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ROLE OF NANOTECHNOLOGY IN HEALTH CARE SYSTEM MANAGEMENT

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Abstract: Nanotechnology is the science that holds the potential to revolutionize the multiple facets of human life. However, it is in only a nascent stage today, thereby enormous technical hurdles and numerous failures are inevitable.Current promises offered by the use of this technology will touch all spheres of our life. Efforts should be made to maximize the enormous benefits of this technology while keeping the associated risks at minimum.

Keywords: Nanotechnology, Healthcare, Diabetes Mellitus, Cardiovascular Diseases, Cancer, Alzheimer's Disease.

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INTRODUCTION

Nanotechnology has the potential to completely change healthcare for the next generation. As a matter of fact, nanotechnology may be ongoing revolution in the drug delivery as well as the diagnostics.

Defining Nanotechnology:

The term 'Nanotechnology' was coined in 1980s by K. Eric Drexler, the founder and chairman emeritus of Foresight Institute, USA [1]. Nanotechnology deals with the systems manufactured at the nanometer scale. Nanotechnology, as it is described by the National Institute of Health, comprises particles or structures that are in the size range of 1-100 nm in diameter [2]. There are basically two approaches for the synthesis of nanostructures, irrespective of the field or discipline: 'Bottom-Up' approach and 'Top-Down' approach. In Bottom –Up technique the building of nanostructures is achieved by growing or assembling of atoms or molecules which are the building blocks. The building blocks may be manipulated through controlled chemical reactions to self assemble and make nanostructures such as nanotubes and quantum dots[3]. 'Topdown' is achieved by breaking, cutting or etching techniques[4] which is achieved by bulk or film machining, surface machining and mold machining employing lithography[5].

Applications of Nanotechnology for Healthcare

Nanotechnology could help medical professionals deal with numerous current excruciating medical issues such as designing of artificial materials resulting in more advanced diagnostics as well as therapeutics [6].

Applications of Nanotechnology for Healthcare: Prevention

Numerous studies have corroborated the fact that that preventive approach is always more cost-efficient than reactive one [6]. Our current healthcare system is based on a reactive approach which offers treatments only after the health issues arise and it may leave the marks of debility afterwards. Nanotechnology would offer a promise to help prevent diseases even before they start to develop.

Microfluidics (Lab-on-a Chip)

Specially designed "Lab-On-A-Chip" devices allow doctors to monitor constantly and on a "real-time" basis hundreds of different health parameters. Doctors can get a immediate assessment of blood lipids, cholesterol, triglycerides, blood pressure, blood oxygen, etc by just reading the signals from a chip that a patient is wearing. There is no wait for results coming from the lab, no possible mistakes in handling those results, no misdiagnosing, etc. This new technology is also

useful in analyzing DNA samples. This device consists of micro-fabricated fluidic channels, heaters, temperature-sensors, electrophoretic chambers & fluorescence detectors. It is capable to analyze DNA samples of nanoliter-size.

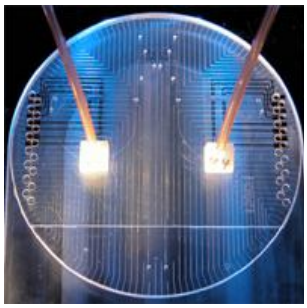

Figure 1: A top view of a lab on a chip system that is structured on a glass-silicon substrate[7].

Nanofilters

Most of the medical issues can be thwarted by minimizing the contact and exposure to pathogenic bacteria and viruses. The nanofilters, with nano size pores are constructed which can remove the smallest of the known viruses.

Antimicrobial Coatings

During the surgical procedures the use of antimicrobial coatings onto the surfaces coming in contact with body fluids would prevent the sticking of viruses and bacteria. The antimicrobial coatings, comprising specific microbicide agents, such as TiO_2 or silver-gold nanoparticles have the ability to directly destroy the microbes [6].

Applications of Nanotechnology for Healthcare: Treatment of Diseases

Nanotechnology can play a pivotal role in the betterment of established treatments for old diseases as well as design of sure shot treatments for new diseases. Nanotechnology can foray into individualization of medications either by designing a new drug or a new delivery technique for existing drug.

Personalized Medicine

Traditionally the physicians consider the “average” response approach in dose deciding. An elaborate understanding of human genome coupled with sophisticated nanotechnological tools has enabled to pinpoint the genes responsible for a certain disease and to identify the best drug for individual patient. It could help to select the best treatment for an individual patient; this is termed as personalized medicine [6].

New Methods of Drug Delivery

The development of nanotechnology products may play a vital role in adding a new armamentarium of therapeutics to the pipelines of pharmaceutical companies. Using nanotechnology, it may be possible to achieve (1) improved delivery of poorly water-soluble drugs[8] ; (2) targeted delivery of drugs in a cell- or tissue-specific manner[9]; (3) transcytosis of drugs across tight epithelial and endothelial barriers[10]; (4) delivery of large macromolecule drugs to intracellular sites of action[11]; (5) co-delivery of two or more drugs or therapeutic modality for combination therapy[12]; (6) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities[13]; and (7) real-time read on the *in vivo* efficacy of a therapeutic agent[14]. Additionally, the manufacturing complexity of nanotechnology therapeutics may also create a significant hurdle for generic drug companies to develop equivalent therapeutics readily. Nanotechnology Victoria Ltd (NanoVic) is delivering the outcomes of nanotechnology research to Victorian industry. It is a joint venture of three major universities; Monash University, RMIT University, Swinburne University of Technology, and the Commonwealth Scientific and Industrial Research Organization (CSIRO). Nanoparticle Delivery is used in a development project for Transdermal Delivery through a MicroArray Patch (MAP); delivering large and small molecules to cross the outer impermeable layer of the skin. Monash University, Eiffel Technologies and MiniFAB are co-investing with NanoVic towards the project over a 12 month period for vaccines, proteins, peptide hormones and drug delivery [15].

New Drugs

Controlled manufacturing systems (top-down or bottom-up) can help design the new drugs. It is possible to tailor a pre-existing lead by removing its toxic part and potentiating the “effective” one.

