Chapter 49

Nanomedicine Marvel

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ABSTRACT

Nanomedicine, which combines nanotechnology and medicine, is a new healthcare frontier. Nanomedicine has transformed diagnostics, treatments, and drug delivery methods, as seen in this chapter. Nanotechnology allows early cancer and infectious disease diagnosis with unparalleled precision and sensitivity. Nano-scale biological sensors and imaging agents help clinicians to diagnose and treat patients by revealing cellular and molecular processes. Nanomedicine also solved medication delivery problems, revolutionizing therapeutic treatments. Nano-formulations improve drug solubility, stability, bioavailability and reduce off-target and systemic toxicity. Site-specific medication delivery technologies like nanoparticles and liposomes maximize the effectiveness of therapy while minimizing tissue damage. Nano medicine also has potential for tissue engineering, regenerative medicine, and customized medicine. Nano-materials scaffold regeneration of tissues and maintenance, while nano-scale devices precisely control cellular activity and function. Nanotechnology is used to personalize nanomedicine treatments, improving outcomes and reducing risks. Nanomedicine offers novel solutions to longstanding diagnosis, treatment, and customized medicine problems, transforming healthcare. Nano-medicine has endless potential to transform healthcare and enhance patient outcomes as nanotechnology advances. So, after reading this chapter one will be able to know deeply about the potential and applications of nano medicines marvels.

KEYWORDS
Nanotechnology, Nanomedicine, History, Formation, Cure and Applications

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INTRODUCTION

The Greek word "nano" denotes diminutiveness or extreme smallness and corresponds to a measurement of a one millionth of a meter (10-9 m). Nanotechnology and nanoscience are distinct terms. Nano-science is exercise of nanotechnology to develop functional products such as electronics and other objects. On the other hand, nanotechnology focuses on the examination of structures and molecules within the size range of 1 to 100 nm (Mansoori and Soelaiman, 2005).

Nanotechnology and bio-nanotechnology are completely new concepts from the late twentieth century, and biotechnology has only been around for a few generations; its scope is still being defined. Biotechnology uses scientific techniques and skills to modify cellular, molecular, and genetic phenomena to create items or commodities that are used in a wide range of industries, from medicine to agriculture (Rani, 2017). Bio-nanotechnology is a subfield of nanotechnology that includes atomic-level engineering and manufacturing that is affected by biological antecedents. It is also directly related to biotechnology, but it includes the ability to design and modify the atomic-level complexities of the organisms produced. Bio Nano technology is built to the atomic size and accomplishes 3D molecular tasks clearly, or in broad terms, including (Tolochko, 2009).

By limiting the applications of digital technology, nanotechnology can be defined as an innovation that allows for the controlled initiation of nanomaterials and their implementation, which is, impacting or simply viewing them for their intended use. As a result, it has the potential to taper many biological sciences pathways, and nanotechnology is already deeply ingrained in common biological matters (Tolochko, 2009) (Boulaiz et al., 2011). It can also change our preconceived conceptions and cognitive processes and clearly distinguish between biology, physics, and chemistry. The loading capacity of biopolymer nanoparticles opens up a different amazing possibility in consumption of those nanoparticles as nano-containers used for important targeted approaches (Yousaf et al., 2024). The development of nanotechnology throughout all fields is based on recently generated nanomaterials that, because of their unique characteristics, rule all fields. Within domains such as medication delivery, diagnostics, aesthetic agents, tissue engineering, and agriculture, the merging of biological topics with nanoparticles is crucial.

It is urged that the biotechnology and pharmaceutical industries use nanobiotechnology more frequently. Throughout the whole pharmaceutical design process, from creating formulations for effective absorption to identifying applications in clinical trials, nanotechnology will be employed The field of nanotechnology is incredibly diverse, ranging from the addition of new techniques based on molecular self-build to the development of novel products using nanoscale real estate and the direct manipulation of atomic barriers. This idea involves applying a wide range of scientific fields, including surface science, organic chemistry, semiconductor physics, cell genomics, and microfabrication (Nasrollahzadeha et al., 2021).

Opponents voiced worries that nanoparticles, such as asbestos, might harm people. A few years back, a study by American experts at the University of Massachusetts revealed that nanoparticles could harm DNA and cause cancer. They caution against the release of nanoparticles into the environment and advocate for strict safety regulations for the manufacturing procedures. Consequently, insurance providers set a maximum coverage amount for nanotechnology-related insurance contracts. International safety standards are what they demand (Nasrollahzadeha et al., 2021).

