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Futuristic and potential phase of nanomedicine

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ABSTRACT

Nanomedicine characterizes an innovative field, with immense potential for improving and exploring an offshoot of nanotechnology. This refers to a highly precise medical intervention, at the molecular scale, for curing diseases and repairing the damaged tissues. Utilities of nanotechnology in biomedical sciences, implies to the creation of new material and devices, designed to interact with the body, at sub-cellular scales with a higher degree of specificity. This could be thus, potentially translated into targeted cellular and tissue-specific clinical applications, and aimed at maximal therapeutic effects with relatively minimal adverse-effects. Nanomedicine, thus offers an impressive resolution for various life threatening diseases. The areas expected to be benefited the most, includes cancer, diseases of the cardiovascular system, the lungs, blood, neurological particularly the Neuro-degenerative diseases, diabetes, inflammatory/infectious diseases etc. The future products of this new discipline, shall enable engineering of molecularly precise structures, microscopically small, so called agents of change, with the application to medicine via exploiting carefully the structured nanoparticles, includes dendrimers, carbon nanotubes, carbon fibers, quantum dots and vesicular approach, principally aimed to target specific tissues and organs. However, as this technology matures into complex nano-structured devices evolved as nanorobots. Considering revolutionary approach, these shall be able to travel even through the body searching out and clearing up diseases. This manuscript highlighted various novel techniques that could be deployed as multistage drug delivery, designed as nanocarrier, aimed at overcoming numerous biological barriers involved in drug delivery, Thus promises an exciting revolution in health care and medical nano technology, thereby emerging as a huge, on the prospect.

KEYWORDS

Nanomedicine;
Nanoparticles;
Dendrimers;
Nanotubes;
Nanorobots.

INTRODUCTION

The expansion of nanotechnologies is the commencement to revolutionize the rudiments of diagnosis, prevention and treatment of disease. These innovations, referred to as nanomedicines having the impending characters to turn molecular discoveries arising from the field of genomics and proteomics into prevalent benefits including nanoparticles that act as biological mimetics, polymeric nanoconstructs as biomaterials and nanoscale

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microfabrication-based devices, sensors and laboratory diagnostics[1]. Nanotechnology can be defined as the technology in the design, depiction, synthesis and application of materials, structures, devices and systems by controlling shape and size at nanometer scale. With the ability to work on the atomic and molecular echelon to craft and employ materials, structures, devices and systems with essentially new chattels. Scientifically, nanotechnology is employed to describe materials and systems with structures and components exhibiting new and significantly improved physical, chemical and biological properties as well as the phenomena and processes enabled by the ability to control properties at nanoscale. This change in properties is due to increase in surface area and dominance of quantum effects which is associated with very small sizes and large surface area to volume ratio for example Copper which is opaque at the macroscale becomes transparent at nanoscale, while platinum which is inert becomes a catalyst at nanoscale Stable aluminium is combustible in nano state and so on. There is a vast collection of intriguing nanoscale particulate technologies capable of targeting different cells and extracellular elements to deliver drugs, genetic materials, and diagnostic agents specifically. This article vitally assesses key feature of nanoparticulate design and engineering, as well as recent advancements in such nanoscale delivery technologies[2,3]

CHALLENGES

Some of the challenges of most drug delivery systems include solubility, intestinal absorption, poor bioavailability, *in vivo* stability, continued and targeted delivery to site of action, therapeutic effectiveness, side effects, and plasma fluctuations of drugs which moreover fall below the minimum effective concentrations or go beyond the safe therapeutic concentrations. Though, nanotechnology in drug deliverance is an approach intended to overcome these challenges due to their development and fabrication of submicron or nanoscale which are mainly polymeric and have multiple advantages of having the capability to defend drugs encapsulated within them from hydrolytic and enzymatic degradation[2,4,5]. Targeting the delivery of a wide range of drugs to various areas of the body for sustained release and thus is able to deliver drugs, proteins and genes through the peroral route of administration they can easily bypass the liver, thereby preventing the first pass metabolism of the incorporated drug. They increase oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a longer time, releasing the incorporated drug in a sustained and continuous manner leading to less plasma fluctuations thereby minimizing side-effects caused by drugs[5,6]. For targeted delivery, nanostructures can be conjugated with