Interfaces between Biological and Other Materials

In the repair of the human body with prosthetics or artificial replacement parts rejection by body occurs at biological interfaces. The nanoscale chemical and topographical details of the implanted materials determine the reaction of the body. It may be possible to surround implanted tissue with a nanofabricated barrier that would thwart the rejection mechanisms of the host, allowing wider utilization of donated organs. Ultimately, better materials and understanding of their interaction with the body may lead to implants that the body will not only accept, but that will actually become integrated into the body[16].

Nanobots

Nanobots are just several nanometers wide. They can be used very effectively for drug delivery. The drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects. These Nanobots are powered locally by deriving energy from glucose metabolism. In a clinical environment the externally supplied acoustic energy can do the powering of Nanobots. After accomplishing the designated task Nanobots could be retrieved via usual excretory channels or fated to removal action of active scavenger systems [17]. Figure below shows a device that uses Nanobots to monitor the sugar level in the blood.

Figure 2: Nanobots for Checking Blood Contents [18]

The drug carriers have walls that are just 5-10 atoms thick and the inner drug-filled cell is usually 50-100 nanometers wide. When they detect signs of the disease, thin wires in their walls emit an electrical pulse which causes the walls to dissolve and the drug to be released. These computer-controlled nanorobotic systems are apt for temporal as well as spacial targeted delivery of pharmaceutical agents at cellular and intracellular levels [19]. Elan Pharmaceuticals has already started using this technology in their drugs Merck's Emend drug and Wyeth's Rapamune[20].

Tissue Reconstruction

Nanoparticles can be designed with a structure very similar to the bone [21]. An ultrasound is performed on existing bone structures and then bone-like nanoparticles are created using the results of the ultrasound. The bone-like nanoparticles are inserted into the body in a paste form. When they arrive at the fractured bone, they assemble themselves to form an ordered structure which later becomes part of the bone [20]. Another key application for nanoparticles is the treatment of injured nerves. Samuel Stupp & John Kessler at Northwestern University, Chicago have made tiny rod like nano-fibers (amphiphiles) capped with amino acids. While suspended in liquid, they start spontaneously arranging themselves like spokes in a wheel and then spaghetti-like nanofibers on coming in contact with living tissue. The amino acids for nerve-healing are nicely arranged on these fibers' surface. [21] An accelerometer is a very useful

nano-device that can be attached to the hip, knee or other joint bones to monitor movements and strain levels. Dressings can be coated with silver nanoparticles to make them infection-resistant [20].

Nanoporous materials

Nanoporous materials offer advantages in many biomedical applications such as dialysis, immunoisolation, bio-analytical devices, biosensors, and targeted drug delivery systems. Nanoporous membranes of desired thickness & well-controlled porosity could be used to design the controlled release capsules [23] or drug eluting stents for the treatment of coronary artery disease [24]. The nanoporous membranes of inorganic materials have been tested recently for the sustained delivery of ophthalmic drugs [25].

Applications of Nanotechnology for Healthcare: Diagnosing Diseases

Quality of life of patients can be greatly improved if proper and fast diagnosis and monitoring is achieved. In addition, better diagnosis tools and monitoring devices have a definite positive effect in the cost of healthcare.

Imaging

The class of compounds known as superparamagnetic iron oxides (SPIOs), also known as monocrystalline iron oxide nanoparticles (MIONs), have shown promise for a number of magnetic resonance (MR) imaging applications both as naked particles and as magnetic labels [26]. Qdots are a type of nanoparticles (roughly 5nm semiconducting nanocrystals) known as fluorophores [27].Uniquely, quantum dots can be altered to emit any desired colours after excitation, solely depending on the size of the nanoparticles. The emission from the Qdots can be controlled by changing its core size; this is called size quantization effect [28]. The smaller particles show emission closer to the blue end of the spectrum while the larger particles near the red end [29]. Qdots can be made to emit even beyond visible light, into the infrared or ultraviolet regions of spectrums for diagnostic purposes [28].Unlike modern day fluorescent dyes, which tend to decompose and lose their ability to fluoresce, quantum dots maintain their ability to withstand more cycles of excitation and light emission before beginning to fade.

Nano-Bioassays

Using recent development in nanotechnology the bioassays have become more sensitive [6]. They are able to detect diseases or potential “markers” of disease at lower levels of concentration of the biomolecule. Quantum dots when coated with certain materials attach specifically to a molecule and help track it. Quantum dots of different materials (each detecting a specific biomolecule) can be arranged on a bioassay plate so as to have a “multiple disease-

detecting bioassay". Semiconductor quantum dots have been used to demonstrate tumour targeting in vivo in mice [30].

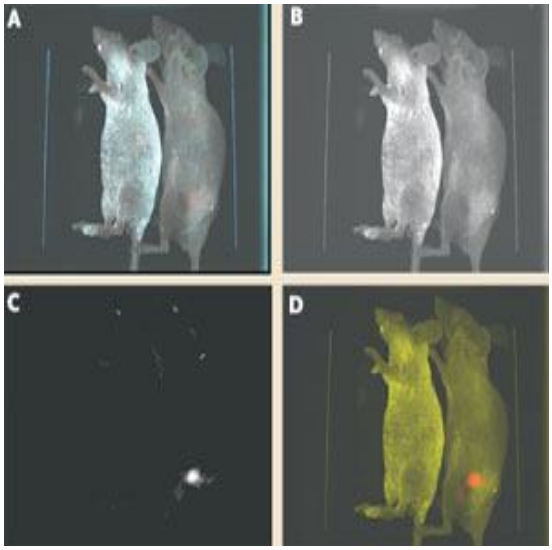

Figure 3: Spectral imaging using quantum dots. Orange - red fluorescence indicate a prostate tumor growing in a live mouse [30]

Nanochips

Nanogen company has developed a "Nanochip" that employs the power of an electronic current to separate DNA probes to specific sites on the array on the basis of charge and size. It accelerated the detection of target DNA sequences to minutes instead of hours with conventional approaches. Once these probes are on specific sites of the nanochip, the test sample (blood) can then be analyzed for target DNA sequences by hybridization with these probes. The DNA molecules that hybridize with target DNA sequences fluoresce, which is detected and relayed back to an onboard system through platinum wiring that is present within the chip [31].

