# A GENERAL OVERVIEW OF NANOMEDICINE-EFFICACY IN THERAPEUTIC SCIENCE AND CURRENT RESEARCH DEMANDS

Rusha Chatterjee and Mahima Banerjee

Department of Chemical Engineering, University of Calcutta, Kolkata-700009, India

***ABSTRACT***

*Nanotechnology's introduction has dramatically improved a number of scientific fields, one of which is medicinal research. Nanomedicine is aimed to offer healthcare medications and chemicals a new dimension. The small size of nanoparticles, permits them to circulate in the body without interrupting oxygenation and escape filtration by both the renal and gastrointestinal networks. These are the few properties that distinguish them apart from traditional therapeutic procedures. The increased permeability and durability effect result in successful penetration inside the tumor tissues, providing cancer treatment a new lease on life. Efficient transportation pathways, on the other hand, produce genotoxicity and mutagenicity by interacting with genes that are essential for smooth functioning. As the specific interactions of nanomedicines with biological systems are still unknown, comprehending nanomedicines' toxicological effects is tough. The lack of regulatory direction in this field remains a research gap that we would want to examine in this study.*

***KEYWORDS***

*Nanomedicine, Drug delivery.*

## 1. INTRODUCTION

Humanity faces a rising variety of communicable diseases, with an expanding population and progressive changes in lifestyle. Most of these diseases affect not only the sufferer, but also the entire associated community, gradually spreading worldwide and, in severe situations, becoming an outbreak. Pandemics in the last century have proven the rapidity with which illnesses spread over the world [1]. According to a World Health Organization (WHO) study, the number of fatalities attributable to noncommunicable diseases is anticipated to rise, with cardiovascular diseases, respiratory sickness, kidney disorders, Alzheimer's disease, and other chronic ailments among the leading causes. Nanomedicine has the capability to provide prompt detection and prevention, while also substantially improving diagnostics and is projected to give therapeutic research a fresh perspective for more effective, and inexpensive healthcare. Nanomedicine's goal can be roughly explained as the total tracking, manipulation, building, healing, resistance, and enrichment of all human biological systems, starting at the atomic level and progressing via designed gadgets and nanostructures to accomplish medicinal values [2]. It is imperative to understand nanoscale to encompass bioactive constituents. The nanostructures could be utilised in a micro-device or a fundamental biological setting. However, nano-interactions within the setting of a bigger device or immediately within celluar body are always the focus.

Employing cell-specific targeting, drug delivery to targeted organs, and other techniques, nanotechnology could alleviate the constraints of traditional delivery, spanning challenging behaviour like bio-distribution to relatively small hurdles like intracellular trafficking [3].

Nanometric size has the advantage of being the scale of many biochemical processes in the human body, permitting nanoparticles to plausibly transcend biological boundaries to unlock additional sites of delivery and interact with DNA or small proteins at various levels, whether in blood or within organs, tissues, or cells [4]. This is so because, at the nanoscale, the surface to volume ratio becomes favourable, allowing surface attributes to play a key role in determining a material's potential behaviours. Due to the obvious rising demand for these nanoparticles in the medical field, it is vital to assess their biocompatibility in terms of NPs entering the body and coming into direct contact with cellular components [5]. Nanomaterials are examined in vivo after being validated in vitro to help comprehend whether their transport and functionality affect behaviour at the cellular level. Their complicated behaviour makes it difficult to fully comprehend the interaction processes between NPs and biological systems. The particles' capacity to bind and engage with biological material, as well as modify their surface structure based on their environment, adds to their complexity. When transitioning from in vitro to in vivo models, the complexity increases. Viscosity effects become significant at the nanoscale which makes studying nanofluids more complex than microfluidics [4]. The nanoparticles on the surface boost the particle's biocompatibility and duration in the bloodstream, as well as ensuring highly selective engagement to the intended target.

Even though the subject of nanomedicine and its impact on the pharmacy sector are both highly anticipated, there are now very limited regulatory guidelines in this field [6]. Certain nanomedicines function by interacting directly with DNA molecules or enzymes that are critical for normal genome synthesis and cell division, causing toxicity that may or may not be carcinogenic but have the potential to cause mutations [7]. There are still a few uncertainties in the case of particles that cannot be tracked after injection, posing possible security risks. The ambiguity produced by a lack of uniformity across the regulatory boards may have a serious effect on sponsorship, innovation, and commercialization of nano-products, damaging widespread approval and impression. The FDA is striving to design a benchmark to guarantee clinically useful production of nano-products, whether they are drugs, devices, or biologics, caused by a lack of information to assess their safety to people and the environment [8]. A further major hurdle is the identification of nanomedicines. These might be considered as medications or diagnostic implants, and worldwide authorities aren't quite in agreement. As a result, nanomedicine may be classified as a drug in one nation and a medical equipment in another, and the rules that must be followed will differ based on its categorization [9]. In the subsequent sections, we will cover the research gap and regulatory problems that require immediate attention, as well as the nanoparticle morphology that is impeding down the progression.