The term "the future technology" that can solve a wide range of issues is frequently used to describe nanotechnology. Some even predict a revolution in nanotechnology. While there are undoubtedly many advantages and possibilities associated with nanotechnology, it is important for everyone to be aware that even this relatively new technology has risks and is still very much understudied. Environmental issues like pollution and climate change are said to be solvable as well. However, there are drawbacks to nanotechnology as well. For instance, creating useable nanoparticles necessitates the use of hazardous chemicals and solvents, as well as significant energy and water usage. Moreover, food is kept fresher for longer thanks to the application of nano packaging, allowing for longer food transportation (Nasrollahzadeha et al., 2021).

What is Nanomedicine?

Nanomedicine is the practice of diagnosing, treating, building, and controlling molecular-level human biological systems through the use of manmade nano-devices and nanostructures. Nanomedicine is exercise of nanotechnology in the field of medicine. It is utilization of nano-materials, nano biosensors andbiological devices (Sahoo, 2021).

Nanomedicine implies to use of nanotechnology in medicinal applications. Nanomaterials, nanobiotech, nano electronic biosensors, and the potential future uses of nanotechnology at the molecular level as biological machinery all contribute to nanomedicine (Chee, 2022).

History of Nanomedicine

The field of nanomedicine is relatively new; it all started in 1959 with presentation titled "There's Plenty of Room at Bottom" delivered by Nobel laureate physicist Richard Feynman at the American Physical Society convention. Nanotechnology has been investigated in the fields of medicine, medical technology, and pharmacology since the 1990s. Nanotechnology has only been in existence for a few decades (Freitas, 2004).

The creation of HD microscopy led to simultaneous advancements in the fields of physics, biologyand chemistry throughout the 20th century. This development gave rise tonew disciplines like biochemistry, microelectronics and molecular biology (Wagner et al., 2006). This research study became feasible in the early 20th century with the advent of groundbreaking microscopes, which were essential in exploring the nano universe across all disciplines.

Classification of Nanostructures

Currently, nanostructures are classified into two categories: those that exist naturally in nature and those that are artificially created by humans. Natural nanoparticles are formed through the decomposition of plant or animal remnants, erosion of geological materials, volcanic emissions, or through the burning of mineral fuels (Griffin et al., 2017). Nanostructures can also be classified based on their chemical makeup.

The criterion allows for the distinction of the following structures: 3-dimensional, 2-dimensional, single-dimensional, and zero-dimensional (Boverhof et al., 2015).

Table 1: Classification of nanostructures according to different criterion (Boverhof et al., 2015)

Source	Formation	Size
Natural	Organic	3D
Man-made	Inorganic	2D
		1D
		Zero dimensional

Formation of Nanostructures: (Top down and Top up method)

The two most widely used approaches for obtaining nanostructures are the "top down" and "bottom up" procedures (Mabrouk et al., 2011). When structures are obtained via top-down processes, it indicates that macroscopic materials are ground, divided, or disintegrated. This technology comprises grinding, normal material processing and lithographic process. High-Energy Ball-Milling is a widely used technique for producing nano materials. The initial substance is finely powdered mixture (<100µm) with distinct chemical composition and crystalline structure, as opposed to mechanical synthesis method which utilizes highly pure metal powders. Throughout the process, the material experiences induced stresses. After a prolonged period of time, an indeterminate substance is acquired. The application of heat treatment induces the reversion to the structure of crystals, known as recrystallization. The lithographic method is widely employed in the electronics industry. Its primary application is in the manufacturing of circuits with integrated circuits and transistors that utilize a substrate made of silicon (Salah et al., 2011). This approach comprises a series of sequential phases.

1. One approach is to coat the outermost part of the substrate with a layer that provides protection and is sensitive to light.
2. During the second stage, a negative or positive pattern of desired structure is applied to the insulating layer.
3. Next, the entire object is exposed to radiation and then treated with an etching process. The etching agent selectively reacts with exposed areas that are not protected by a layer of protection. By following this approach, the intended layer arrangement is achieved.

The "bottom up" approach involves the synthesis of nanoparticles by assembling individual atoms, essentially building structures from the ground up. This approach encompasses molecular beam epitaxy, plasma aided deposition, and vapor deposition (Salah et al., 2011).

Physical Vapor Deposition (PVD) is a technique that involves the deposition of solid materials onto a surface by spraying them, using an electron beam, from a target material. A well-prepared surface, known as the substrate, is positioned in close proximity to the material being sprayed, while maintaining a carefully regulated temperature. The sprayed substance gradually descends onto the underlying surface. The thickness and structure of the resulting layer are influenced by the duration of deposition, the velocity of spraying, the temperature of the substrate, and composition of the diluted gas environment (Salah et al., 2011).

