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Nanotechnology In Health Sciences: Past, Present and Future

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Abstract
Health sciences is one of the vast fields with profound impact on mankind and global economy. Post COVID Pandemic, medical sciences and life sciences witnessed a mammoth progress aided by fields like Artificial Intelligence, Nanotechnology, Bioinformatics etc. Nanotechnology as a branch of science started to expand its branches around 4th and 5th centuries BC where the two Asian giants, India and China achieved a good success in developing Gold Colloids for treatment. The gateway between Biosystems and Nano systems emerged as one of the potential thrust areas in science and technology with wide spread roots in medicine, biotechnology, engineering, vaccine industry etc. In association with positive aspects of Nanomedicine, many scientists are exploring the significance of Nanotechnology in diagnosis, therapy, disease control and prevention. Nanotechnology delivered fruitful results in the fields of biotherapeutics, pharmacy, microbiology, vaccinology, regenerative medicine, gene therapy, Oncology, dental sciences. It gained maximum momentum because of collaborative work done by scientists, clinicians, physicians, IT industry. Field of Nanotechnology gained immense success in producing nano sized devices, diagnostic tools, tissue engineering, nano sized implants.
Aim of formulating this review article is to enlight the role of Nanotechnology in multiple disciplines under one common roof with special focus on recent developments and advancements and the future impact in health sciences.

Keywords:
Nanotechnology, Nano devices, Vaccinology, Gold Colloids, Regenerative Medicine, Oncology, Tissue engineering.

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Pioneers In Nanotechnology- An Over View

Nanotechnology is understanding and control of matter at nanoscale between 1 &100nm with immense novel applications, precisely manipulating matter at nano levels in a useful way. Sir **"Richard P Feynman" and "K. Eric Drexler**" laid firm foundation on theoretical and conceptual foundation for Nano technology in medical field. Richard P Feynman considered as "father of Nanotechnology" discussed the concept in 1959, which laid the foundation for Nano science, exploring the concept of building and controlling structures at atomic level. He received Nobel prize in Physics for his work on **"Quantum Electrodynamics**" (1) in 1965. Sir K. Eric Drexler expanded on Molecular Engineering in 1986 through his book on "Engines of Creation" (2). His work aided in expanding Nanomedicine and the concept of "Cellular repair" through molecular assemblers.

Japanese scientist Sir "**Norio Taniguchi"** coined the term "Nanotechnology" in 1974(2). British Chemist Sir "Geoffrey Ozin" is widely recognized as "Father of Nano chemistry"

Sir **"Chad Mirkin"**, a modern pioneer invented nano particle-based bio-barcodes and diagnostic methodologies that use gold Nanoparticles to interpret disease biomarkers.

With the invention of "**Scanning Tunneling Microscope**" by "**Gerd Binning" and "Heinrich Rohrer" in 1981 considered as "Golden Period" of Nanotechnology (2)**

Professor CNR Rao till date is widely regarded as **"Father of Indian Nanotechnology**", led major studies in Solid -state and material Chemistry, focusing on inorganic nano materials, nanotubes. His work paved the way for developing national research programs and infra structure for the development of Nanoscience in India. He received India's highest civilian honor**, "Bharat Ratna" on February 4th 2014.**

I. Introduction

Nanotechnology is a pivotal tool in medical research rendering in expansion of biological process at both cellular and molecular level (3). Nanotechnology is a form of transformation in medical science creating a new sector for human development. Applications of Nanotechnology are broad which include control, repair, extensive surveillance of all biological systems with the advent of nanodevices, nanostructures (4). Nano drugs have potential impact in enhancing Bio availability with minimal side effects and more efficient rate of absorption of therapeutic medicine (5). Understanding the concept of biological processes is vital as it is the core force behind

the massive development of Nanotechnology (6). Major advantage in Nanotechnology application vests in targeting only damaged cells sparing the healthy cells which is primarily aided by nano devices, nano fibers, nano particles (7). Taking Brain tissue as an example which is structurally a highly selective membrane barrier which is permeable for the entry of molecules. Nanoparticles were employed on this membrane in recent past as a form of medication carrier system which can cross the brain membrane. Liposomal nanoparticles and polymeric nanoparticles were commonly used owing to their bio degradability and biocompatibility (8) Nanoparticles were made from different metals such as Silver, Gold, Zinc, Titanium, Silicon and their oxides, Inorganic materials, polymeric materials and Lipids. Many products were extracted from these substances which are used as biomarkers in disease diagnosis (9).