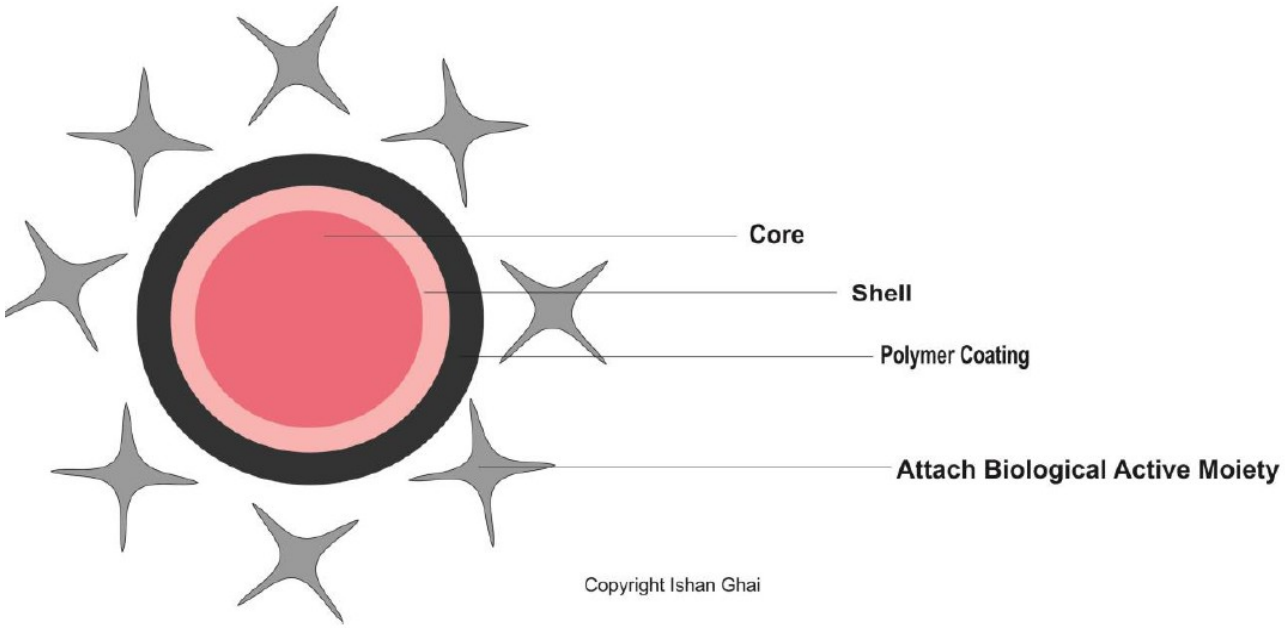

Figure 1 : Structural depiction of nano crystal size ranging in between 10-25 nm

targeting moieties such that the linkage between the polymer and the active substance can be manipulated to control the site and duration at which the drug is released. The linkage may be achieved by incorporation of amino acids, lipids, peptides or small chains as spacer molecules[7-9]. Drug targeting is crucial in chemotherapy, where a drug delivery system can target only the malignant tumor while shielding the healthy cells from a uniform distribution of chemotherapy in the body and their harmful effects[10-12]. The use of nanostructures such as polymeric nanoparticles is a non-invasive approach of penetrating the blood brain barrier for management of neurodegenerative disorders, cerebrovascular and inflammatory diseases[1,2,12]. Nanotechnology is strategic in developing drug delivery systems which can expand drug markets. Nanotechnology can be applied to reformulate existing drugs thereby extending products' lives, enhance their performance, improve their acceptability by increasing effectiveness, as well as increase safety and patient adherence, and ultimately reduce health care costs. Nanotechnology may also enhance the performance of drugs that are unable to pass clinical trial phases. It provides drug delivery carriers[5,13], as well as treatment and management of chronic diseases which include cancer, diabetes etc.

THE POTENTIAL LOOM OF NANOTECHNOLOGY IN NANOMEDICINE

Nanotechnology is beginning to change the scale and methods of vascular imaging and drug delivery. nanoscale technologies will begin yielding more medical benefits including the development of nanoscale laboratory-based diagnostic and drug discovery platform devices such as nanoscale cantilevers for chemical force microscopes, microchip devices, nanopore sequencing, etc. These outline the foundation of multifaceted interactions inherent to the fingerprint of a nano vehicle and its microenvironment.

Nanopore sequencing

This is an ultra-rapid method of sequencing based on pore Nanoengineering and assemblage. A small electric potential draws a charged strand of DNA through a pore of 1–2 nm in diameter in a hemolysin protein complex, which is inserted into a lipid bilayer sorting out two conductive compartments. The current and time profile is recorded and are translated into electronic signatures to recognize each base[14-16]. This technique can sequence more than 1000 bases per second and has much potential for the detection of single nucleotide polymorphisms, and for gene diagnosis of pathogens.