Plasma Assisted Chemical Vapor Deposition (Plasma Assisted Deposition) is a technique that utilizes low frequency and radio frequency current discharges to deposit thin layers on both electrically conducting and non-conductive materials. Its goal is to produce layers with unique surface and volume characteristics as well as hard surface layers. Typically, chemical reactions occur when the gaseous atmosphere is electrically activated in this process. (Salah et al., 2011).

Molecular Beam Epitaxy is a procedure that uses molecular beams to deposit thin semiconductor layers in a high vacuum setting with pressures less than 10-7. By employing a diverse range of methodologies, it is feasible to achieve the desired nanostructures based on their intended purpose and application orientation (Salah et al., 2011).

What are the Reasons for Selecting the Nanomedicine Approach?

Nano materials can acquire additional functionalities by integrating them with biological molecules or structures. Nano materials possess a size comparable to that of typical biological molecules and structures. Consequently, they hold potential for biomedical research and applications in both in vivo and in vitro settings. In the realm of physical therapy applications, nano-materials have facilitated the creation of diagnosing devices that employ contrast agents, instruments, and drug delivery passage (Sahoo et al., 2020).

Nano-medicine aims to provide a valuable collection of research tools and clinically beneficial gadgets in future. Advanced drug delivery, innovative therapeutics, and in vivo imaging are possible pharmaceutical applications of the Nanotechnology Initiative. Nanotechnology enables targeted drug delivery to specific cells within the body through the use of nanoparticles (Sahoo et al., 2020).

The advantage of utilizing nanoscale materials in medical technology lies in their reduced invasiveness and potential for implantation within the body. Additionally, the use of such materials results in significantly quicker biochemical reaction times. These devices exhibit superior speed and heightened sensitivity compared to conventional drug testing methods (Lavin et al., 2003).

Applications of Nano-Medicine

Cancer cell-imaging

Cadmium selenide nano-particles, often known as quantum dots, emit light when they are subjected to UV radiation. When injected, these substances permeate cancerous tumors. The surgeon is able to visually perceive the luminescent tumor, which serves as a reference point for doing more precise procedures to remove the tumor (Rani, 2006).

For Cancer

Gold nanoparticle shells specifically can directed to adhere to the malignant cells. By locating tumor area using infrared lasers, flesh is not burned while the alloy of gold is heated enough to kill the cancer cells.

Utilization in Medicine

This innovation has the potential to address the challenges and hemorrhaging that arise when surgeons attempt to suture blood vessels that have been severed during kidney or cardiac transplantation procedures (Lavin et al., 2003).

As Nano Electronic Biosensors

Nanotechnology refers to the progress made in joints swelling recognition equipped with lights and recording devices, enabling surgeons to do surgery through smaller incisions.

For Physical Therapy

Photodynamic therapy utilizes a tiny particle that is inserted into the body and then detected using external light. When a particle absorbs light, it can heat up if it is made of metal. This heat can then affect both the particle and the tissues around it (Cavalcantiet al., 2008).

As Neuro-electronic Interfaces

The Neuro-electronic interfacing aims to develop nano technologies that enable the integration and connection of computers with the neural system.

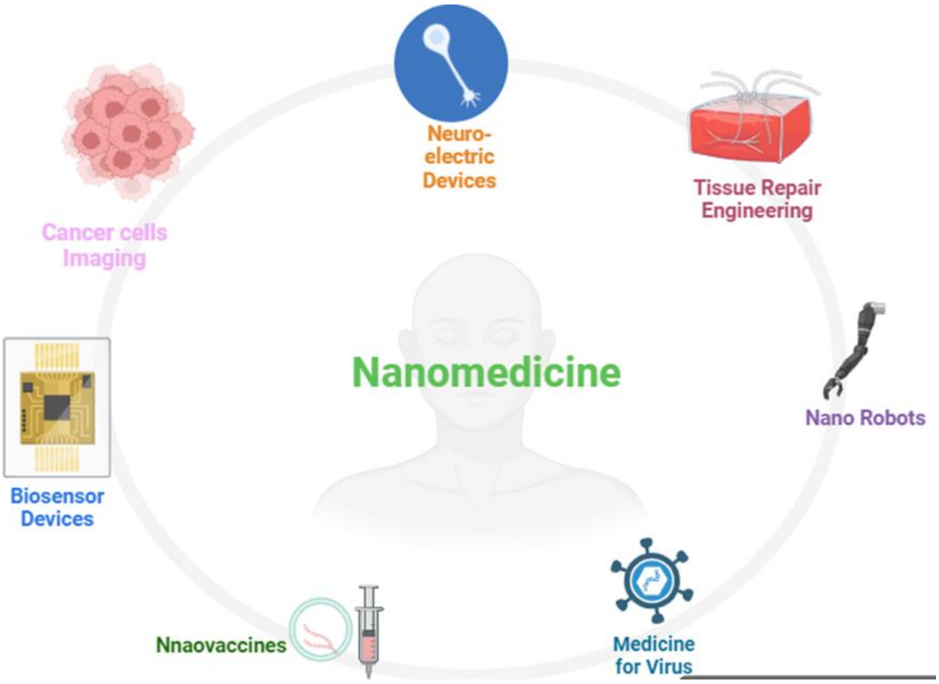

Fig. 1: Illustrates the various applications of Nanomedicine across several areas.

