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Review Article

GLIMPSES OF CURRENT ADVANCES OF NANOTECHNOLOGY IN THERAPEUTICS

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ABSTRACT

Nanotechnology is the science that deals with the processes that occur at molecular level and of nanolength scale size. There are numerous examples from nature like DNA, water molecules, virus, red blood corpuscles (RBC) etc., which are of nanodimensions. Recent developments in nanotechnology offer researchers opportunities to significantly transform various therapeutics. This technology has enabled the manipulation of the biological and physicochemical properties of nanomaterial to facilitate more efficient drug targeting and delivery. The size of nanomaterial is similar to that of most biological molecules and structures; therefore, nanomaterial can be useful for both *in vivo* and *in vitro* biomedical research and applications. Clinical investigations suggest that therapeutic nanoparticles can enhance efficacy and reduced side effects compared with conventional therapeutic drugs. Nanotechnology is on its way to make a big impact in Biotech, Pharmaceutical and Medical diagnostics sciences. A dynamic collaboration is observed within the Researchers, Government, Pharmaceutical - Biomedical companies and educational institutions all over the world in developing the nanotechnology applications in advanced medicine and patient care.

Keywords: Nanotechnology, Nanoparticles, Nanosensors, Cancer Imaging, Drug Delivery.

INTRODUCTION

Nanotechnology is the science of the small; the very small. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently, and provide a variety of surprising and interesting uses**.** The prefix of nanotechnology derives from 'nanos' – the Greek word for dwarf. A nanometer is a billionth of a meter, or to put it comparatively, about 1/80,000 of the diameter of a human hair.

It is becoming increasingly important in fields like engineering, agriculture, construction, microelectronics and health care. The application of nanotechnology in the field of health care has come under great attention in recent times. There are many treatments today that take a lot of time and are also very expensive. Using nanotechnology, quicker and much cheaper treatments can be developed. By performing further research on this technology, cures can be found for diseases that have no cure today. Nanotechnology, when used with biology or medicine, is referred to as Nanobiotechnology.

The field of nanotechnology was first predicated by Professor Richard P. Feynman in 1959 (Nobel laureate in physics, 1965).[1] Nanotechnology has achieved the status as one of the critical research endeavors of the early 21st century, as scientists harness the unique properties of atomic and molecular assemblages built at the nanometer scale. Ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the capability to rationally design and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes.[2] New technologies using metal and semiconductor nanoparticles are also under intense development for molecular profiling studies and multiplexed biological assays.[3-6]

Recently functional nanoparticles have developed that are covalently linked to biological molecules such as peptides, proteins, nucleic acids, or small-molecule ligands.[7-14] Medical applications have also appeared, such as the use of superparamagnetic iron oxide nanoparticles as a contrast agent for lymph node prostate cancer detection [15] and the use of polymeric nanoparticles for targeted gene delivery to tumor vasculatures. [16, 17]

NANOTECHNOLOGY AND NANOPARTICLES

Nanotechnology is the willful manipulation of matter at the atomic and molecular level to create better and entirely new materials, devices and systems (0.1-100nm), Technology which takes advantage of the unique properties of the material when its particle size is in Nano scale.

Nanoparticles are defined as particles with at least two dimensions less than 100 nanometers.[18] 'Nanomedicine' is defined as submicron size (<1um) modules, used for treatment, diagnosis, monitoring, and control of biological system. Most side effects of drugs are a result of them not going to the desired locations in the body. Other adverse effects can be attributed to impure drugs. Often in making pharmaceuticals, undesired products resulting from the chemical reaction are mixed in with the desired product (the drug). Sometimes these are toxic and can cause health complications. [19] These two problems can be solved with nanotechnology. Nanocatalysts designed at the molecular level are more selective and will only make the drug molecule that is desired. [20]

Properties of Nanoparticles

The properties of materials can be different at the Nanoscale for two main reasons:

- Nanomaterials have a relatively larger surface area when compared to the same mass of material produced in a larger form. This can make materials more chemically reactive (in some cases materials that are inert in their larger form are reactive when produced in their Nanoscale form), and affect their strength or electrical properties.
- Quantum effects can begin to dominate the behavior of matter at the Nanoscale - particularly at the lower end - affecting the optical, electrical and magnetic behavior of materials.