Cantilevers with functioned tips

The enhanced spatial, force and chemical resolution of the atomic force microscope (AFM) and chemical force microscope can be taken into advantage for designing nanoscale diagnostic assays. The AFM probes intramolecular forces between a very fine and functioned silicon or single-walled carbon nanotube tip, located at the end of a small cantilever beam, and a surface. The probe is attached to a piezoelectric scanner tube, which scans the probe across a selected area of the sample surface.[14,17,18] Interamolecular and intraatomic forces between the tip and the sample cause the cantilever to deflect; the cantilever deflection is then measured by a laser light reflected from the back of the cantilever to a detector. The tip can be chemically modified in order to probe a molecular structure of interest in drug discovery and measure biochemical interactions such as those between antigens and antibodies[15].

Microchips based drug delivery

These are micro fabricated devices allow controlled release of single or multiple drugs on demand and are chiefly useful for long-term treatment of conditions requiring pulsatile drug release after implantation in a patient[18,19]. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering micro reservoirs which are filled with drugs.

Nucleic acid lattices and scaffolds

Programming of Deoxyribose nucleic acid to self-assemble into an array of remarkable nanometer-scale structures into a different from of double helix. Stick cube, a construct shaped like a cube formed from sticks, and truncated DNA octahedron are two examples. For instance, the cube self-assembles from DNA fragments that are deliberate to adhere to one another. The free ends are associated by ligases, resultant a six closed loops[14,15], one for each face of the cube. Due to the

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helical nature of DNA, each of these loops is twisted around the loops that flank it, thus ensuring that the cube cannot come apart. Such scaffolds and assemblies can hold biological molecules in an ordered array for x-ray crystallography[18-22]. This approach could be particularly useful for those materials that do not form or possess a regular crystalline structure on their own.

Nanofibers as biomaterials

By means of applying molecular self-assembly, nanofibers of a variety of arrangement and chemistries can be formed. These may be designed to present high densities of bioactive molecules such as those which support cell adhesion and growth[18-20].

Carbon nanotubes

Carbon nanotubes are a type of nanotechnology consists of graphite sheets rolled up into a tubular form and can be obtained either as single nanotubes containing a single graphene sheet with the diameter varying between 0.5–3.0 nm and multi-walled nanotubes containing forms from several concentric graphene sheets[2,22]. The diameter and the length of single-walled nanotubes with the diameter between 20–1000 nm. The corresponding dimensions for multi-walled nanotubes are in the range between 1.5–100 nm and 1–50 nm, correspondingly. Carbon nanotubes can in fact cross the cell membrane as 'nanoneedles' without disturbing or disrupting the membrane and confine into mitochondria and cytosol[25-27]. They can be made water soluble by surface fictionalization. Molecular and ionic migration through carbon nanotubes offers opportunities for fabrication of molecular sensors and electronic nucleic acid sequencing. A number of carbon nanotubes derivatives, such as tris-malonic acid derivative of the fullerence C60, express superoxide dismutase mimetic properties and are protected in cell culture and animal models of injury example degeneration of dopaminergic neurons in Parkinson's diseases and nervous system ischemia.

Quantum dots

These are nano-scale crystalline structures made from a variety of different multifaceted compounds Figure 02. such as cadmium selenide, that can transform the color of light. Quantum dots absorb white light and then re-emit it a couple of nanoseconds later at a specific wavelength. By varying the size and composition of quantum dots, the emission wavelength can be tuned from blue to near infrared. For example, 2nm quantum dots luminesce bright green, while 5nm quantum dots luminesce red[28-33]. Quantum dots have greater flexibility, when compared to other fluorescent materials, and this makes them suitable for use in building nano-scale computing applications where light is used to process information[34-37]. These structures offer new capabilities for multi-color optical coding in gene expression studies, high throughput screening, and *in vivo* imaging.