## 2. NANO- BASED DRUG DELIVERY SYSTEM

### 2.1. Drug Delivery Mechanism

Nanotechnology in drug delivery has the ability to revolutionize the treatment methods for diseases such as cancer, diabetes, neurodegenerative diseases, and vascular diseases [10]. Because of its potential advantages, such as the ability to modify properties like solubility, drug release profiles, diffusivity, bioavailability, and immunogenicity, drug design at the nanoscale has been widely researched [11]. The biophysical and biochemical properties of the targeted drugs chosen for treatment are the primary determinants of the use of a suitable nano-drug delivery system [12]. Moreover, considering the use of nanomedicine, issues such as nanoparticle toxicity must be taken into account. For this reason, nanoparticles have lately been used to reduce toxicity by incorporating them with natural products. The use of green chemistry to design drug-loaded nanoparticles is widely endorsed because it reduces the amount of toxic ingredients used in the biosynthetic process. As a result, using green nanoparticles to deliver drugs can reduce

medication side effects [13]. Furthermore, changes in the size, shape, hydrophobicity, and surface of nanostructures can also improve their bioactivity.

The goals of drug entrapment in nanoparticles are either improved delivery to or take-up by target cells, or reduced toxicity of the free drug to non-target organs. In both cases, the therapeutic index will rise, as will the dose margin, resulting in therapeutic efficacy (e.g., tumor cell death) and toxicity to other organ systems [14]. To prevent agglomeration, nanoparticles may need to be coated. Various polymers such as polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP), natural polymers such as dextran, chitosan, pullulan, and surfactants such as sodium oleate, dodecylamine, and others can be used to avoid agglomeration and keep the particles in colloidal suspension [15].

Using the properties of chitosan and carboxymethyl starch to create hydrogels loaded with insulin, *Makham* researched the use of chitosan cross linked starch polymers as carriers for oral insulin delivery. The major difficulty of this process is due to the proteases breaking down during insulin delivery [16].

The nasal route of administration can also be thought of as a potential substitute to the subcutaneous route of drug administration since it is highly vascularized and advantageous for drug delivery as drugs administered via this route do not undergo first-pass metabolism. However, it is essential to get past obstacles to nasal drug delivery, such as the lipophilic epithelium and muco-ciliary clearing, in order for this route to be successful [17]. Novel colloidal nanocarriers can be used to deliver naftifine in an efficient and nonhazardous manner. For dermal delivery, naftifine-loaded colloidal nanocarrier microemulsions were created. Microemulsions expanded the power of naftifine delivery in in vitro pig skin and in vivo human penetration experiments [18,19]. With the help of nanocarriers, it is possible to co-encapsulate various medications and regulate the timing of their release (as with the lipid-polymer hybrid nanoparticle), as well as to cause drug release in response to environmental factors like pH, temperature, light, and mechanical stress. Targeting nanoparticles immobilised on a scaffold's surface may be able to improve cell adhesion and direct cell migration with adjustments like cell-specific ligands or signalling molecules [20,22]. Furthermore, these controlled-release nanotechnologies can be used to efficiently deliver biological molecules to cells, such as DNA and siRNA, to control how they behave. This idea has been revealed in light of the relatively recent development of poly(-amino esters)-DNA nanoparticles, which were used to genetically modify stem cells for improved angiogenesis [24].

In the upcoming years, nanomedicine will find its use in gene therapy. Desirable genes can be introduced into the human subject by means of non- viral nanoparticles for successful transfer. Recent studies have shown that biodegradable, polymeric gene delivery nanoparticles successfully eliminated glioma cells in rat brain [25]. In the domain of tissue regeneration and cosmetic surgery, nanoporous carrier materials are now being used as matrices through which controlled cell growth occurs [26]. Nanoparticles can also be used to target defective nerve cells to treat neural disorders such as Alzheimer’s and Parkinson’s. Therefore, drug delivery using nanoparticles will usher in an era of advanced healthcare with cures available for previously considered untreatable diseases.

## 2.2. Nanoparticles Used

Today, scientists can encapsulate medicine in nanoparticles which are as minuscle as the average size of viruses. These nanoparticles work well for drug delivery. Nanoparticles used in medical science are divided into sections that cover inorganic (metallic and metal oxide) nanoparticles, liposomes, organic nanoparticles, and hybrid nanoparticles [23]. Each section discusses the

special abilities of nanoparticles for in vitro detection, in vivo diagnosis, multimodal imaging, chemo-, photo-, gene-, immunotherapy, theranostics, and their clinical translation [24].

As it quite often makes up the majority of the particle, the non-payload segment of NPs is not simply inert matter; it also interacts with the surrounding biology in both implicit and explicit ways. In particular, if the effects go beyond the NPs' envisioned use, there hasn't been much research into how the payload-independent composition of NPs affects and affects the biological systems with which it makes contact [27].