In health care sector Nanotechnology spawned new avenues in the field of life sciences.

Nanoprobes, Nano sensory electronic systems in pharmaceutical industry, targeting the infected cells, tumor cells, combating antibiotic resistance, with the advent of drug delivery systems were the core thrust areas of Nanotechnology (10). Research work by Haleem etal. analyzed the core medical areas of Nanotechnology implementation especially in hospital critical intensive care units (11). Roots of Nanotechnology modified multiple aspects of medical sciences such as disease monitoring, host-pathogen interactions, disease diagnosis, Regenerative medicine, Vaccine development and delivery of medicines (12)

Primary objective of this review article is to deliver major applications of Nanotechnology in health sciences, present scope and future of Nanotechnology in health care sector and life sciences and characteristics of nanotechnology in medical domain and to analyze different nano materials and their classification for human purpose in medical field.

Nanotechnology in medical sciences

Area of Nanotechnology and nano drug discoveries were broad which underwent many modifications. It is essential to study the significant potential of Nanotechnology in health and disease in current situation with ongoing broad research in the fields of Cancer, Nephrology, Microbiology, Genetics, Cardiology, Gene Therapy etc. Nanotechnology in medicine employs minuscule materials and devices to revolutionize health care . It offers precise drug delivery, advanced disease detection and innovative novel methods of treatment, capitalizing nano particles and nano devices for targeted therapy and diagnosis. Moreover, nano materials such as Nano Silver can counter antibiotic resistance . Silver exhibits Pleiotropic action by inducing changes in bacterial cells and enhanced susceptibility to antibiotics (13). Silver ions and silver nano particles interact with Phospho lipid membrane of bacteria and enhanced membrane permeability and leakage of the contents of bacterial cell. Gene therapy has taken mammoth advantage of nano drugs. Investigations done by many scientists revealed the applications of Viral vectors are crucial for the delivery of medication (14). Nanoparticles in the present scenario have emerged as most potent and versatile tools in advanced diagnostic devices, targeted drug delivery, biomedical implants, tissue engineering. Nanotechnology revolutionized health care sector by improving accuracy, sensitivity, speed of medical diagnostic tests.

Nanotechnology in health care management:

1. Liposomes
2. Nano shells
3. Nano wires
4. Dendrimers
5. Cantilevers
6. Quantum dots or Nanocrystals

Role of Liposomes

British hematologist Alec D Bangham and colleagues discovered Liposomes in 1960s. Liposomes are a class of self-assembled Phospholipid bilayer membranes appearing as closed structures with internal aqueous atmosphere formed when dry Phospholipids or a combination of Phospholipids and Cholesterol immersed in water under optimum laboratory conditions and appear as fluid filled sac like structures (15). Liposomes were the first engineered nanoparticles for drug delivery.

Immunological & Toxicological of Liposomal formulations

The delivery procedure of Liposomes enhanced drug targeting and pharmacokinetics. It is essential to address their adverse effects based on major immunological and toxicological conditions. Pegylated Liposomes invigorate complement activation related Pseudo allergy a form of Hypersensitive reaction and stimulate anti PEG-antibodies (16). PEGylated Liposomes augment accelerated blood clearance which is attributed to enhanced immune responses after repeated administration (16). Studies reported accumulation of Liposomes in major visceral organs like Liver, Spleen, Kidneys, bone marrow, intestines in people after I.V. injection which cause diminished levels of core cells of immune system. (17)

Tasks In the Production of Nanoparticles

Inspite of having multiple benefits, production of Nanoparticles faces some core challenges which include a. Production process b. lack of knowledge and required infrastructure for production c. Stability problems. Novel products with Liposomes were generated every year. At present Liposomes were developed as drug carriers for the treatment of Cancer, infectious diseases caused by bacteria, viruses, fungi (18) Studies reported that Liposomes produced a breakthrough in the treatment of a rare , progressive and potentially life threatening disease known as "Hereditary Transthyretin Amyloidosis"(19)Apart from this , Liposomes were employed in the development of COVID vaccines in 2021 and are also used in the treatment of dreadful infections like AIDS, Vector borne fevers like Malaria, Cancer. Liposomes were used as Adjuvants in Immunology which depicts their importance in Immunology and medicine.