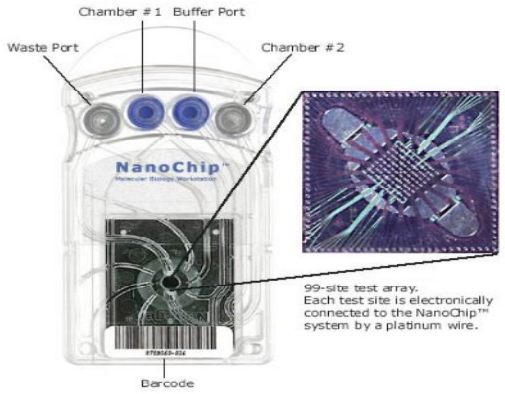

Figure 4(a): (Left) Nanogen's Nanochip device.

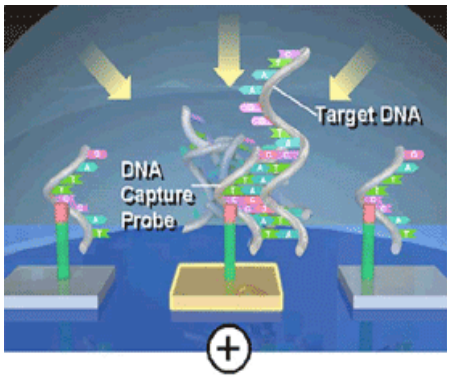

Figure 4(b): Close-up of DNA hybridization on different sites[32]

Colorimetric and Magnetic Bead Technologies

A colorimetric sensor is that can selectively detect biological agent DNA; it is in commercial development with successful tests against anthrax and tuberculosis [33]. Compared to present technology, the sensor is simpler, less expensive (by about a factor of 10), and more selective.

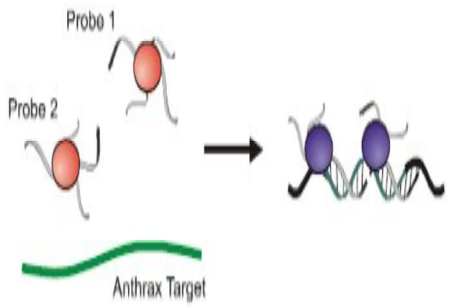

Figure 5: Detection of Anthrax[34]

A complementary effort is based on atomic force microscopy with a sandwich immunoassay attaching magnetic beads to a microfabricated cantilever sensitive to small displacements [34]. Both colorimetric and magnetic bead technologies might be implemented in detector arrays that provide simultaneous identification of multiple pathogens.

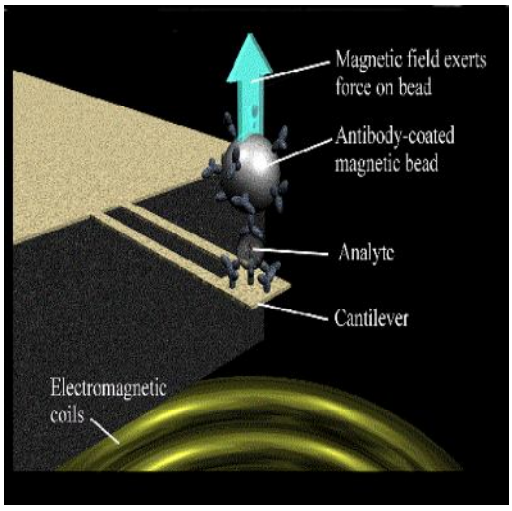

Figure 6: AFM for Immunoassay[34]

Home Pregnancy Test

A pregnancy test measures the Human Chorionic Gonadotropin (HcG) hormone in urine. This kit uses gold nanoparticles (less than 50 nanometers in diameter). If HcG hormone detected nanoparticles reflect red, otherwise blue [35].

Nano Mask

Nano masks utilize nanoparticle enhanced filters [36]. They block potentially harmful airborne contaminants in inhaled as well as exhaled air.

NANOTECHNOLOGY AND DIABETES MELLITUS

Diabetes mellitus often referred to simply as diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia).

Use of nanotechnology in the detection of insulin and blood sugar

Nanotechnology has made it possible to rapidly measure the small amounts of insulin and blood sugar levels. Such developments help determine the efficiency of insulin-producing cells. It can be achieved by following ways-

By microphysiometer:

The microphysiometer is built from multiwalled carbon nanotubes that operate at pH levels characteristic of living cells. These nanotubes comprise of flat carbon sheets which are stacked and rolled together to form very small electrically conductive tubes. In the presence of glucose the insulin molecules get oxidized and the current detection sensor continuously detects the insulin levels by measuring the number of electrons transferred. More the production of insulin molecules in the cells, more the current will flow through the sensor making it possible to monitor the insulin levels in real time [37]. Scientists have developed a multiwalled carbon nanotube/dihydropyran (MWCNT/DHP) composite sensor for the electrochemical detection of insulin in a microfluidic device [38] .

Implantable Sensor ('Smart Tattoo')

A number of biological or artificial receptors for glucose have been described, which can transduce glucose concentrations into changes in fluorescence, including lectins, enzymes, bacterial binding proteins and boronic acid derivatives [39] , and which might be engineered as nanosensors. With the plant lectin concanavalin A (Con A), which has four binding sites for glucose, sensing can be based on the competitive binding to Con A of either glucose or a labelled carbohydrate derivative such as dextran [40] or Sephadex beads [41]. Nanosensors consisting of encapsulated, fluorescently labelled glucose-receptor molecules (e.g. glucose-binding protein [GBP]) are implanted in the skin (dermis or subcutaneous tissue) and can be excited using NIR light and the fluorescence is detected from the skin surface. Sensors that use fluorescence for detecting analyte changes have some advantages compared to the implanted

electrochemical electrodes, as they need not to be susceptible to electroactive tissue interferents that contribute to the instability of current sensors, and because near infrared (NIR) light with a wavelength above about 600 nm pass through several centimetres of tissue, allowing implantation and non-invasive measurement at the body surface [42].