Dendrimers

These are highly branched macromolecules Figure

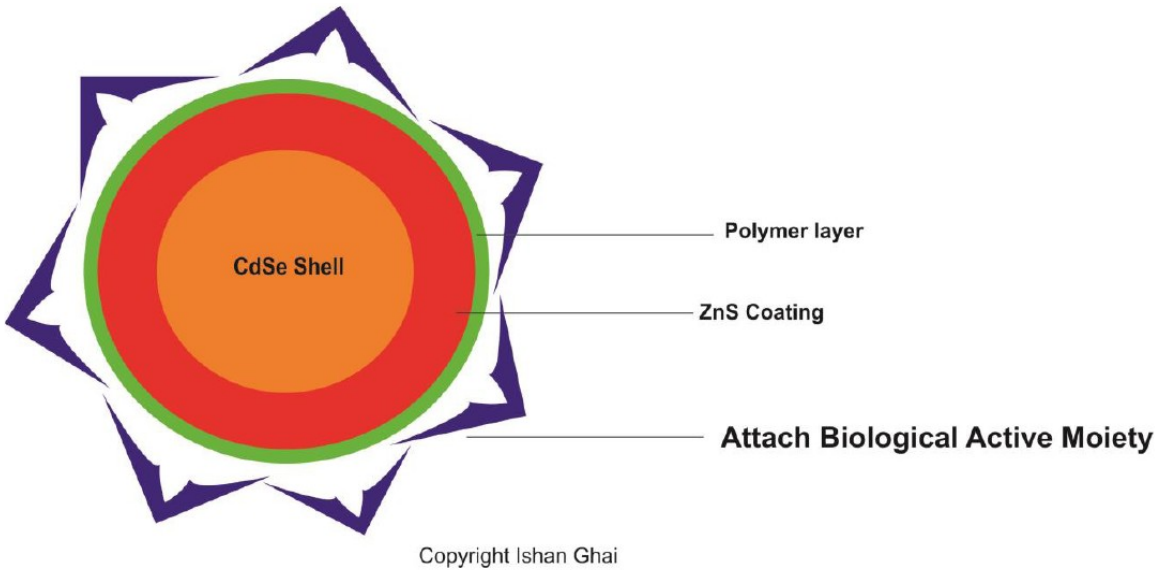

Figure 2 : Structural depiction of quantum dot with CdSe core, ZnS coating and size ranging in between 10-15 nm

03. with controlled near monodisperse three-dimensional architecture emanating from a central core[6,18,19]. Polymer growth starts from a central core molecule and growth occurs in an outward direction with a series of polymerization reactions. Hence, precise control over size can be achieved by the extent of polymerization, starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are acquiescent to adjust and can be tailored for specific applications. Therapeutic and diagnostic agents are usually attached to surface groups on dendrimers by compound alteration[38,39].

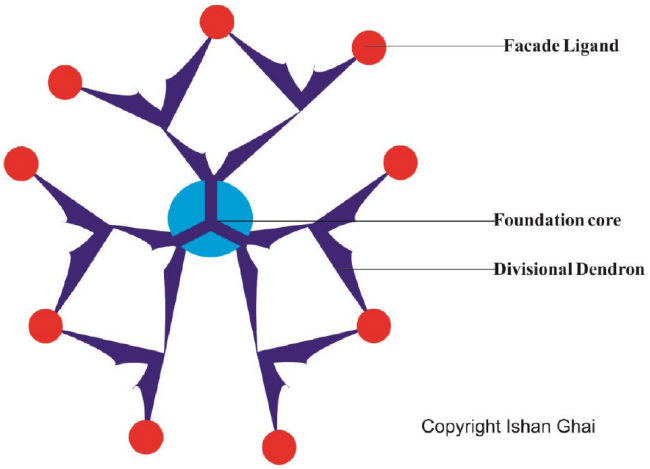

Figure 3 : Diagrammatically representation of basic components of a dedrimer

Polymeric micelles

Micelles are formed in solution as aggregates in which the component molecules (e.g., amphiphilic AB-type or ABA-type block copolymers, where A and B are hydrophobic and hydrophilic components, respectively) are generally arranged in a spheroidal structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups[20]. These dynamic systems, which are usually below 50 nm in diameter, are used for the systemic delivery of water-insoluble drugs. Drugs or contrast agents may be trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle[40-45].

Liposomes

These are closed vesicles that form of hydration of dry phospholipids above their transition temperature. Liposomes Figure 01 are classified into three basic types based on their size and number of bilayers. Multilamellar vesicles consist of several lipid bilayers separated from one another by aqueous spaces. These entities are heterogeneous in size, often ranging from a few hundreds to thousands of nanometers in diameter. On the other hand, both small unilamellar vesicles and large unilamellar vesicles consist of a single bilayer surrounding the entrapped aqueous space. small unilamellar vesicles are less than 100 nm in size whereas large unilamellar vesicles have diameters larger than 100 nm. Drug molecules can be either entrapped in the aqueous space or intercalated into the lipid bilayer of liposomes, depending on the physicochemical characteristics of the drug. The liposome surface is amenable to modification with targeting ligands and polymers. Other conventional vesicular approaches employed are Niosomes these are microscopic size vesicles composed of a bilayer of non-Ionic surface active agents. Proteosomes these are the vesicles containing high molecular weight enzyme complexes with catalytic activity. Genosomes these are the vesicles with macromolecular complex for functional