The Application of Tissue Repair

Nanotechnology has the potential to facilitate the replication or restoration of impaired tissue. Tissue engineering utilizes nano materials, such as scaffolds and growth factors, to stimulate cell proliferation. For instance, carbon nano tube scaffolds can be used to regenerate bones. Tissue engineering has the potential to replace traditional treatments like transplants of organs or artificial implants (Bissau and Baton, 2011).

Molecular Nanotechnology

Nanomedicine employs nanorobots that are introduced into body to detect and repair infections and damages. Carbon, specifically diamond/fullerene composites, is the preferred material for constructing these nanorobots due to its inherent strength and other desirable properties. Dedicated desktop nano factories are used exclusively for fabricating these nanorobots. Nanomedicine utilizes nanorobots as miniature surgeons capable of repairing damaged cells and intervening in intracellular structures. These nanomachines have the potential to self-replicate and address genetic deficiencies by modifying or substituting DNA molecules (Raoet al., 2014).

Nanotechnology for Cancer Treatment

In recent years, there has been a significant increase in the use of nanomedicines for antitumor therapy, with a particular focus on developing efficient and low-toxic nanoscale drug delivery systems (NDDSs). Among these, liposomes have gained considerable attention and several antitumor liposomes are currently available in the market. DOX liposomes are among the anticancer liposomes that have been investigated the most. By preventing tumor cells from synthesizing DNA and RNA, DOX has strong anticancer effects (Nirmala et al., 2022). On the other hand, DOX also has negative consequences such heart disease and stem cell suppression, in addition to its mutagenic and carcinogenic qualities. Through the enhanced permeation as well as retention (EPR) effect in solid tumors, liposomes provide the benefit of passive medication targeting to tumor tissues, hence lowering drug toxicity. Doxil® is the first commercially marketed DOX liposome product, created in the US by Sequus. It is primarily used for the treatment of recurrent ovarian cancer and Kaposi's sarcoma induced by human immunodeficiency virus (HIV) (Boulaziet al., 2011).

Utilizing Nanomedicine to Combat Infectious Disorders

Three primary categories can be used to categorise pathogenic microorganisms: bacteria, fungus, and viruses. The different types of anti-infective medications are classified according to the particular infections they aim to eradicate. They include antiviral medications like albendazole; antibacterial medications like macrolides, penicillin, and metronidazole; antifungal medications like itraconazole, fluconazole, and voriconazole; and antiparasitic medications like albendazole. Based on the various illnesses that these bacteria can cause, this classification was created (Clercq, 2002).

Nanomedicine for HIV

HIV/AIDS is now the most common infectious cause of death in adults across world. Despite a lot of research, a cure for HIV/AIDS has not been found yet. There have been 25 approved medications which, for use in environments with limited resources, are available in generic and fixed-dose combinations. However, the 1990s saw a revolution in the treatment of AIDS with the development of protease inhibitors and triple-drug therapy. Because of this, highly aggressive anti-retroviral therapy (HAART) was created, which entails taking three or more medications at once (Clercq, 2002).

Antiviral Activity against Influenza Virus

According to Tavakoli et al. (2017), influenza viruses are major causes of respiratory tract illnesses in humans and can lead to seasonal epidemics and even worldwide pandemics. There are just two drugs that have been authorized by the FDA at the moment (Toledo et al., 2018), but the rise of drug-resistant strains in the past few years is really concerning. Consequently, nanotechnology is essential in the search for alternative treatments to combat drug-resistant bacteria. When treating influenza, it is common practice to provide antiviral drugs using metal-based NPs (Levina et al., 2016). In order to create an influenza medication that targets NA inhibitors, the nicotinic antagonist amantadine and the not competitive N-methyl-D-aspartate antagonist have been associated with silver-nanoparticles (AgNPs). Influenza viruses can have their reproduction slowed by these substances. Nanoparticles coupled with antiviral drugs can halt influenza invasion and protect cells by preventing intracellular ROS generation and caspase 3-controlled apoptosis (Li et al., 2016).