Use of Nanotechnology in the treatment of diabetes

The treatment of diabetes includes the proper (controlled) delivery of insulin in the blood stream [43] which can be achieved by nanotechnology in the following ways:

Development of oral insulin:

Oral delivery of insulin has certain limitations, including low oral bioavailability due to degradation in the stomach, inactivation and digestion by proteolytic enzymes in the luminal cavity, poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity [44]. Consequently, various approaches have been examined to overcome these delivery problems [45] .The carrier systems, such as liposomes [46], nanoparticles [47-48], solid lipid nanoparticles [49], and nanoemulsions [50] have shown to improve the gastrointestinal absorption of insulin.

Artificial Pancreas:

Development of artificial pancreas could be an unprecedented solution for diabetic patients. Its working principle is very simple. A sensor electrode continuously measures the blood glucose levels and sends this information to a small computer system which cues the entry of insulin into the bloodstream through an infusion pump.In an alternate approach, a tiny silicon box containing animals' pancreatic beta cells is surrounded by a nanoporous material. The pores of these materials (about 20 nanometers in diameter) allow the transit of insulin and glucose, but impede the larger immune cells. These boxes when implanted under the skin could restore the glucose control feedback loop without requiring the powerful immunosuppressant, thus minimizing the risk of serious infections [51], [52].

The Nanorobots:

Scientists are trying to develop a nanorobot bearing glucose sensors on the surface and insulin departed in its inner chambers. On the increase of blood glucose levels, the sensors would automatically direct the insulin release [53][54].

The Nanopump:

The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time [55].

SmartCell technology:

Todd Zion, Nanostructure Materials Research Labs has developed SmartCell technology for the treatment of diabetes. Use of this technology would stop the tiresome processes of checking & rechecking the glucose levels and injecting insulin as per need. When glucose level rises in the bloodstream, the SmartCell protein matrix breaks down, prompting the insulin release. Higher the glucose level in blood, faster will be the rate of matrix erosion [56].

NANOTECHNOLOGY AND CARDIOVASCULAR DISEASES

Although the benefits of nanotechnology transcend all specialties of medicine, one of the important applications of nanomedicine is in the field of cardiovascular sciences.

Design and Development of Miniature Surgical Instruments

During the traditional surgical procedures the chest is opened through sternum, the patient is connected to a cardiopulmonary bypass machine, the heart is arrested, and different surgical techniques are carried out on the arrested heart. However, these techniques can provoke central nervous system disturbances, and gastrointestinal complications in some patients. These complications are more probable in obese and elderly patients. Nanotechnology helps design and develop new tiny and more effective cardiac instruments [57]. Robotic surgical systems are being developed to provide surgeons with unprecedented control over instruments to offer precision. This is particularly useful for minimally invasive cardiac surgery. Instead of manipulating surgical instruments, surgeons use their fingers to move joystick handles on a control console to maneuver robot arms containing miniature instruments that are inserted into ports in the patient [58]. Nanorobots, operating in the human body, could be rapidly used in the examination of a given tissue, surveying its biomechanical and histometrical features in greater detail [59].

Figure7: Nanobots eating away dead flesh

Nanobots can assume the function of replacement helper-T cells in case of compromised immune system, rebuild or "re-grow" damaged tissue, produce synthetic clotting material at the sites of injury in order to stop bleeding, eat away the dead flesh at the sites of injury to allow quick healing with no nasty scar and closing a split vein at the same time [60]. Nanobots can also be used to prevent heart-attacks by removing fat deposits.

NANOTECHNOLOGY AND ORTHOPEDICS

Poor osseointegration can be a major contributor to implant loosening and subsequent failure. Modification of implant surfaces using nanotechnology has great potential to extend the life of implant [61]. Many nanofiber scaffolds made for tissue engineering have shown increased mesenchymal stem cell osteogenic differentiation[62] [63] as well as increased osteoblast attachment and proliferation onto bone nanostructured surfaces, including ceramics and metals[64] [65]. A porous bioresorbable nanocomposite bone scaffold have been created that chemically, structurally and mechanically matched natural bone & it could be recognized and remodeled by natural bone. This nanocomposite scaffold demonstrated excellent bioactivity for promoting cell attachment and proliferation [66]. In another study, gross specimen, X-ray,histomorphology and bone mineral density assay demonstrated that recombinant human bone morphogenetic protein-2 (rhBMP-2)-loaded gelatin/ nanohydroxypatite (nHAP) / fibrin glue (FG) scaffold had good osteogenic capability and potential to repair the segmental bone defect completely in 12 weeks [67].

NANOTECHNOLOGY AND CANCER

Atomic Force Microscopy in Cancer Detection

A new characteristic of cancerous cells, the surface stiffness, could be proven a breakthrough in cancer detection. The nanomechanical analysis can recognize the cancerous cells even when they look similar to normal noncancerous cells in their shape. Atomic force microscopy has

displayed that the stiffness of metastatic cancerous cells was more than 70% soft than the benign cells lining the body cavity. These nanomechanical analyses have shown correlation with immunohistochemical testing commonly used for cancer detection [68].

Quantum dots in Cancer Targeting & Imaging

Size-tunable light emission of Quantum dots along with MRI (magnetic resonance imaging) produces exceptional images of tumor sites. These nanoparticles with quantum confinement properties are brighter than conventional organic dyes and require only single source of light for excitation. Highly stable phospholipid micelle encapsulated silicon QDs were found to be robustly taken up by pancreatic cancer cells in vitro, thereby highlighting their potential to be used as a non-toxic optical probe for biomedical diagnostics [69]. The QDs might be integrated with targeting, imaging and therapeutic agents to develop 'smart' nanostructures for noninvasive imaging, diagnosis and treatment of cancer.