APPLICATIONS OF NANOTECHNOLOGY

Bacterial and toxic detection

The sensitive detection of bacteria (*Mycobacterium avium* spp. *paratuberculosis* – MAP) can possible in milk and blood within 30 minutes, using dextran-coated iron oxide nanoparticles conjugated with antibodies that recognize surface proteins found on the bacteria. With this technology, one can potentially detect a single bacterium (1-10 CFU), under interference introduced by the presence of six different bacterial species (10^9 CFU). Utilizing magnetic nanosensors, one can target the development of toxin-specific nanosenors that can determine the presence of a particular toxin in environmental, food, and clinical samples. (Fig.1)

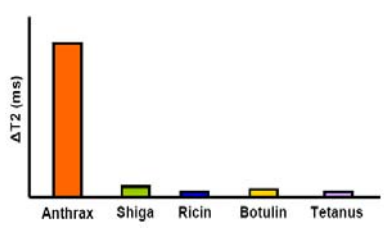

Fig. 1: Anthrax- toxin specific Nanosenors

Bacterial drug resistance assessment

Utilizing either gold or iron oxide nanoparticles, it is possible to assess bacterial drug resistance and identify the minimum inhibitory concentration (MIC) of an effective antibiotic within a couple of hours without compromising reliability. It is possible to achieve this by developing nanosensors that can monitor the bacterial metabolic activity, through the levels of free complex carbohydrates in the growing medium.

Cancer biomarker detection

Utilizing iron oxide nanoparticles, it is possible to assess the levels and enzymatic activity of telomerase, a key oncogene that is upregulated in most tumors leading to their immortalization due to aberrant continuous maintenance of the chromosomal telomeric repeats.

Table 1: Applications of various nanosystems in cancer therapy

Nanosystem	Applications in cancer therapeutics
Carbon nanotubes	DNA mutation detection, disease protein biomarker detection
Dendrimers	Controlled release drug delivery, image contrast agents
Nanocrystals	Improved formulation for poorly-soluble drugs
Nanoparticles	MRI and ultrasound image contrast agents, targeted drug delivery, permeation enhancers, reporters of apoptosis, angiogenesis, etc.
Nanoshells	Tumor-specific imaging, deep tissue thermal ablation
Nanowires	Disease protein biomarker detection, DNA mutation detection, gene expression detection
Quantum dots	Optical detection of genes and proteins in animal models and cell assays, tumor and lymph node visualization.

Cancer imaging

Researchers design biodegradable soft polymeric or polymer-coated fluorophore-encapsulating iron oxide nanoparticles for the targeted *in vitro* and *in vivo* imaging of cancer cells and tumoric lesions. These nanoparticles possess limited cytotoxicity, are stable in buffer solutions, and can be used for MRI, or near-infrared imaging using fluorescence molecular tomography.

Table 2: Approved Nanoparticles as imaging agents and drug carriers

Modality	Compound	Status	Use
Imaging Agents Endorem® Gadomer®	superparamagnetic iron oxide nanoparticle	Market	MRI agent
	Dendrimer-based MRI agents	Phase III clinical trial	MRI agent-cardiovascular
Drug delivery Abraxane®	Albumin nanoparticle containing paclitaxel	Market	Breast cancer

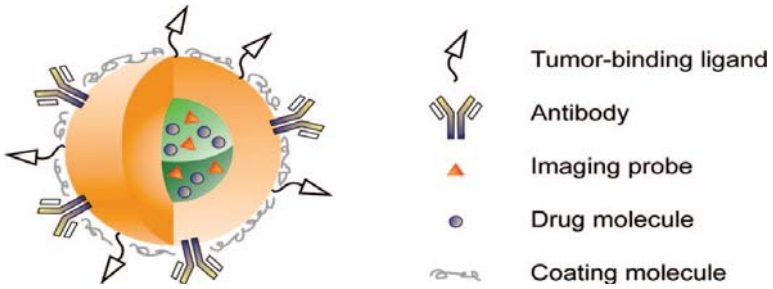

Fig. 2: Schematic of a multifunctional nanoparticle with imaging probes and/or anticancer drugs encapsulated inside and tumor-specific ligands and/or antibodies presenting on the surface

Nanotechnology in drug delivery

The use of nanotechnology in drug delivery in vivo is a rapidly expanding field. This is particularly important for cancer treatment, as most chemotherapy drugs are toxic to both normal and cancer cells. Nanotechnology offers solutions to these problems. For example, coating a drug in different molecules can make it more soluble in water (for easier application), allow it to penetrate cell membranes more easily or even target it to a specific tissue or organ. In addition, a new device such as iMEDD incorporates nanoscale pores which, by varying their size and length, control the release of drugs such as insulin. Such devices can be implanted and allow continued release of a drug over the period of weeks, thus avoiding the need for regular injections. Example of drugs that use nanotechnology for improved delivery include ABRAXANE which is a nanoparticle formulation of the chemotherapy drug paclitaxel and the protein albumin, and is more effective and less toxic than the free form of the drug.