Combatting Hepatitis C Virus

Hepatitis C, the most common viral infection transmitted through the bloodstream, primarily stems from the hepatitis C virus (HCV) and primarily impacts the liver. The failure of the body to eradicate the virus is accountable for roughly 80% of acute HCV infections progressing into chronic infections (Hekmatet al., 2017). Initially, interferons were employed as the initial treatment for HCV, succeeded by direct-acting antivirals (DAAs) and host-targeted antivirals (HTAs).

Considerable work is currently addressed on nanoparticles (NPs) for delivering several treatments, including anti HCV vaccines and diagnosis of therapeutic agents. These drugs are either attached to or enclosed within nanoparticles of different compositions, such as lipid, metallic and polymeric NPs (Hekmatet al., 2017). NPs are designed with specific characteristics to address challenges, such as maintaining the effectiveness of the medication while reducing the dose of administration and minimizing potential side effects. The sustained impact of anti-HCV medications is achieved through Pegylation of nanoparticles, controlling drug diffusion from the NP matrix (Ishihara et al., 2014), and utilizing electrostatic interactions with oppositely charged carriers (Lee et al., 2012).

Nano-vaccines

A crucial element of nanotechnology medicine is the advancement of nano immunizations for several infectious illnesses, including HIV and the virus that causes influenza. Nanotechnology has been discovered to have a pivotal impact in the creation of vaccinations, augmenting their efficacy and specificity. Recently, there has been considerable interest in using nano size materials such as virus-like fragments, liposomes, polymeric nanoparticles, and protein nanoparticles as possible carriers for vaccination antigens and adjuvants (Jangraet al., 2021). These materials have several benefits, such as enhanced stability of antigens, precise administration, and continuous discharge, as they are either enclosed within or connected to the exterior of the NP. The obstacles faced in the process of vaccine development may be surmounted by influencing the immune system through the flexible design of nanomedicine (Mamo and Poland, 2012).

Nano-Vaccine for HIV

Since the first report of HIV/AIDS, the search for a safe and dependable vaccine has been challenging for almost thirty years. Extensive research has been conducted on lipid-based techniques for administering HIV/AIDS vaccinations. In a prior investigation conducted by Sakaueet al. (2003), it was demonstrated that when the HIV gp160 protein was enclosed in a liposome and delivered nasally to mice, it resulted in the production of significant levels of neutralizing antibodies that specifically targeted gp160. The liposomes were formed by the amalgamation of cholesterol levels, a substance phosphatidylserine, and phosphatidylcholine. In addition, the HIV gp41 protein was administered using liposomes of varying sizes (ranging from 110 to 400 nm), resulting in the mice and rabbits developing strong antibody responses (Letvin, 2006).

These nano-delivery systems need to include a variety of HIV maybe even ones that are meant to boost the production of antibodies and give them access to parts of the HIV forming glycoproteins that aren't activated during acute HIV infection. Though NPs were used as a transport system, the study found that less HIV antigen and flagellin (adjuvant) was needed to get the same cell reaction (proliferation and IFN-γ production) as Freund's adjuvant (Rostami et al., 2017).