Table showing Liposomes Preparation methods

Classical Methods	Physical Methods	Drying based Methods	Advanced Methods
Thin film hydration: Heterogenous vesicles	Sonication: Generates small vesicles	Spray drying: Mass production	Microfluidic: Continuous production
Reverse phase evaporation: Forms Water in oil emulsion	French pressure cell: Protein restoration	Freeze drying: High stability due to cryo protectants	Super critical reverse phase evaporation: Eco friendly
Solvent Injection	pH change	Spray freeze drying	Cross flow injection
Detergent removal	Dehydration- rehydration		

Some of the anti-cancer drugs such as Amphotericin delivered more beneficial effects when used in combination with Liposomes. Liposomes transport Hydrophilic drugs inside the core and Hydrophobic drugs between the bilayer (20)

Quantum Dots / Nanocrystals

Another positive aspect of Nanotechnology in health sciences is the application of small sized (2-10nm)particles called as Quantum Dots which are light emitting crystals and can protrude into the cells. When applied in combination with MRI they produce more broad, clear images of Tumor cells (21). Quantum dots reduce the necessity of biopsy in clinical pathology as they themselves can be used in the body(22) due to greater stability than normal dyes.

Nano shells

These are the first engineered nanomaterials paved their way into human trials . These are small sized sphere like glass structures coated with Aurum(gold). Nano shells when conjugated with Immunoglobulins, Radioisotopes, therapeutic agents, deliver more beneficial, therapeutic effects and function as better diagnostic tools (23). Gold Nano shells exhibit more optimistic effects in biomedical imaging studies, drug delivery systems, gene therapy. Main advantage of using Nano shells in medical imaging and in cancer studies is their neutral or zero toxic effects when compared to Chemotherapy and no harm as that of Ionizing radiations as observed in Radio therapy (23).

Cantilevers (Nano Electro Mechanical Sensors-NEMS)

Bio-sensors based on nano electrical mechanical stimulation have gained promising development in the recent past. Nanoscale Cantilevers are based on biological interaction between Analyte (e.g.: Microbes such as Viruses or chemical component) and the surface of Cantilever. (24). Tumor sites , infected tumor cells and their associated molecules can be detected by Nano scale Cantilevers and provide rapid detection. In general, a biosensor is constituted with Bioreceptor and Transducer. The Bioreceptor detects the target bio molecule or the analyte and the transducer converts the recognition event into a measurable signal.

Dendrimer

The term Dendrimer is derived from Greek which means a dendron or tree like. In medical sciences Dendrimers are used for targeted drug delivery and as a contrast agent in high end imaging technology like MRI (25).

Nanowires

Nanowires are extensively used as building blocks for the development of biosensors. Nanowires are smaller than the smallest Capillaries in human body and they can be used in such a way to any point in the body through the circulatory system without hampering the blood flow or disturbing the gaseous exchange. An individual Nanowire or it's component are useful to record the electrical activity of a nerve cell and this feature is useful to interpret the site of damage in conditions like Stroke, Epilepsy and other brain abnormalities(26) Nanowires have shown

beneficial output in providing electrical stimulation exactly for the affected area in patients with Parkinson's disease which is a Progressive Neuro degenerative disorder affecting Dopaminergic neurons of Nigro striatal pathway leading to multiple motor disturbances and Gait abnormalities (27). Nanowires provide enhanced drug delivery system and deep stimulation of the affected site. Apart from this, Lipid based Nanoparticles, Carbon based and metal based (Iron, Cerium oxide) are widely used in treating Parkinson's disease.