Nanotechnology as biosensor and biolabels

Nanomaterials, which measure 1–1000 nm, allow unique interaction with biological systems at the molecular level. They can also facilitate important advances in detection, diagnosis, and treatment of human cancers and have led to a new discipline of nano-oncology. [22, 23] Traditionally, the most common cancer treatments were limited to chemotherapy, radiation, and surgery. Limitations in cancer treatment are a result of current challenges seen in established cancer therapies, including lack of early disease detection, nonspecific systemic distribution, inadequate drug concentrations reaching the tumor, and inability to monitor therapeutic responses. Poor drug delivery and residence at the target site leads to significant complications, such as multi-drug resistance.[24]

Nanotechnology in medicine

Diabetes mellitus

Polyethylcyanoacrylate nanospheres as biodegradable polymeric carriers have been found good for oral insulin delivery in streptozotocin-induced diabetic rat model.

Respiratory disorders

Polymeric nanoparticles with polylactide-co-glycolide have demonstrated clear advantages over traditional drug carriers in case of intermittent chemotherapy in experimental tuberculosis.

Ophthalmic disorders

Dendrimers have a potential for treatment of ocular disorders.

AIDS

VivaGel is an anti HIV drug based on dendrimer technology.

Table 3: Brief descriptions of nanotechnology in drug delivery [21]

Types of Nanosystems	Size	Characteristics	Applications
Polymeric Nanoparticles	10-1000 nm	Biocompatible, biodegradable, offer complete drug protection	Excellent carrier for controlled and sustained delivery of drugs. Stealth and surface modified nanoparticles can be used for active and passive delivery of bioactives.
Nanocrystals Quantum dots	2–9.5 nm	Semi conducting material synthesized with II-VI and III-V column element; Size between 10-100 Å; Bright fluorescence, narrow emission, Broad UV excitation and high photo stability	Long term multiple color imaging of liver cell; DNA hybridization, immunoassay; receptor mediated endocytosis; labeling of breast cancer marker HeR_2 surface of cancer cells
Carbon Nanotubes	0.5–3 nm diameter and 20–1000 nm length	Third allotropic crystalline form of carbon sheets either single layer (single walled nanotubes, SWNT) or multiple layer (multi-walled nanotube, MWNT). These crystals have remarkable strength and unique electrical properties (conducting, semi-conducting, or insulating)	Functionalization enhanced solubility, penetration to cell cytoplasm and to nucleus, as carrier for gene delivery, peptide delivery
Dendrimer	<10 nm	Highly branched, nearly monodisperse polymer system produced by controlled polymerization; three main parts core, branch and surface	Long circulatory, controlled delivery of bioactives, targeted delivery of bioactives to macrophages, liver targeting
Metallic nanoparticles	<100 nm	Gold and silver colloids, very small size resulting in high surface area available for functionalization, stable	Drug and gene delivery, highly sensitive diagnostic assays, thermal ablation and radiotherapy enhancement
Polymeric Micelles	10-100nm	Block amphiphilic copolymer micelles, high drug entrapment, payload, biostability	Long circulatory, target specific active and passive drug delivery, diagnostic value.
Liposome	50-100 nm	Phospholipid vesicles, biocompatible, versatile, good entrapment efficiency, offer easy	Long circulatory, offer passive and active delivery of gene, protein, peptide and various others.