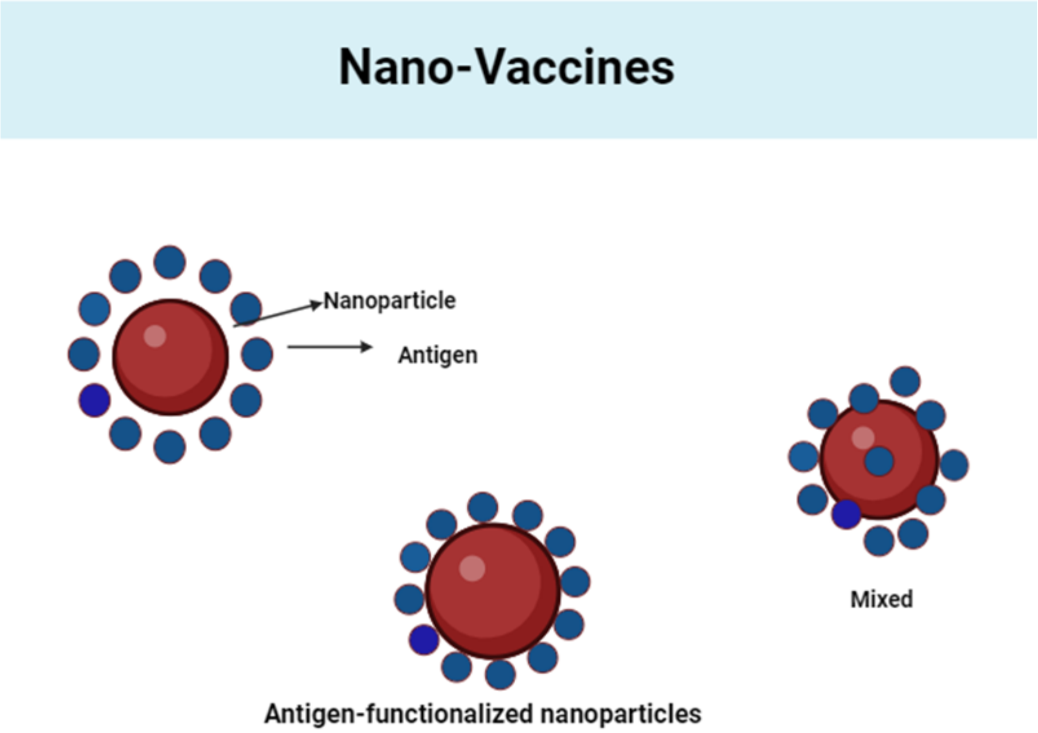

Fig. 2: Design of the Nanovaccine

Nano-Vaccine for HIV

Complete mucosal respiratory tract influenza protection is excellent. Thus, influenza NP vaccine research is conducted. One of the simplest influenza NP vaccines is a mouse VLP-TIV combo. The VLP/TIV combination induced anti-influenza immunity better than free TIV, especially after intranasal vaccination, based on blood and broncho-alveolar lavage IgG, IgG2a, and IgA titers. Rabbits inoculated with influenza entire virus (WV) encased in chitosan were also able to receive vaccinations via their nasal cavity with NPs (Rioux et al., 2014; Dehghan, 2014). Encapsulating H5 hemagglutinintrimer in polyanhydride NCs created an H5N2 NP vaccination in mice. This method produced high TCD4+ and neutralizing antibody titers. Following an H5N2 nasal challenge, animals were significantly protected (Narasimhan et al., 2014).

Benefits of Nanomedicine

Benefits of medicines include: Precise drug delivery to the specific place, to minimize adverse consequences, nano designed devices for molecular targeting, detecting the sickness is pretty straightforward, surgical intervention is unnecessary, the diseases can be readily treated, determine the most effective pharmaceutical medicines for treating the current medical condition or specific infections., conduct diagnostic assessments to identify medical problems and reveal the presence of disease-causing microorganisms, maximize the efficient manufacture of corresponding medications, locate, implant, or affix integrated or target tissue; structures or microorganisms and administer the optimal dosage of a compatible biological agent to the designated target sites.

Recent Progress in Nano Medicine

Drug delivery systems have the potential to prevent tissue damage by employing controlled drug secrete methods, lessen drug clearance rates, decreasing distribution volume, and minimizing impact on non-target parts. Nanoparticles can be utilized in therapy to combat antibiotic resistance and take advantage of their antimicrobial properties. Additionally, nanoparticles can be employed to bypass mechanisms of multidrug resistance (MDR).

Some significant applications include the use of iron nanoparticles or gold shells for cancer treatment. Nanotechnology plays a crucial role in discovering new possibilities in drug delivery systems. However, the rapid advancement in this field may lead to challenges related to toxicity, and the effectiveness of drugs may decrease when their concentration falls below the desired levels (Ratner and Ratner, 2002).

Issue with Nano-medicines

The current challenges in nanomedicine revolve around understanding the toxicity and environmental impact of materials at the nanoscale, which refers to structures that are billionths of a meter in size (Freitas, 2005). Despite the numerous benefits, the harmful effects of nanomaterial toxicity remain a significant concern for human health and the environment (Gardner and Dhai, 2014). Risks include leakage, spillage, circulation, and agglomeration of nanoparticles. When nanoparticles enter the body through the skin, ingestion, inhalation, or other routes, they can cause damage to vital organs over time (Ali, 2012). The toxicity of nanoparticles also leads to increased reactivity of chemicals and the production of reactive oxygen species.

Conclusion

Nano medicine, a novel field of nanotechnology, has had a significant impact on human lives. It encompasses a wide range of medical applications, including drug delivery systems, cancer therapies, and tissue culturing. The potential for nano medicine to enhance health outcomes is vast. However, to fully capitalize on its benefits for both individuals and populations, it is crucial to involve public health expertise. This involvement will aid in identifying areas with the greatest need for technological advancements, optimizing funding allocation, and shaping policies to safeguard human well-being and environmental integrity, thereby promoting better health maintenance.

REFERENCES

Ali, I. (2012). New generation adsorbents for water treatment. *Chemical Reviews*, *112*(10), 5073-5091.

Boisseau, P. and Loubaton, B. (2011). Nanomedicine, nanotechnology in medicine. *Comptes Rendus Physique*, *12*(7), 620-636.