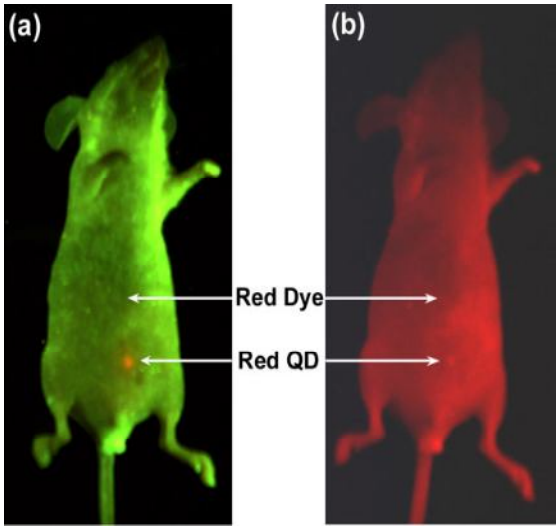

Figure 8: *In vivo* optical imaging of red-emitting QDs & red organic dyes [70]

Research has indicated that PEG-shielded QDs are able to circulate in blood for as long as 48–72 h, with a half decay time of 5–8 h . At the same time, these probes are small enough for efficient binding to cell surface receptors, for internalization through endocytosis or peptide translocation and for passing through the nuclear pores to enter the cell nucleus. *In vivo* imaging results indicated that these QD probes can be targeted to tumor sites through both passive and active mechanisms [70]. QD 710-Dendron and Arginine-Glycine-Aspartic Acid (RGD) modified nanoparticles have also demonstrated successful tumor imaging properties [71].

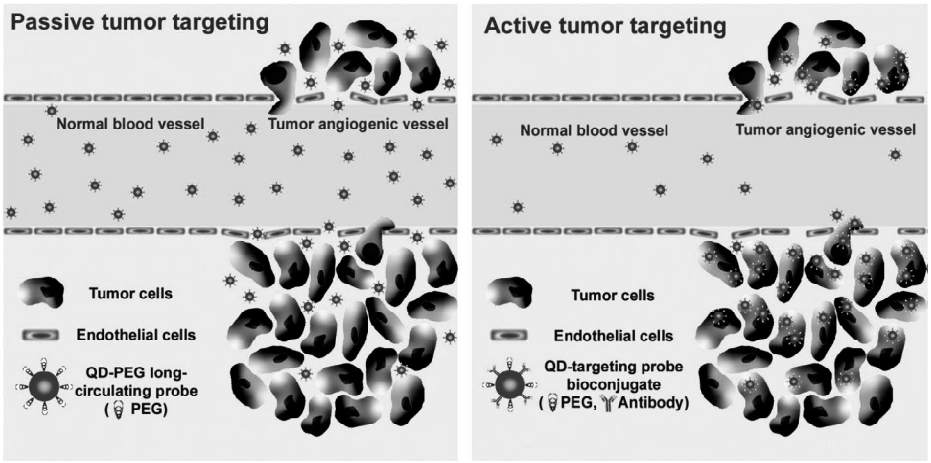

Figure 9: Permeation and retention of QD probes via passive targeting (leaky tumor vasculatures) and active targeting (high affinity binding of QD-antibody conjugates to tumor antigens)

Photothermal Ablation of Tumor (Frying Tumors)

In this therapy the iron nanoparticles are taken as oral pills and they get attached to the tumor. Then a magnetic field is applied and this causes the nanoparticles to heat up and literally cook the tumours from inside out [20].

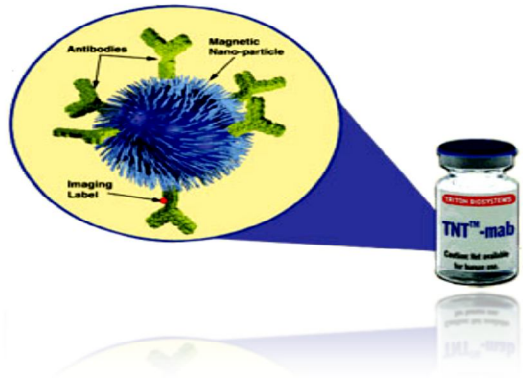

Figure 10: Cancer Cooker- Triton Biosystems is Developing an Anticancer

Therapy using Antibody-Coated Iron Nanoparticles [16].

Antibody-coated magnetic- iron nanoparticles have been found to effectively heat & cook the tumors [72]. The tumor growth in mice was arrested using selective photo-thermal ablation properties of polyethyleneglycol-coated gold nanoshells (130 nm size) and animals survived for up to 90 days more than the controls [73].

Buckyball /Fullerene in Cancer

Fullerenes contain only pentagonal and hexagonal faces, which form a cage structure. In general, for a fullerene C-n there will be 12 pentagonal faces and half of n minus 10 (n/2-10) hexagonal faces; thus, the C-60 fullerene has 12 pentagonal faces and 20 hexagonal faces. Fullerenes have a high strength to weight ratio, due to their hollow structure. Due to their spherical shape, they create many gaps between molecules which make it difficult for them to move against each other. These gaps can be filled with group one or two metals, which give them the additional property of being superconducting at low temperatures. The fact that they absorb light and can give out that energy to neighboring molecules could be useful in treating cancer. If C_{60} is in the bloodstream around a tumor and a light is shone on that tumor, toxic excited O_2will be formed and will attack the cancer in that localized area [74]. In recent studies the fullerene C_{60} nanoparticles (nC_{60}) have induced autophagy and sensitized chemotherapeutic killing of cancer cells, but the details still remain unknown [75]. Further, the ability of different fullerene preparations to modulate TNF-induced oxidative stress and subsequent cell death suggests their potential value in the TNF-based cancer therapy or prevention of TNF-dependent tissue damage [76].