Table 4: Applications of various nanosystems as biosensor and biolabels [25]

Nanosystem	Applications
Gold Nanoparticles	For ssDNA detection; in immunohistochemistry to identify protein-protein interaction
Iron oxide Nanocrystals	Monitor gene expression; detect the pathogens such as cancer, brain inflammation, arthritis and atherosclerosis
Nanopores	Sensing single DNA molecules by nanopores
Cantilever array	Diagnosis of diabetes mellitus, for detection of bacteria, fungi, viruses; for cancer diagnosis
Carbon nanotubes	Blood glucose monitoring; sensors for DNA detection
Nanowire	Electrical detection of single viruses and biomolecules
Nanoparticle-based biodetection	Detection of pathogenic biomarkers, Ultra-sensitive detection of single bacteria

Table 5: List of Companies that manufacture Nanoparticles

Company	Product
CytImmune:	Gold Nanoparticles for targeted delivery of drugs to tumors
Nucryst:	Antimicrobial wound dressings using silver nanocrystals
Nanobiotix:	Nanoparticles that target tumor cells
Oxonica:	Disease identification using gold Nanoparticles (biomarkers)
Nanotherapeutics:	Nanoparticles for improving the performance of drug delivery
NanoBio:	Nanoemulsions for nasal delivery to fight viruses
BioDelivery Sciences:	Oral drug delivery of drugs encapuslated in a nanocrystalline structure called a cochleate
NanoBioMagnetics:	Magnetically responsive nanoparticles for targeted drug delivery and other applications
Z-Medica:	Medical gauze containing aluminosilicate nanoparticles which help clot faster in open wounds

Table 6: Examples of targeted nanoparticles in preclinical and clinical development

Name	Targeting agent	Therapeutic agent	Status
FCE28069 [26]	Galactose	DOX	Phase I
MCC-465 [26]	F(ab')2 fragment of human antibody GAH	DOX	Phase I
MBP-426 [27]	Transferrin	Oxaliplatin	Phase I
CALAA-01 [28]	Transferrin	Small interfering RNA	Phase I
Dtxl-NP-Apt [29]	RNA aptamer	DOX	Pre-clinic
Pt-NP-Apt [30]	PSMA	Cisplatin	Pre-clinic

Table 7: Examples of non-targeted Nanoparticles in clinical development

Type of Nanoparticle	Name	Therapeutic agent	Status
Albumin-based naoparticles	Abraxane [31] or ABI-007	Paclitaxel	Approved
Liposomes	DaunoXome® [32]	Dox	Approved
	Aroplatin [33]	Oxaliplatin	Phase II
	Myocet® [34]	Dox	Approved
Polymeric micelles	Genexol-PM [35-37]	Paclitaxel	Approved
Polymer-drug	Prothecan [38, 39]	Camptothecin	Phase II
Conjugate-based nanoparticles	PK1; FCE28068[40, 41]	Dox	Phase II

Nanoparticles overcome anticancer drug resistance

Too often, chemotherapy fails to cure cancer because some tumor cells develop resistance to multiple anticancer drugs. In most cases, resistance develops when cancer cells begin expressing a protein, known as p-glycoprotein that is capable of pumping anticancer drugs out of a cell as quickly as they cross through the cell's outer membrane.

New research from the University of Kentucky shows that nanoparticles may be able to get anticancer drugs into cells without triggering the p-glycoprotein pump.

Since nanodelivery promises precision administration, smaller dosages will be required to have the same effect as the nonnanodelivered drugs. With these smaller doses come fewer harmful side effects.

PATENTS AND FUTURE PROSPECT

More than 100 Nanopharmaceutical patents were granted by US patent office during 2001-05. United States Patent 6933331 entitled "Nanotechnology for drug delivery, contrast agents and biomedical implants" has been granted for nanoscale powders as composite and device components. About $2.6 trillion worth of goods worldwide are expected to use nanotechnology by 2014, up from $50 billion in 2006.

CONCLUSION

In the past 20 years, significant attention has been paid to nano science and nanotechnology. The main aim of this review article is to concentrate on nanotechlogy used in therapeutics with recent development. An additional area enabled by nanotechnology is known as "intelligent therapeutics" which involves responsive devices and drug delivery system that can detect, capture, isolate and treat undesirable biologicals and trigger an action that will release therapeutics. Nanoparticles with various shapes such as quantum dots, nanotubes, nanohorns, and nanocages and made of different materials, from organic dendrimers, liposomes, gold, carbon, semiconductors, silicon to iron oxide, have already been fabricated and explored for cancer imaging and therapeutic applications.[42-48] However, there are various concerns associated with their use as the carrier system, including the *in vivo* safety profile, stability, drug releasing efficiency, and clearance kinetics.[49-53] Consequently, development of nontoxic biocompatible nanoparticles with favorable *in vivo* pharmacokinetics and efficient delivery to tumors is still much needed for medical applications. Although certain applications of nanotechnology may be toxic, the majority of medical applications will be beneficial and nanotechnology has great impact as next door technology in therapeutics.

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