Boulaiz, H., Alvarez, P. J., Ramirez, A., Marchal, J. A., Prados, J., Rodríguez-Serrano, F., & Aranega, A. (2011). Nanomedicine: application areas and development prospects. *International Journal of Molecular Sciences*, *12*(5), 3303-3321.https://doi.org/10.3390/ijms12053303

Boverhof, D. R., Bramante, C. M., Butala, J. H., Clancy, S. F., Lafranconi, M., West, J., & Gordon, S. C. (2015). Comparative assessment of nanomaterial definitions and safety evaluation considerations. *Regulatory Toxicology and Pharmacology*, *73*(1), 137-150.

Cavalcanti, A., Shirinzadeh, B., Freitas, R. A., & Hogg, T. (2007). Nanorobot architecture for medical target identification. *Nanotechnology*, *19*(1), 015103.

Coombs, R. R and Robinson, D.W. (1996). Nanotechnology in Medicine and the Biosciences. *(No Title)*.

De Clercq, E. (2002). Strategies in the design of antiviral drugs. *Nature Reviews drug discovery*, *1*(1), 13-25.

Dehghan, S., Tafaghodi, M., Bolourieh, T., Mazaheri, V., Torabi, A., Abnous, K., & Kheiri, M. T. (2014). Rabbit nasal immunization against influenza by dry-powder form of chitosan nanospheres encapsulated with influenza whole virus and adjuvants. *International Journal of Pharmaceutics*, *475*(1-2), 1-8.

Freitas, Jr R. A., (2005). What is nanomedicine?. *Nanomedicine: Nanotechnology, Biology and Medicine*, *1*(1), 2-9.

Gardner, J. and Dhai, A., (2014). Nanotechnology and water: ethical and regulatory considerations. *Application of Nanotechnology in Water Research*, 1-20.

Goodsell, David. S. (2004). "Bionanotechnology: lessons from nature." John Wiley and Sons, 2004.

Griffin, S., Masood, M. I., Nasim, M. J., Sarfraz, M., Ebokaiwe, A. P., Schäfer, K. H., & Jacob, C. (2017). Natural nanoparticles: a particular matter inspired by nature. *Antioxidants*, *7*(1), 3.

Hekmat, S., Aslani, M. M., Shafiee Ardestani, M., Aghasadeghi, M. R., Siadat, S. D., Sadat, S. M., & Tohidi, F. (2017). Preparation and characterization of PLGA Nanoparticles containing recombinant core-NS3 Fusion protein of hepatitis C virus as a nano-vaccine candidate. *Vaccine Research*, *4*(1), 13-18.

Ishihara, T., Kaneko, K., Ishihara, T., & Mizushima, T. (2014). Development of biodegradable nanoparticles for liver-specific ribavirin delivery. *Journal of Pharmaceutical Sciences*, *103*(12), 4005-4011.

Jangra, S., Landers, J. J., Rathnasinghe, R., O'Konek, J. J., Janczak, K. W., Cascalho, M., & Wong, P. T. (2021). A combination adjuvant for the induction of potent antiviral immune responses for a recombinant SARS-CoV-2 protein vaccine. *Frontiers in Immunology*, *12*, 729189.

Lang, L. (2009). FDA grants tentative approval for 75th generic antiretroviral drug. *Gastroenterology*, *136*(1), 5.

Lavan, D. A., McGuire, T., & Langer, R. (2003). Small-scale systems for in vivo drug delivery. *Nature Biotechnology*, *21*(10), 1184-1191.

Lee, M. Y., Yang, J. A., Jung, H. S., Beack, S., Choi, J. E., Hur, W., & Hahn, S. K. (2012). Hyaluronic acid–gold nanoparticle/interferon α complex for targeted treatment of hepatitis C virus infection. *ACS Nano*, *6*(11), 9522-9531.

Letvin, N. L. (2006). Progress and obstacles in the development of an AIDS vaccine. *Nature Reviews Immunology*, *6*(12), 930-939.

Levina, A. S., Repkova, M. N., Mazurkova, N. A., & Zarytova, V. F. (2016). Nanoparticle-mediated nonviral DNA delivery for effective inhibition of influenza a viruses in cells. *IEEE Transactions on Nanotechnology*, *15*(2), 248-254.

Li, Y., Lin, Z., Zhao, M., Xu, T., Wang, C., Hua, L.,& Zhu, B. (2016). Silver nanoparticle based codelivery of oseltamivir to inhibit the activity of the H1N1 influenza virus through ROS-mediated signaling pathways. *ACS Applied Materials and Interfaces*, *8*(37), 24385-24393.

Mabrouk, M., Das, D. B., Salem, Z. A., & Beherei, H. H. (2021). Nanomaterials for biomedical applications: Production, characterisations, recent trends and difficulties. *Molecules*, *26*(4), 1077.