Gene Therapy

Conventional viral vectors used in gene therapy may spur adverse immunologic responses, inflammatory reactions, or other diseases in host animal. A novel tumor suppressor gene called FUS1 has shown effective systemic treatment of lung cancer using nanoparticle based gene therapy without aforementioned drawbacks [77]. Oral gene delivery using poly-l-lysine modified silica nanoparticles resulted in distribution of particles throughout the intestinal mucosa with superior transgene expression, low cytotoxicity, and long-term survival of mice [78]. Studies using low-intensity pulsed ultrasound (1 MHz; 1.3 W/cm^2) and nano/microbubbles have demonstrated the potential of US/NB as a new physical gene delivery method for cancer gene therapy [79]

NANOTECHNOLOGY AND ALZHEIMER DISEASE

Alzheimer's disease (AD), is a neurodegenerative dementia characterized by memory loss and cognitive impairment [80].

Nanotechnology to Detect Alzheimer's Disease

Amyloid beta-derived diffusible ligand (ADDL) is an important biomarker for Alzheimer's disease (AD). The neurotoxicity of ADDLs [81], and high levels of these proteins in the patients' brains explicit their role in the disease progression [82]. ADDL-specific monoclonal antibodies [83] along

with nanoparticle-based protein detection strategy called as biobarcode amplification (BCA) [84] are used in the AD detection. Cerebrospinal fluid (CSF) is exposed to anti-ADDL monoclonal antibodies linked to magnetic microparticles. The ADDLs present in the CSF bind to these anti-ADDL antibodies which are then separated using magnetic field and washed. Now the secondary antibodies bound to DNA: Gold nanoparticle conjugates are added to the system. These DNA: Gold nanoparticle conjugates bear complementary "barcode" DNA attached through hybridization. The antibody: DNA: Gold nanoparticle conjugates that remain unreacted are separated by magnetic field application. The reacted barcode DNA is released using high temperature and low-salt conditions and further analyzed [85] [86].

Nanotechnology to Treat Alzheimer's Disease

Recently, an approach to deliver the neurotransmitter acetylcholine (ACh) to the brain to remedy the disrupted cholinergic neurotransmission in AD has been proposed based on the use of single-wall carbon nanotubes (SWCNTs) as the carrier [87] .The well-known buckminsterfullerene (C_{60}), also referred as a "free radical sponge" owing to its potent anti-oxidant activity[88] , is soluble only in a limited number of biologically unattractive solvents, such as toluene and benzene. As a biologically more suitable alternative, water-soluble carboxylic acid-functionalized forms of C_{60} (carboxyfullerenes) have been investigated for their neuroprotective potential against free radicals. In a study on cultured cortical neurons [89], the malonic acid derivative of C_{60} was found to be able to eliminate both the superoxide anion and the hydroxyl radical, and to reduce the apoptotic neuronal death induced by exposure to the AD amyloid-beta(1-42) peptide.

NANOTECHNOLOGY IN COSMETICS

A number of modern cosmetic-related products contain nano-sized components, such as moisturizers, haircare products and make-up. Modern sunscreens contain zinc oxide (ZnO) and titanium dioxide (TiO2) nanoparticles which reflect/scatter more UV rays with no white chalky appearance of traditional sunscreens [90]. Meanwhile, a number of modifications to the standard ZnO or TiO_2 UV protection system have been reported to increase the sun protection factor (SPF) [91].Buckminster Fullerenes, C_{60}, show excellent scavenging capacities against ROS (radical oxygen species), hence, they have been considered for skin rejuvenation cosmetic preparations [92]. Lipid nanoparticles have also been investigated to improve the treatment of skin diseases such as atopic eczema, psoriasis, acne, skin mycosis and inflammations [93].Vesicles, other than liposomes[94] are being used these days that claim to further enhance the penetration of substances across the skin, such as transferosomes[95] niosomes[96] and ethosomes[97].

NANOPARTICLE TOXICITY ASSESSMENT

Although public awareness of nanotechnology based products in daily life (e.g., burn and wound dressings, dental-bonding agents, cosmetics & sunscreens, optics, fuel cells, tires, electronics and stain-free clothing) may be quite low, it would be certainly prudent and necessary to assess and address human as well as environmental concerns before making this technology widespread. The nano-sized particles show biokinetics different from their larger counterparts. On inhalation they evade specific defense mechanisms and get translocated out of respiratory tract via various mechanisms (endocytosis & transcytosis).When come in contact with skin, these nanoparticles first penetrate the dermis, then translocate to regional lymph nodes via lymph. The uptake into sensory nerves is also probable. When ingested, they can show lymphatic uptake, and through blood circulation, they may reach the liver, spleen, heart, bone marrow, and other vital organs. The biokinetics & biologic activity of these NPs may depend on many parameters: shape, size, chemistry, surface properties (charge, area, porosity, weathering of coating, surface modifications), agglomeration state, dose and biopersistence.

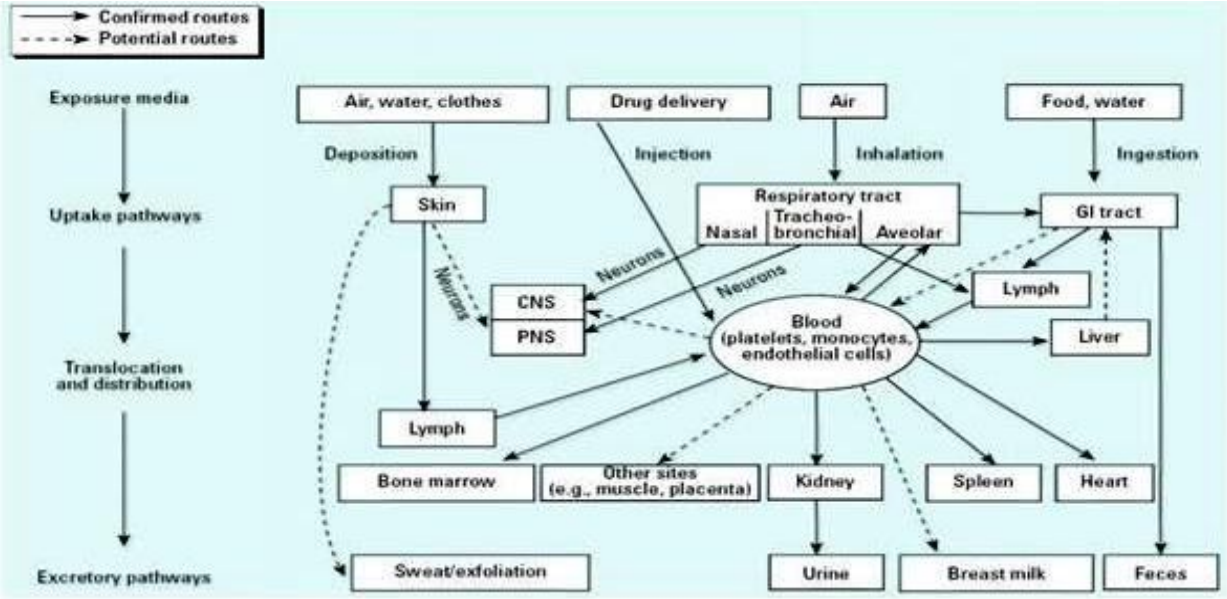

Figure 11: Biokinetics of Nanoparticles [98]

