TREATMENT

Polymeric nanoparticles

Strategies for controlled drug-delivery have made a considerable progress in the field of medicine where polymeric nanoparticles play a key role. Polymeric nanoparticles are the most promising drug carriers due to their structural and functional characteristics. They deliver drugs for long periods, increasing the drug efficacy, maximizing the patient compliance thereby enhancing the ability to use highly toxic, poorly soluble or relatively unstable drugs. They are used for the development of highly selective and efficient therapeutic and diagnostic modalities (McCarthy *et al.*, 2005). Polymeric nanoparticles can circulate freely in the body and penetrate tissues by means of mechanisms such as endocytosis. The uptake of nanoparticles depends on the various factors such as particle size, surface charge and surface hydrophobicity. Polymeric nanoparticles form a versatile drug delivery system as they can potentially overcome physiological barriers, and guide the drugs to specific cells or intracellular compartments (Storm *et al.*, 1995).

Carbon nanotubes

Carbon nanotubes (CNTs) have fascinated scientists with its extraordinary properties. These nanomaterials have become increasingly popular in various fields because of their extremely small size and amazing optical, electronic and magnetic properties when used alone or with modifications. CNTs are graphene sheets rolled up into the cylinderical shape which may be open or closed at the ends. To be precise, they are graphene cylinders which have diameter in nanoscale and capped with end-containing pentagonal rings. Carbon nanotubes have potential therapeutic applications in the field of drug delivery. They can be functionalized by various biomolecules such as bioactive peptides, proteins, nucleic acids and drugs, and are used to deliver their cargos to cells and organs (Tiwari and Dhakate, 2009). Carbon nanotubes show effectiveness in treatment of wide range of diseases but its major role is in cancer treatment. CNTs on combination with anticancer drugs, enhances their chemotherapeutic effects. Thus, carbon nanotubes have a potential to revolutionize health care sector for wide future applications.

Dendrimers

Diversity of molecules holds potential therapeutic value out of which dendrimers clutch a wide applicability in drug delivery. Dendrimers have many flexible branches containing voids where drug molecules can be physically trapped (Bianco *et al.*, 2005). This dense architecture enables an excellent encapsulation. Dendrimers are effectively used in drug delivery as they deliver a drug at controlled rate by chemically modifying them either by fine tuning of hydrolytic release conditions and the selective leakage of drug molecules on the basis of their size or shape or by pH-sensitive materials. Dendrimers with high payload also showed rapid pharmacological response with improved efficacy. Dendrimers have their major stress in the treatment of cancer as these nanometric particles passively accumulate at the site of tumors. The recent research indicates that dendrimers might be considered as potential drug carriers for treatment of diseases with the capability to provide a sustained release along with reduced side effects.

Nanoshells

Nanoshells are concentric particles in which one material is coated with a thin layer of another material by various synthesis methods. They are multifunctional with tailored properties. Nanoshells are dielectric metal nanospheres. Nanoshells have unique optical properties that totally depend upon the size of that particle, thus its surface plasmon resonance can be tuned in broad spectrum of wavelength. Foremost methods of synthesizing nanoshells are layer by layer precipitation and one pot synthesis. Till date varieties of nanoshells are synthesized out of which gold nanoshells gave fruitful results to destroy the cancer completely.

Quantum dots

As described earlier in diagnosis section, quantum dots are semiconductor nanocrystals which fluoresce on excitation with a light source. Recent developments have shown that quantum dots with near-infrared emission can be applied for biopsy and surgery of cancer patients. Conjugation of quantum dots with various biomolecules such as peptides, antibodies etc. can be used *in vivo* for targeting tumours (Zhang *et al.,* 2008). Quantum dots are revolutionizing the field of targeted drug delivery and are considered as one of the major components of multifunctional nanodevices that can provide treatment to animals.

Liposomes

Liposomes have been extensively used as a potential drug delivery system due to their diversity of structure. Structurally liposomes are made up of amphiphillic unilamellar/ multilamellar membranes of natural lipids. Liposomes can encapsulate hydrophobic drugs within the membrane and hydrophilic drugs in their aqueous spaces. Liposomes interact with cells and release the drug contents in one of the four ways: adsorption, lipid exchange, fusion or endocytosis. Thus liposomes are considered as one of the best drug delivery systems. They are also used as adjuvants for vaccination, solubilizers for various ingredients and immunological enhancers.