Mamo, T and Poland, G. A. (2012). Nanovaccinology: the next generation of vaccines meets 21st century materials science and engineering. *Vaccine*, *47*(30), 6609-6611.

Mansoori, G. A. and Soelaiman, T. F., (2005). *Nanotechnology--An Introduction for the Standards Community*. ASTM International.

Mahmoud, N., Mahamb, M. and Nasrin, (2021). "Toxicity of biopolymer-based (nano) materials." Biopolymer-Based Metal Nanoparticle Chemistry for Sustainable Applications: Volume 1: Classification, Properties and Synthesis, Vol. 1 p. 215.

P. L. Chee, W. L., Toh, P. Y., Yew, S. Peng, and D. Kai, (2022). In Sustainable Nanotechnology, ed. Z. Li, J. Zheng, and E. Ye, The Royal Society of Chemistry, 2022, ch. 1, pp. 1-32.

Kandula Usha, (2017). Nanomedicine. 37-40.

Ratner, M. A. and Ratner, D. (2003). *Nanotechnology: A Gentle Introduction to the Next Big Idea*. Prentice Hall Professional.

Richman, D. D., Margolis, D. M., Delaney, M., Greene, W. C., Hazuda, D., & Pomerantz, R. J. (2009). The challenge of finding a cure for HIV infection. *Science*, *323*(5919), 1304-1307.

Rioux, G., Mathieu, C., Russell, A., Bolduc, M., Laliberté-Gagné, M. E., Savard, P., & Leclerc, D. (2014). PapMV nanoparticles improve mucosal immune responses to the trivalent inactivated flu vaccine. *Journal of Nanobiotechnology*, *12*, 1-6.

Ross, K. A., Loyd, H., Wu, W., Huntimer, L., Ahmed, S., Sambol, A., & Narasimhan, B. (2015). Hemagglutinin-based polyanhydride nanovaccines against H5N1 influenza elicit protective virus neutralizing titers and cell-mediated immunity. *International Journal of Nanomedicine*, 229-243.

Rostami, H., Ebtekar, M., Ardestani, M. S., Yazdi, M. H., & Mahdavi, M. (2017). Co-utilization of a TLR5 agonist and nano-formulation of HIV-1 vaccine candidate leads to increased vaccine immunogenicity and decreased immunogenic dose: A preliminary study. *Immunology Letters*, *187*, 19-26.

Sahoo, M., Vishwakarma, S., Panigrahi, C and Kumar, J. (2021). Nanotechnology: Current applications and future scope in food. *Food Frontiers*, 2: 3–22. https://doi.org/10.1002/fft2.58

Sakaue, G., Hiroi, T., Nakagawa, Y., Someya, K., Iwatani, K., Sawa, Y., & Kiyono, H. (2003). HIV mucosal vaccine: nasal immunization with gp160-encapsulated hemagglutinating virus of Japan-liposome induces antigen-specific CTLs and neutralizing antibody responses. *The Journal of Immunology*, *170*(1), 495-502.

Salah, N., Habib, S. S., Khan, Z. H., Memic, A., Azam, A., Alarfaj, E., & Al-Hamedi, S. (2011). High-energy ball milling technique for ZnO nanoparticles as antibacterial material. *International Journal of Nanomedicine*, 863-869.

Tavakoli, A., Rezaei, F., Nasab, G. S. F., Adjaminezhad-Fard, F., Noroozbabaei, Z., & Mokhtari-Azad, T. (2017). The comparison of sensitivity and specificity of ELISA-based microneutralization test with hemagglutination inhibition test to evaluate neutralizing antibody against influenza virus (H1N1). *Iranian Journal of Public Health*, *46*(12), 1690.

Toledo-Rueda, W., Rosas-Murrieta, N. H., Muñoz-Medina, J. E., González-Bonilla, C. R., Reyes-Leyva, J., & Santos-López, G. (2018). Antiviral resistance markers in influenza virus sequences in Mexico, 2000–2017. *Infection and Drug Resistance*, 1751-1756.

Tolochko, N. K. (2009). "History of Nanotechnology." Encyclopedia of Life Support Systems.

Wagner, V., Dullaart, A., Bock, A. K., & Zweck, A. (2006). The emerging nanomedicine landscape. *Nature Biotechnology*, *24*(10), 1211-1217.

Walensky, R. P. (2006). The survival benefits of AIDS treatment in the United States. *The Journal of Infectious Diseases*, *194*(1), 11-19.

Yousaf, S., Sidrah, A., Asrar, R., Kiran, S., and Abd-Elsalam, K. A. (2024). Nanostructured silica for enhanced fungicidal activity in agriculture. In *Nanofungicides* (pp. 349-373). Elsevier