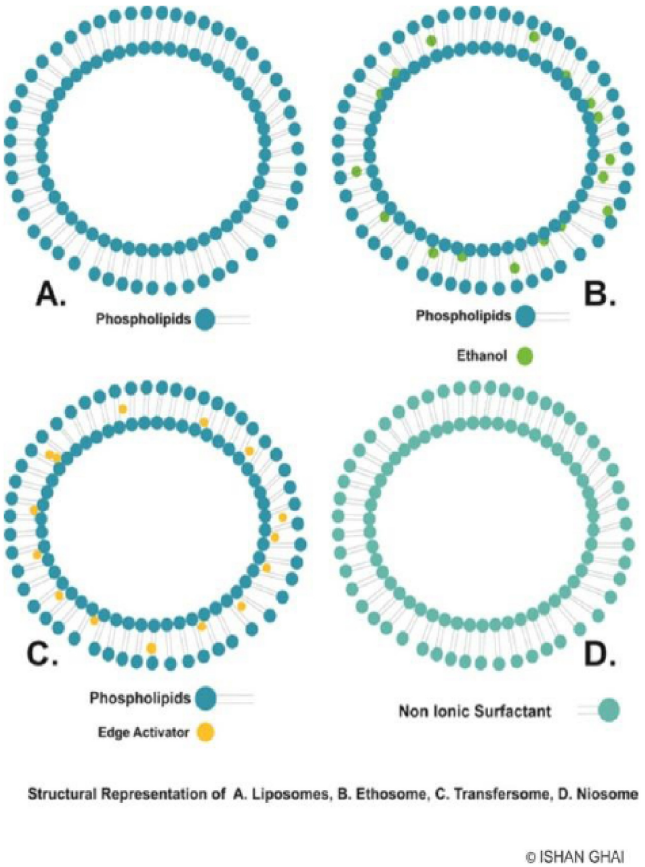

Figure 4 : Structural representations of different vesicular approaches

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gene transfer using cationic lipids. Ethosomes they are the Lipid malleable vesicles composed of a phospholipid, ethanol and water for targeted delivery in the skin. Cryptosomes Lipid vesicles with a surface coating composed of Phosphatidyl ethanolamine employed in ligand mediated drug targeting Emulsomes These are the nanosized lipid particles consisting of a microscopic lipid assembly with a polar core. Discomes These are the niosomes solublized with non-Ionic surfactant solutions for ligand mediated drug targeting. Sphinosomes These are the concentric, bilayered vesicles with an aqueous volume enclosed by a membrane of a lipid bilayer composed of natural or synthetic sphingolipid[46-52].

Nanospheres

These are spherical objects, ranging from tens to hundreds of nanometers in size, consisting of synthetic or natural polymers example collagen, albumin etc. The drug of interest is dissolved, entrapped, attached or encapsulated throughout and within the polymeric matrix[53-55]. Depending on the method of preparation, the release of a drug is characterized and can be suitably controlled. This technology also allows precision surface modification of nanospheres with polymeric and biological materials for specific applications or targeting to the desired locations in the body.

Aquasomes (carbohydrate-ceramic nanoparticles)

These are spherical particles used for drug and antigen delivery. The particle core is composed of nanocrystalline calcium phosphate or ceramic diamond with the size of the particle ranging between 60–300 nm, and is covered by a polyhydroxyl oligomeric film. Drugs and antigens are then adsorbed on to the surface of these particles[19,24].