Nanogels and ceramic nanoparticles

Hydrogels when miniaturized forms nanogels which are generally formulated using solvent evaporation or emulsification technique. Nanogel particles can be used for loading oligonucleotides which are stable in aqueous phase, do not agglomerate, get inserted within intestinal cell layers. Oligonucleotide coated nanogels do not degrade with time and are effective in gene transcription (Tessler*et al.*, 2011). Ceramic nanoparticles with entrapped biomolecules based systems reflect an emerging area for healthcare and have great potential in drug delivery. Nanoparticles consisting of calcium phosphate, silica, alumina or titanium are known as ceramic nanoparticles. They have a wide variety of advantages such as high biocompatibility, low size range, high stability, easier synthesizing techniques. Their ultra low size range helps them to evade by the reticulo endothelial systems (Cherian *et al.,* 2000).

Toxicity assessment

The advancements in diagnosis and treatment using nanoscience depend in part on exploiting the size specific properties of nanoscale materials. The exotic feature of nanomaterials enables nanoscale particles to cross or circumvent barriers that are impenetrable to larger particles. Many biological processes occur at nanoscale and hence there are numerous opportunities for precisely sized nanoparticles to interfere with normal biological functions. These unique behaviours of nanoparticles (*i.e*. to interact with biological systems) are requiring new tools and concepts within this field of toxicology to understand and predict how emerging engineered nanoparticles will interact with humans and animals. In light of the above, it is mandatory that each new nanomaterial must be subjected to new health and safety assessment prior to its commercial and public use.

Future prospective of nanotechnology

In Surgery

With nanotechnology, minute surgical instruments and robots can be made which can be used to perform microsurgeries on any part of the body. Instead of damaging a large amount of the body, these instruments would be precise and accurate, targeting only the area where surgery should be done. Visualization of surgery can also be improved. Instead of a surgeon holding the instrument, computers can be used to control the nano-sized surgical instruments. "Nanocameras" can provide close up visualization of the surgery. There is less chance of any mistakes or faults. Surgery could also be done on tissue, genetic and cellular levels. The workings of cells, bacteria, viruses *etc.* can be better explored. The causes of relatively new diseases can be found and prevented.

Tissue engineering

Tissue engineering could also be done using nano-materials. Tissue engineering makes use of artificially stimulated cell proliferation by using suitable nanomaterial-based scaffolds and growth factors. Advances in nanotechnology-based tissue engineering could also lead to life extension in humans and other animals.

Nano-robotics

"Nanobots" will be devices as small as a microbe, but they will not possess the ability to self-replicate. These engineered nanodevices or nanomachines, will repair the damage that accumulates as a result of metabolism (being alive) by performing nanorobotic therapeutic procedures on each of the ~75 trillion cells that comprise the human body. They will contain various substructures such as an onboard power supply, nanocomputer, sensors, manipulators, pumps and pressure tanks. Future medical nanotechnology expected to employ nanorobots injected into the patient to perform treatment on a cellular level.

Respirocytes

A Mechanical Red Blood Cell Respirocytes are a design for an artificial red blood cell. The human body contains approximately 30 trillion natural red blood cells which circulate in the blood stream and occupy roughly half of the blood volume. Respirocytes will be much smaller about the same size as a bacterium. A respirocyte will be an atomically-precise arrangement of 18 billion structural atoms. Just 5 ml (or one thousandth of our total blood volume) worth of respirocytes added to a person's blood could double their natural oxygen-carrying and carbon dioxide removing capacity. A single respirocyte will be capable of transporting hundreds of times more bioavailable oxygen than a natural red blood cell, at only a fraction the size. Half a liter - the most respirocytes that could be safely added to a person's blood - would allow them to sprint at top speed for twelve minutes, or remain underwater for up to four hours without taking a single breath. Alternatively, respirocytes would buy valuable time in the event of a heart attack or drowning, and due to their diminutive form factor they would be able to supply needed oxygen to cells following a crushing or other accident that constricts blood flow.

Microbivores or nanorobotic phagocytes (artificial white blood cells)

Microbivores introduced into the blood stream would form a synthetic immune system, a search and destroy task-force constantly on patrol for pathogenic microbes, viruses and fungi. Multiple-drug resistant strains of bacteria stand no chance against the microbivore. Even the deadliest of infectious pathogens could be completely cleared from the system within just minutes or hours with no negative effect to the patient, and using only a few milliliters of microbivores. With additional programming, similar nanobots could be used to detect and selectively destroy cancerous cells or even clear obstructions from the blood stream in just minutes, preventing ischemic damage in the event of a stroke.