Nanotechnology: Research & Development In Health Sciences

Novel drug delivery methods were being tried for cripling conditions like Cancer, Chronic Viral and Mycotic (fungal) infections, endocrine disorders such as Diabetes mellitus, and in Gene therapy

Given below table depicts the significance of Nanomaterials in numerous medical disciplines and in Life Sciences

1.	Drug delivery and detection of damaged Gene / Tumor detection
2.	Bio detection of Pathogens
3.	Detection of bio molecules such as Proteins
4.	Tissue Engineering
5.	Vaccine development and in Immunology
6.	Fluorescent biological labels
7.	Contrast enhancement in radio imaging techniques such as PET Scan, MRI
8.	Phagokinetic studies

Uses of Nanoparticles / Nano carriers through Nano technology

1. Nano carriers can penetrate the Sub Mucosal layers.
2. More intracellular uptake
3. Can be used in systemic circulation as nanocarriers cause no particle accumulation or capillary blocking.

Positive role in Tissue Engineering

Tissue Engineering is the study of growth of new tissues, organs by replacing or repairing the damaged cells or tissues or organs from the base of the cells and scaffolds (28). Products developed from Tissue engineering are constituted by 3 major components:

a. Isolated Cells
b. Extracellular matrix
c. Signal molecules

Of these three, extracellular matrix is crucial and plays as vital role as it facilitates the localization and delivery of cells and facilitates the presence of appropriate three-dimensional space for the development of new tissues in the engineered area. Cell interaction and extra cellular matrix is of profound significance in generating final desired product through Tissue engineering. These Nanofibers have greater bio degradability, adequate porosity and high surface area (29)

Antibacterial applications of Nanoparticles

By the end of 2050 more deaths may be witnessed due to multiple forms of cancerous lesions caused by Multi drug resistant microbes such as Bacteria, Viruses etc.. Nanoparticles especially silver oxide Nanoparticles have greater antibacterial properties and provide greater Wound healing (30). Work done by Xing et al evaluated the antibacterial activity of Poly nanofibrous silver scaffolds. This property has been employed in Joint Arhtroplasty (31). Moreover, other metal oxide nanoparticles are effective bactericidal agents which include magnesium and Bromium oxide and their Chlorine components. Studies conducted by "Stoimenov" etal on three different bacteria which include Escherichia coli, Bacillus megaterium, Bacillus subtilis interpreted that Nano particulate formulations were able to destroy Escherichia coli and Bacillus megaterium with in 20 minutes. It is essential to address the application of Selenium nanoparticles as Selenium has the ability to kill the bacteria through other mechanisms rather than depending on Reactive Oxygen Species (ROS) because nanoparticles which depend on Reactive Oxygen Species leads to development of Mutants. Selenium Nanoparticles are more effective in destroying both Gram Positive and Gram-negative group by alteration of Thiol containing protein function and antibiotic resistance has not been reported (32)

Another milestone in Nanoparticle application is the role of Iron oxide (Feo) which can penetrate Biofilms and kill the bacteria after the formation of Biofilms as antibiotics cannot kill the bacteria under intense magnetic fields (33).

Studies reported that antibiotics in combination such as Ampicillin, Chloramphenicol, Neomycin with Silver ions or with Silver nano particles can augment the antibacterial activity of both the compounds in treatment of bacterial infections