TABLE 1 : Futuristic approach of nanotechnology towards nanomedicine

Unprocessed Nanomaterials	Nanoparticle coatings
	Nanocrystalline materials
Nanostructured materials	Cyclic peptides
	Detoxification agents
	Drug encapsulation
	Fullerenes
	Functional drug carriers Smart drugs
	MRI scanning (nanoparticles)
	Nanobarcodes
	Molecular medicine
	Nanoemulsions
	Nanoshells
Synthetic binding sites	Artificial antibodies
	Artificial enzymes
	Artificial receptors
	Molecularly imprinted polymers
Control of surfaces	Artificial surfaces-adhesives
	Artificial surfaces—nonadhesive
	Artificial surfaces—regulated
	Biocompatible surfaces
	Biofilm suppression
	Engineered surfaces
	Pattern surfaces (contact guidance)
	Thin-film coatings
	Immunoisolation
	Molecular sieves and channels
Cell simulation and analysis	Cell chips,
	Cell stimulator
DNA manipulation, sequencing and diagnosis	Genetic testing
	DNA microarrays
	Ultrafast DNA sequencing
	DNA manipulation and control
Tools and diagnostics	Bacterial detection systems
	Biochips
	Biomolecular imaging
	Biosensors and biodetection
Diagnostic and defense applications	Endoscopic robots and microscopes
	Fullerene-based sensors
	Imaging (cellular, etc.)
	Monitoring
	Lab on achip
	Nanosensors
	Point of care diagnostics
	Protein microarrays
	Scanning probe microscopy

	Intracellular devices
	Intracellular biocomputers
	Intracellular sensors/reporters
	Implants inside cells
	BioMEMS
	Implantable materials and devices
	Implanted Bio MEMS, chips, and electrodes MEMS/Nanomaterials-based
	Prosthetics
	Sensory aids (artificial retina, etc.)
	Microarrays
	Microcantilever-based sensors
	Microfluidics
	Medical MEMS
	MEMS surgical devices
Biological research	Nanobiology
	Nanoscience in life sciences
	Drug delivery
	Drug discovery
	Biopharmaceutics
	Drug encapsulation
	Smart drugs
Molecular medicine	Genetic therapy
	Pharmacogenomics
Artificial enzymes and enzyme control	Enzyme manipulation and control
Nanotherapeutics	Antibacterial and antiviral nanoparticles
	Fullerene-based pharmaceuticals
	Photodynamic therapy
	Radiopharmaceuticals
Synthetic biology and early nanodevices	Dynamic nanoplatform nanosome
	Tecto-dendrimers
	Artificial cells and liposomes
	Polymeric micelles and polymersomes
Biotechnology and biorobotics	Biologic viral therapy
	Virus-based hybrids
	Stem cells and cloning
	Tissue engineering
	Artificial organs
	Nanobiotechnology
	Biorobotics and biobots
	Nanorobotics
	DNA-based devices and nanorobots
	Diamond-based nanorobots
	Cell repair devices

Polyplexes

These are the nano assemblies also entitled as lipopolyplexes, which form spontaneously between nucleic acids, polycations and cationic liposomes that are conjugated to targeting ligands and hydrophilic polymers, used in transfection protocols. The shape, size distribution, and transaction capability of these complexes depends on their composition and charge ratio of nucleic acid to that of cationic lipid/polymer[20,24].

APPLICATIONS OF NANOTECHNOLOGY AS AN ADVANCE NANOMEDICINE

Nanoparticles with inherent diagnostic properties

The aim of nanomedicine may be broadly defined as the comprehensive monitoring, repairing and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures to achieve medical benefit with an opportunity to build a broad range of economically complex molecular machines resulting in edifice of computer controlled molecular tools much smaller than a human cell with the accuracy and precision of drug molecules. Such tools will allow medicine, for the first time to intervene in a sophisticated and controlled way devoted to the manipulation of atoms and molecules leading to the construction of structures in the nanometer scale[30-32]. For instance Colloidal gold, iron oxide crystals, and quantum dots, semiconductor nanocrystals are some of the examples of nanoparticles, whose size is generally in the region of 1–20 nm, and have diagnostic applications in biology and medicine. Gold nanoparticles have application as quenchers in fluorescence resonance energy transfer measurement studies. These technologies have proven very successful in monitoring gene expression to detect pathologies such as cancer, brain inflammation, arthritis, atherosclerotic plaques etc. Quantum dots can label biological systems for detection by optical or electrical means in vitro and to some extent in vivo[33-35,56]. Their fluorescence emission wavelength can be tuned by varying the particle size, thus they have the potential to revolutionize cell, receptor, antigen, and enzyme imaging. Unquestionably, application of such optical nanotools may eventually aid our understanding

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of the complex regulatory and signaling networks that govern the behavior of cells in normal and disease states.