Chromallocytes

Chromallocytes, one variety of cell-repair nanobot, would enter the nucleus of a cell and extract all of the genetic material (chromosomes) and replace it with a synthetically produced copy of the original that has been manufactured in a laboratory to contain only non-defective base-pairs. The result of this cytosurgical “Chromosome Replacement Therapy” (CRT) process would be the removal of all inherited defective genes, reprogramming of cancerous cells back to a healthy state and a permanent cure for all genetic diseases or any combination thereof desired by the patient. CRT will enable us to exchange our old defective chromosomes with digitally-precise new copies of our genes, manufactured in a laboratory by a bench top size production device, using the patient’s genome as the blueprint. Through a combination of nanobot therapies, say once a year or less frequently, accumulated metabolic toxins and other nondegradable material will be cleansed from your body, while chromallocytes delete any genetic mutations or damage. Any remaining structural damage to cells that they are unable to auto-repair such as disabled or enlarged mitochondria will be dealt with using dedicated cellular repair nanobots. These rejuvenation procedures will need to be repeated once a year (or less frequently) to revert all of the damage that occurs on a continual basis as a result of metabolism.

Clottocytes

Clottocytesare a design for micron-scale, oxygen/glucose-powered, artificial mechanical platelets. Clottocytes would be 100 to 1,000 times faster in response than the body’s natural platelets, stopping bleeding almost instantly (within about one second) even in the event of fairly large wounds. The clottocyte is conceived as a two micron diameter, spheroidal nanobot that contain a tightly-folded (biodegradable) fiber mesh payload which, when commanded by its internal nanocomputer, deploys in the general vicinity of a damaged blood vessel. The overlapping nettings of multiple activated clottocytes trap blood cells and stop bleeding immediately. The clotting function performed by clottocytes is essentially equivalent to that of biological platelets, and much quicker acting.

THE END OF AGING AND DISEASE

The result of these technological advances will be the effective end of aging as well as the reversal of one’s current biological age to any new age that is desired. These procedures are anticipated to become common place as the technology evolves, a few decades hence. With routine annual checkups/ repairs, and the occasional major tune-up, you could remain virtually constantly your ideal biological age. Even if such procedures can keep you “clinically immortal,” if you’re hit by a flying car, you may still die, though cell repair nanobots and other advanced future medical techniques will be able to repair much more extensive injuries than are now possible. Based on projected rates of accidental death and suicide, a life expectancy of at least one thousand years is expected - if we don’t annihilate ourselves in the interim. Perhaps the most significant danger in curing aging is in the cultural and intellectual stagnation of human kind that may result if the current generation were stopped in time. Aging and Disease result from the molecules in our tissues sliding into disorder, first destroying health, and eventually taking life itself. Nanotechnology will give us numerous novel approaches to repair our aging bodies and undo the disastrous results of the ravages of time. The advancements anticipated in the Nano age offer the first promising hope of a science-based fountain of youth.

CONCLUSION

In the recent years, the application of nanotechnology in human and veterinary medicine has shown a great progress. Nanotechnology and its applications are specific and varied in continuous development, with a high potential for improving domestic animals production and flora and fauna in general. Nanomaterials such as carbon nanotubes, quantum dots, liposomes, polymeric nanoparticles, magnetic nanoparticles, etc. are explored for their potential use in diagnosis and treatment of diseases. The above discussed nanomaterials are used for early diagnosis, which includes detection of molecular interactions with use of nanoarrays, and nanochips. Nanomaterials offer a vast number of breakthroughs like cost effective and faster approach that will further advance the clinical aspect of veterinary sciences in future. In the future, it can be conceived that bacterial infections can be eliminated in the patient within minutes, instead of using treatment with antibiotics over a period of weeks. With the advancement in technology, we can expect to generate capability to perform surgery at cellular level, thereby removing individual diseased cells and even repairing defective portions of the individual cells. Innovations in technology and identification of novel hybrid materials with time will provide significant lengthening of the human lifespan by repairing cellular level conditions that cause the body to age. Several nanotechnology based products are already in the market and many are under development or in experimental stages.

Nanomaterials have revolutionized the field of diagnosis and treatment but at the same time these particles have the potential to affect vital organs of the body. Thus, extensive research is still required to support the effectiveness and mainly the safety of nanotechnology, avoiding any harm to the environment or to human beings and animals.

POTENTIAL RISKS

Potential risks of nanotechnology can broadly be grouped into three areas: the risk to health and environment from nanoparticles and nanomaterials; the risk posed by molecular manufacturing (or advanced nanotechnology); and social risks.

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