Entry Portals of Nanomaterials

Many natural as well as anthropogenic sources may lead to human exposures to these NSPs, the latter being either unintentional or intentional sources. Inhalation(respiratory tract) may be the most common route responsible for exposure to these NPs, yet ingestion (gastrointestinal

tract) and dermal(skin) exposures also may serve as important entry portals during manufacture, use & disposal of engineered NSPs. Specific biomedical applications (diagnostic and therapeutic) need these engineered NSPs to be taken up via intravenous, intramuscular or subcutaneous routes.

Deposition of NSPs in respiratory tract

Diffusion on collision with air molecules is mainly responsible for deposition of these inhaled NSPs in the respiratory tract. The electrostatic precipitation is involved in deposition only if the particles carry significant electrostatic charges. The distribution pattern of NSPs in the different respiratory tract regions will be dependent on their particle size. For 1-nm particle size, 90% deposition happens in the nasopharyngeal compartment, 10% deposition in tracheobronchial region, and no deposition in the alveolar region. Whereas, 5-nm particles show almost same deposition (~ 30%) in all three respiratory regions. 20-nm size particles display the maximum deposition in the alveolar region (~ 50%), with 15% deposition efficiency in the tracheobronchial and the nasopharyngeal regions each. The different deposition efficiencies will indicate the disposition to extra-pulmonary organs besides their potential effects.

Disposition of inhaled NSPs

The particles deposited in respiratory tract may adopt either classical clearance pathways (i.e., physical translocation through various mechanisms or chemical clearance processes) or neuronal uptake and translocation (i.e., the translocation pathway involving neuronal axons).

Exposure via Gastrointestinal and Skin Routes

NSPs can be ingested directly with food/water or when used drug delivery devices. Alternatively, they can enter the GI tract via mucociliary clearance mechanism of respiratory tract. Dermal exposure could be another important uptake route. Broken skin provides entry portal to even larger particles, and for the unbroken skin the epidermis becomes more permeable during flexion movements (wrist movements) [100].

Table 1: Various Entry Portals of Nanomaterials [99]

Portal of Entry	Cell/Tissue Type	Effect	Endpoint
Lung	Epithelium	Toxicity	Trypan blue, LDH, apoptosis
		Inflammation	Gene expression, oxidative stress, signal transduction pathways
		Translocation	Transfer of nanoparticles across membranes
		Carcinogenesis	Genotoxicity, comet, *hprt* & proliferation assays
	Macrophages	Toxicity	Trypan blue, LDH, apoptosis
		Chemotaxis	Chemotaxis assay
		Phagocytosis	Particle uptake into cells, cytoskeletal staining
		Inflammation	Gene expression, oxidative stress, signal transduction pathways
	Immune Cells	Immune response	Cytokine profile, adjuvant effects
	Endothelium	Inflammation	Adhesion molecules, oxidative stress
		Coagulation	Von Willebrand factor, tissue factor
	Fibroblasts	Inflammation	Oxidative stress, cytokine & gene expression profile
		Fibrosis	Collagen synthesis, cell proliferation
		Translocation	Particles across membranes
		Fibrosis	Collagen synthesis
Skin	Cell systems (e.g. HEK)	Cytotoxicity Inflammation	Cell viability – MTT, neutral red, Cytokine profile
	Flow-through diffusion systems	Absorption	
	Isolated Skin Flap Model	Absorption, Cytotoxicity, Inflammation	Glucose utilization, any other markers depending on end points (cytokine profiles, histopath, etc.)
Mucosa	Buccal, Intestinal &Vaginal epithelium	Cytotoxicity	Cell viability – MTT, neutral red, trypan blue Apoptosis
		Inflammation	Cytokine profile, oxidative stress, signal transduction pathway

	Translocation	Permeability assays
GALT	Inflammation	Cytokine profile, oxidative stress
	Immune response	Adjuvant effects

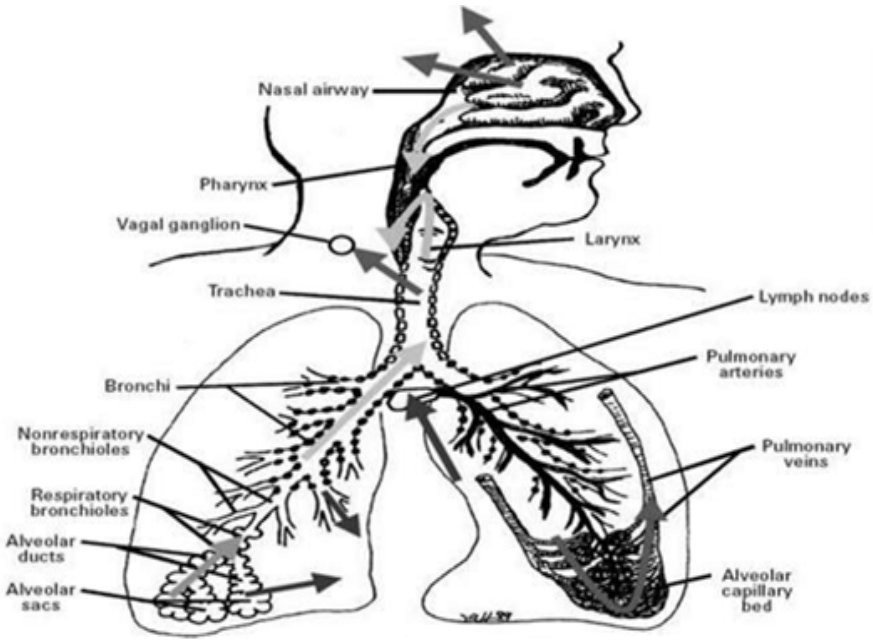

Figure 12: Pathways of particle disposition through respiratory tract [98]