Nanomedicine in cancer management

At a cellular level, cancerous tissues are typically different from normal tissues. As they change the chemicals on their surface, and are consequently easy to recognize. However, most of them grows faster and change their shape and involves a genetic change that causes a difference in the chemicals inside the cell. The immune system takes advantage of surface markers to destroy cancer cells; but this is not enough to keep us cancer-free By employing Nanobots as a for treatment have shown several advantages likewise they can physically enter cells and scan the chemicals inside as they have on board computers that allow them to do calculations which are not available to immune cells, nanobots can be programmed and deployed after a cancer is diagnosed, whereas the immune system is always guessing about whether a cancer exists. Nanobots can also scan each of the body's cells for cancerous tendencies, and subject any suspicious cells for careful analysis; if a cancer is detected, they can wipe it out quickly, using more focused and vigorous tactics than the immune system is designed for. Given such molecular tools, a small device can be designed to identify and kill cancer cells. The device would have a small computer, several binding sites to determine the concentration of specific molecules, and a supply of some poison which could be selectively released and able to kill a cell identified as cancerous. The device would circulate freely throughout the body and would periodically sample its environment by determining whether the binding sites were occupied or not. Occupancy statistics would allow determination of concentration. Today's monoclonal antibodies are able to bind to only a single type of protein or other antigen, and not proved effective against most cancers[57-60].

Nanomedicine as drug carter

There are numerous engineered constructs, assemblies, architectures, and particulate systems, whose unifying feature is the nanometer scale size range ranging from a few to 250 nm and often carry drug with them for targeted and specific delivery of drug. These include polymeric micelles, dendrimers, polymeric and ceramic nanoparticles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes, and vesicular delivery example liposomes. These can easily overcome drug solubility issues, particularly with the view that large proportions of new drug candidates emerging from high-throughput drug screening initiatives their reduced particle size entails high surface area and hence shows a strategy for faster drug release[61-66]. Such approaches, may enhance detection sensitivity in medical imaging, improve therapeutic effectiveness, and decrease side effects. Some of the carriers can be engineered in such a way that they can be activated by changes in the environmental pH, chemical stimuli, by the application of a rapidly oscillating magnetic field, or by application of an external heat source. Such modifications offer control over particle integrity, drug delivery rates, and the location of drug release, for example within specific organelles. Some are being designed with the focus on multifunctionality; these carriers target cell receptors and delivers simultaneously drugs and biological sensors. Some include the incorporation of one or more Nanosystems within other carriers, as in micellar encapsulation of quantum dots[37].

For the management of disease

Due to emergence of antibiotic-resistant strains of microorganisms the medicine cannot do much potential attack against them. There are many kinds of parasites that may need individual medical techniques. The effective dealing of our body immune response with most infections needs to learn about it by experience. It is generally more effective at fighting organisms that it can recognize on a molecular level. Some diseases, such as Ebola, progress too rapidly for the immune system to respond. Syphilis survive by being stealthy and by surrounding it with the chemicals of the body to camouflage itself. Herpes splice itself into the genes of the body's cells, so the immune system cannot detect it and wipe it out. HIV directly attacks the immune system[67] Development of Nanobots has several advantages over the immune system. They will not be susceptible to attack by natural pathogens and have the computational resources unavailable to immune cells. They can be programmed to find and fight diseases they have never encountered. Likewise, the system can be activated based on external knowledge of the likelihood of a disease.

Nanotech will provide more options for cleaning up after a disease, since corrupted genes will be repairable without killing the affected cell[68-71].

Management of Traumatic healing

Nanobots embedded in a tissue can strengthen it against tearing, or repair once it is torn. It is common for a blow to the head to rattle the brain against the skull; a specially shaped nano-built device could cushion the brain, preventing this damage. Other devices could vacuum up common poisons before they could cause damage, or barricade poisoned areas to keep the poison from spreading through the body. 'Respirocytes' the artificial red blood cells could the body to function normally for several minutes without breathing or blood circulation, giving more opportunity to restore normal functioning. In cases of extreme injury, heterostasis could be used to stabilize the body until help can arrive. As long as the brain is not physically damaged, it can be functionally separated from the body and forced into a low-power state[72-75].

Drug targeting

The network of blood and lymphatic vessels investing the body provides natural routes for the distribution of nutrients, clearing of unwanted materials, and delivery of therapeutic agents. Superficially, however, this network appears to provide little in the way of obvious controlled and specific access to tissues, and the science of these processes has been scant. Regardless of these limitations, nanoparticulate systems provide possibilities for access to cell populations and body compartments. When injected intravenously, particles are cleared rapidly from the circulation and predominantly by the liver and spleen macrophages[65,66]. This site-specific, but passive, mode of clearance is a facet of the immune cells' primary scavenging role for particulate invaders and self-effete products. This is particularly important with the view that macrophages are heterogeneous with respect to phenotype and physiological function, even within the same tissue. Hence, a particular population of phagocytes may employ one predominant recognition mechanism. The dynamic process of protein adsorption together with deposition of a variety of opsonic factors onto the surface of nanoparticles may indicate an arrangement based on a recognition hierarchy, or cooperativity, among macrophage receptors for clearance. Indeed dendrimers and QDs are well known to flocculate in biological media[76]. Another case is the interaction between certain lipid-based Nanosystems and lipoproteins leading to dramatic size changes[75].