Nano Technology in Virology

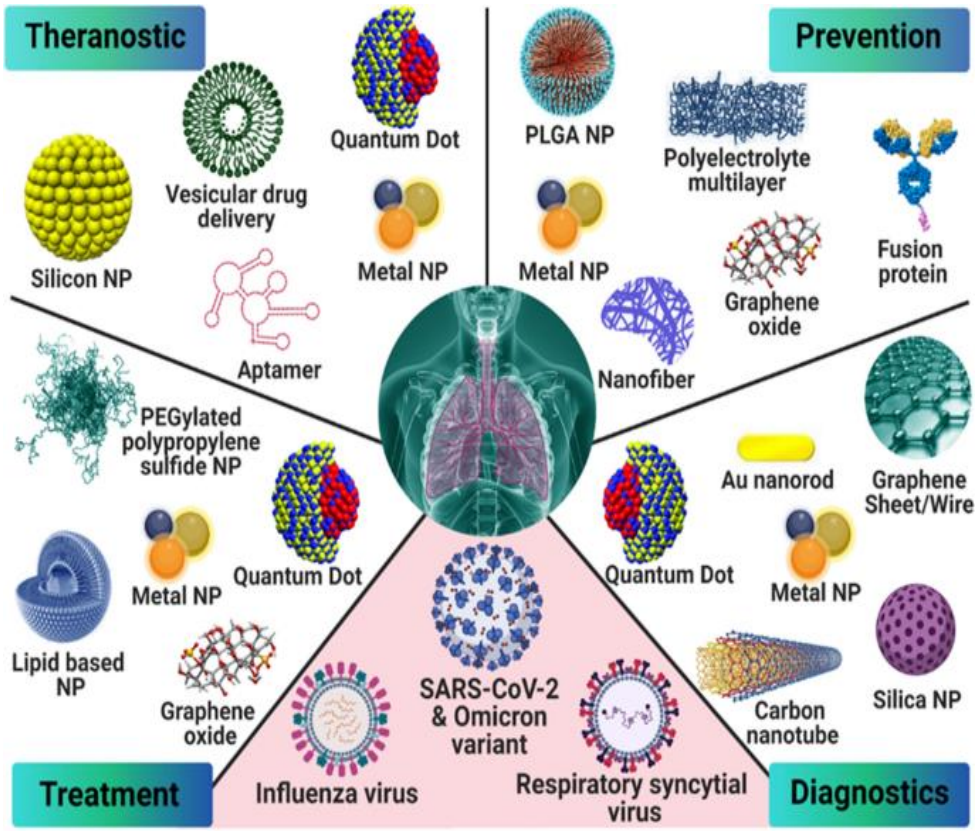
Nanotechnology plays an important role in Viral invasion into human cells and is based on Single Virus tracking Technology (SVT). This method helps the researchers to track different stages of life cycle in viruses and helps to analyze the viral multiplication and underlying mechanisms inside the living cells (Liu etal 2020). Quantum dots and metal nanoparticles are employed in Single Virus tracking technology. Advantage of using Quantum dots is their brightness, long term stability and can be visualized even under low LASER intensity (Liang etal, 2019). Rearrangements in cortical actin barrier caused by HIV can be detected by using Quantum dots encapsulated fluorescent virus particles and SVT and helps in HIV invasion into the target cell (Yin etal 2020).

Flow chart:

1. Nanoparticle Design and Drug Encapsulation
   Encapsulate drugs in nanoparticles (10 – 200 nm)
   ↓
2. Circulation And Biodistribution
   Prolong circulation time
   Passive accumulation in tissues
   ↓
3. Passive Targeting (EPR Effect)
   Accumulation in inflamed tissues
   ↓
4. Active Targeting
   Surface ligands blind to target cells
   ↓
5. Cellular Uptake and Controlled Release
   Release triggered by pH, Enzymes & Redox
   ↓
6. Therapeutic Outcomes in HIV
   Deliver drugs to HIV reservoir sites

Sun etal addressed that during Virus internalization using Quantum dots based Viral tracking technology a GTPase based enzyme called as “Dynamin” is involved and drives the most important Clarithrin based pathway during cellular uptake of Influenza virus and assists in maturation and division of Clarithrin coated pits as the virus invades the host cell.