Reactive oxygen species in NPs toxicity

On concomitant exposure to UV light or transition metals the nanoparticles have been shown to produce reactive oxygen species (ROS) [101] [102]. It has also been shown that NSPs of different sizes and various chemistries preferentially mobilize to mitochondria, a redox active organelle altering ROS production. The exact mechanism for the production of ROS by these nanoparticles is not clear yet, but suggested mechanisms could include photo-excitation to give rise the free electrons, metabolism to create intermediates having high redox potentials, and *in vivo* inflammatory responses inducing macrophages to release oxy-radicals. Further studies may elucidate more possible mechanisms of NP toxicity [103] [104] [105].

Exposure dose–response considerations

While studying toxicological effects of inhaled nano to fine solid particles, dose–response relationships with better fit were demonstrated when dose calculated on the surface area basis

not the mass basis was indicated[106] [107] [108].Besides the particle mass, their number or tremendous surface area, dose-level also holds important significance in nanoparticles' toxicity evaluations. In general practice the primary cell lines are exposed to very high doses *in vitro* without any consideration of actual *in vivo* exposure levels. The mechanistic pathway operating at the realistic low dose levels are most probable to be different from those operating at very high dose levels in vitro. Therefore, a combination of in vivo and in vitro studies with justified dose levels would provide logical and precise information on the NPs' toxicity and their mode of action.

Nanoparticles in environment

NPs can enter the environment in the form of manufacturing effluent or spillage during handling. These NPs can also enter the environment from washing off of personal-care products, e.g., cosmetics [109]. Some of the nanoparticulate materials have tendency to be worn off with use. The NSPs show sorption and get immobilized onto sediment & soil particles as they possess a high surface area to mass ratio [110]. Biologic transport could also happen from ingested sediments & the food chain.

SUMMARY AND OUTLOOK

Nanotechnology opens tremendous opportunities for therapeutic as well as diagnostic applications. However, during the life cycle (manufacturing, usage & disposal) of such products, it is probable that they get introduced in the environment, and there is no established method to examine their ecotoxicologic effects till now. And it also becomes necessary to determine the stability of surface modifications & coatings of these NPs both *in vivo &* in ecologic settings too. But the scarcity of toxicological data on these NPs hinders adequate risk assessment & it could also result in a precautionary secession of nanotechnology based research. However, the precautionary principle to halt nanotechnology based research is not justifiable. Instead, there is a need to strive for a sound balance between future nanotechnological developments and the research required to identify potential hazards and thorough risk assessment.

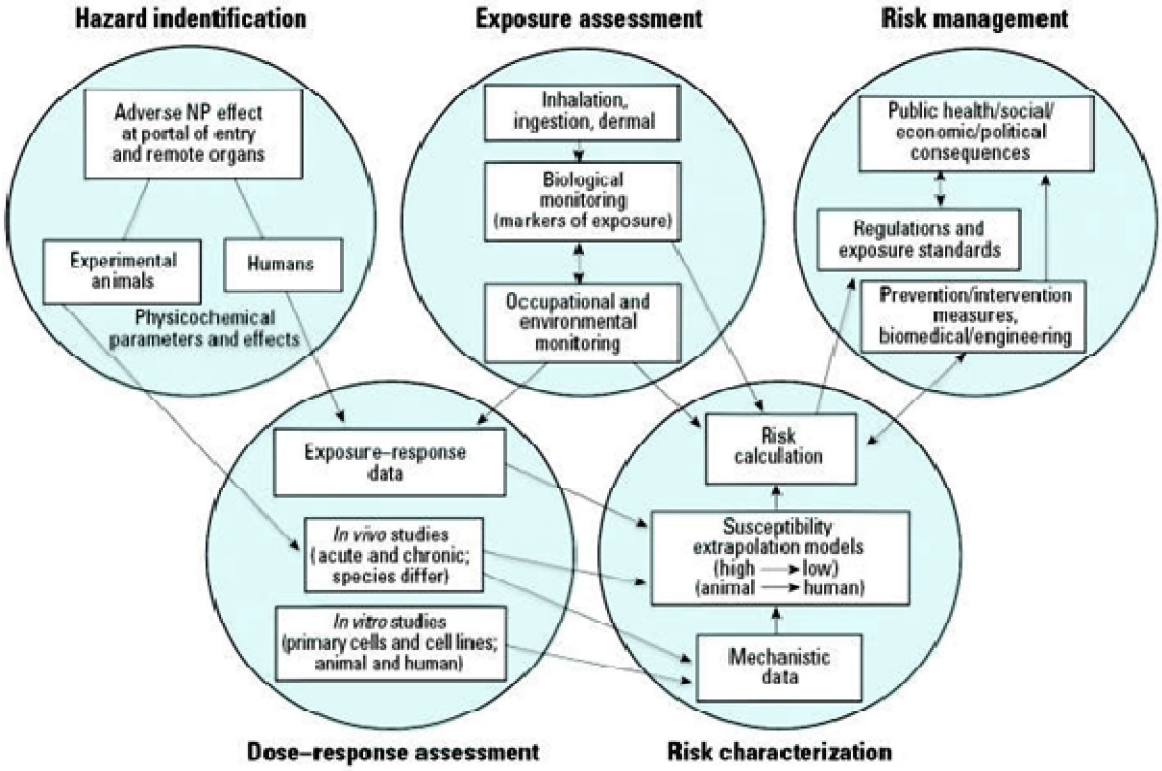

Figure13: Risk Assessment/Risk Management[98]

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