Nanomedicine in homological disorders

Many diseases, from heart strokes to sepsis and metastasizing cancer, involve the blood in some way. An aggressive nanomedical device, a Vasculoid which could replace the blood volume and take over its functions by lining the entire vascular system with a multi-segmented robotic system. In addition to preventing many diseases, and limiting the scope of others e.g. poisoning this system is a single, complex, multi-segmented nanotechnological medical robotic system capable of duplicating all essential thermal and biochemical transport functions of the blood, including circulation of respiratory gases, glucose, hormones, cytokines, waste products, and cellular components[18,76].

Nanomedicine in endocytic delivery

Breaching of the endosomal membrane is particularly important for priming MHC class I-restricted cytotoxic T lymphocyte responses, for survival of genetic materials against nuclease degradation in the lysosomal compartment.[58,64,60] for those drugs that must reach the cytoplasm in sufficient quantities as for treatment of cytoplasmic infections or reaching nuclear receptors after endocytic delivery with nanoparticulate carriers[77-80].

ANTAGONISTIC EFFECTS OF NANOMEDICINE

Nanocarriers may overcome solubility or stability issues for the drug and minimize drug-induced side effects. But there could be significant toxicity issues associated with the nanocarriers themselves, which requires resolution. Over the past couple of years, a number of toxicology reports have demonstrated that exposure to nanotechnology derived particles pose serious risks to biological systems. For example, exposure of human keratinocytes to insoluble single-wall carbon nanotubes was associated with oxidative stress and

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apoptosis.[18,19] The issue of toxicity becomes even more serious for intravenously injected nanoparticles, as size partly determines tissue distribution. Thus, what is the ultimate fate of nanocarriers and their constituents in the body, and particularly those which are not bio-degradable such as functionalized carbon nanotubes and coating agents such as poly ethylene glycol these constituents or their degradation products exert untoward immunological and pharmacological activities these polymeric vectors used for gene delivery as well as other polymer-based biomaterials interfere with cellular machineries or induce altered gene expression[12,23].

Cell bereavement and distorted gene expression

Recent evidence is drawing attention to some of the above questions, but investigation in this avenue of research is scant. For example, though much has been made of the promise of cadmium selenide QDs in imaging, little is known about their metabolism and potential deleterious effects. However, cadmium selenide QDs are lethal to cells under UV irradiation, as this release highly toxic cadmium ions. Some polymeric micelles depending on the nature of their monomer constituents, can induce cell death via apoptosis or necrosis, or both. Differential gene expression has been reported in certain cells after cisplatin delivery with polymeric micelles when compared with that of free cisplatin treatment. Degradation products arising from poly (L-lactic acid) particles show cytotoxicity, at least, to immune cells, thus rising concern over their application for sustained cytosolic drug release[37,76,23]. A very clear warning is evident from the poor success in human gene therapy with viruses. Although, viral vectors are extremely efficient delivery systems for nucleic acids, they can induce severe immunotoxicity as well as inadvertent gene expression changes after random integration into the host genome. These issues have generated a surge in the design and engineering of synthetic polycationic nonviral gene transfer systems.

Pseudo allergy and idiosyncratic response

Another potential pitfall associated with nanocarrier infusion into human subjects is the generation of non-IgE-mediated signs of hypersensitivity. These reactions are idiosyncratic and are believed to be secondary to complement activation, and presumably are a reflection of an individual's immune cell sensitivity to complement-derived mediators. Hypersensitivity can be ameliorated by slowing the rate of infusion or by patient premedication, and often fails to appear in the repeat administration of the nanocarrier. Idiosyncratic reactions occur after infusion of stealth systems, such as poly ethylene glycol grafted liposomes[80]. Refined surface engineering may eventually eliminate such side effects, for example by better polymer design, linkage modification, controlling the conformation and packing of grafted polymers and/or by introducing complement regulatory proteins or inhibitors on to the nanoparticle surface. However, the ultimate goal is to understand the molecular mechanism of complement activation related pseudo allergy, which operates in a small population of individuals.

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