Image showing Nanoparticles application in some Viral infections



Potential risks

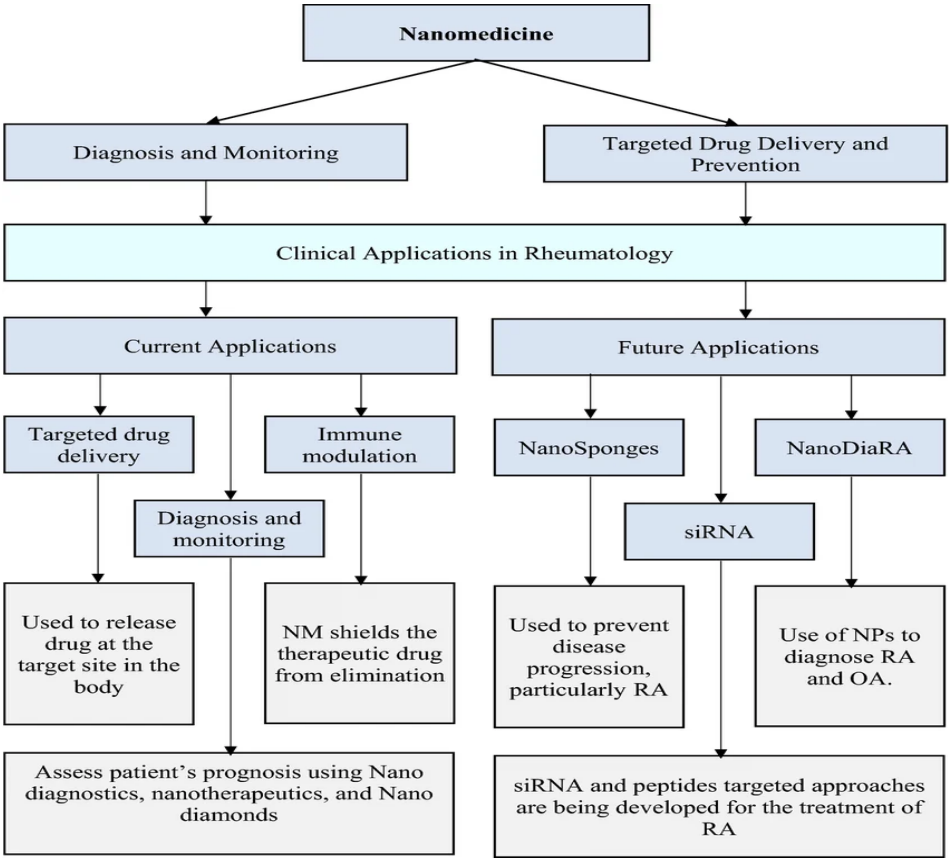
Owing to their small-size, Nanoparticles have potential risks on health of the individuals. Studies available reported that Nanoparticles can cause serious infections of Cardiovascular, Respiratory and Intestinal system (34). Animal models on mice depicted that Carbon based Nanotubes may lead to severe pathology of Lungs leading to Granuloma formation, Necrosis with more toxic effect (34). Nano particles may enter CNS and may lead to brain inflammation (35). Nano materials have the ability to interact with the cells of Innate Immune System and stimulate the pro-inflammatory mediators and alter the functions of Macrophages or the Phagocytic cells (36) and these types of situations are critical where immune response plays a pivotal role. Inspite of having broader applications, Nanotechnology has certain limitations, because of evasion of immune system and can accumulate in specific sites .

Future Scope

Nanotechnology with its components has significant role from the point of disease diagnosis to treatment and monitoring. Nanotechnology is having broad scope on induction procedures in Anesthesia, which is an important step in sensitive surgeries like Brain surgeries, dental surgeries. On this aspect scientists are working on the formulation of Nanorobotic suspension mixtures with colloidal suspension containing millions of Analgesic nanoparticles. Nano technology has opened new pathway in dentistry through which multiple range of oral health related issues can be studied (37). Prime challenge in near future is developing instruments based on Nano technology to analyze and evaluate the exposed nanomaterials in water and air (38) as exposure of living organisms to an atmosphere which is contaminated with nanomaterials may pose potential health hazard . Nanotechnology in near future needs a balanced approach between beneficial effects and associated hazards.

Moreover, quality academicians, research scholars must enlighten the importance of this specialized field in health sciences and life sciences and adequate skills, training, knowledge should be inculcated to the students who are opting this branch as a career.

Schematic model of Nano technology and future perspectives in reference to Rheumatology



II. Conclusion

Integration of Nanotechnology in medical field opens new avenues on a promising note for early disease diagnosis, accuracy, sensitivity as nanoparticles deliver positive results in radio imaging technology, cancer detection, drug delivery, gene therapy etc. In spite of having positive aspects, the key concern is the long-term usage of these materials and broad acceptance in clinical practice. Nano medicine is a key subset of Nanotechnology which makes use of Nanorobotics which covers multiple fields such as Vaccine development, diagnostic and imaging techniques and development of antimicrobial products. Nanotechnology undoubtedly enhances the global economy and has the potential to augment the novel drug development and detection of infectious diseases.

At present many highly reputed research institutes, medical universities, IITs are offering graduation, postgraduation and PhD programs in Nanoscience and Nanotechnology in India and in abroad which provides a nurturing, promising career for future generation.

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