Applications include the usage of biodegradable polymers in nanoparticle drug delivery provides an improved, less hazardous solution to problems encountered with conventional anti-cancer drugs used during chemotherapy. These drugs which are aimed at the tumor tissue have poor specificity and dose-limiting toxicity [28]. The polymer specificity can be changed depending on the type of drug and the delivery can be either active or passively done.

Types of Nanoparticles used in drug delivery:

### 2.2.1. Polymeric Nanoparticles

They are biocompatible in nature and the formulation is quite simple. Therapeutics can be incorporated inside the NP core, encapsulated in the polymer matrix, chemically conjugated to the polymer, or confined to the surface of the NP. This allows for the delivery of a wide range of drugs, including hydrophobic and hydrophilic compounds and those with varying molecular weights such as small molecules, biological macromolecules, proteins, and vaccines [29-35].

### 2.2.2. Inorganic Nanoparticles

They have nanostructures composed of inorganic materials such as gold, iron, and silica. Gold nanoparticles are especially of interest to researchers owing to their unique adaptabilities and distinct physical, electrical, magnetic, and optical properties [36]. Inorganic NPs are best equipped for implementations such as diagnostics, imaging, and photothermal therapies due to their magnetic, radioactive, or plasmonic properties. Low solubility and toxicity concerns, – particularly in compositions using heavy metals, however, restrict their therapeutic applications [37,38].

### 2.2.3. Lipid-Based Nanoparticles

They are the most prevalent category of nanomedicines with FDA approval [39,40]. Phospholipids, which can create unilamellar and multilamellar vesicular structures, make up the majority of the NPs. As a result, the liposome can transport and deliver drugs that are lipophilic, hydrophilic, and hydrophobic [41]. However, LNP systems may still be constrained by low drug loading and biodistribution [40].

## 2.3. Targeting Strategies

Meticulous drug delivery strategies are an essential area of research as they not only deliver the pharmaceuticals to their targeted sites in active form with enough dosage but also reduce accumulation at the unwanted tissues which also prevent healthy cells from coming in contact with immunosuppressive substances. The nucleus being the ultimate focus for many therapeutics makes it crucial for precise nanoparticle modeling and implementation to result in good uptake of the medication molecule [42]. The methods used to direct drugs toward the desired organ are briefly covered here.

### 2.3.1. Passive Targeting

The capacity of a drug nanocarrier to circulate around the target site and accumulate over an extended period of time is referred to as passive targeting [43]. The endothelium of blood arteries becomes more porous due to inflammation/hypoxia, a state that is typical of malignancy. In such a situation, the blood arteries that already exist are clogged, and the tumor's absence of normal lymphatic outflow leads to the accumulation of NPs. Small molecule medications, which have nearly instantaneous circulation and rapid excretion from the tumour, are exempt from this special property [42]. Making the nanoparticle surface hydrophilic by adding a polyethylene glycol (PEG) coating on it is the most typical alteration utilised to avoid macrophage trapping and lengthen circulation time. The particles' hydrophobic interactions with the reticuloendothelial system (RES) give them this feature, which allows the drug-loaded nanoparticle to circulate for considerable durations [44].

### 2.3.2. Active Targeting

In order to make the drug delivery more site specific, active targeting improvises on the effects of passive targeting [45]. This technique involves the attachment of nanoparticles (NPs) to the target location via ligand-receptor linkages. The associated NPs are absorbed before the drug is administered inside the cell, resulting in improved drug penetration compared to passively targeted systems. The first indication of this phenomena was put forth in 1980 with the grafting of antibodies onto the liposome surface [46]. Many varied types of ligands, including as peptides, nucleic acids, and aptamers, were then added [47]. Folic acid (FA), which is prevalent in TME and preferentially attaches to the folate receptor (FAR), is one of the more well-known instances of ligands. Various strategies have been introduced in this situation, including the creation of FA-drug conjugates and the FA-grafting onto nanocarriers that promote their cellular uptake in tumor cells [48].

### 2.3.3. Inverse Targeting

Inverse targeting seeks to change the drug's pharmacokinetics in a specific way that moves it away from areas where it could cause toxicity [49]. In order to accomplish this, a significant amount of blank colloidal carriers or macromolecules, such as dextran sulphate, are pre-injected to block the normal function of the RES (ReticuloEndothelial Systems). This strategy makes it easier to deactivate defence mechanisms and saturate RES [50].

### 2.3.4. Dual Targeting

The ability to target two or more receptors and subsequently deliver more medications to the cells is one benefit of dual-targeted liposomes. Another benefit is that the carrier molecule itself has therapeutic action, which boosts the drug's activity and therapeutic efficacy. Reduced normal tissue toxicity might also be achieved through dual targeting [49].

## 3. APPLICATION OF NANO-DRUG DELIVERY SYSTEM

In the fields of medicine and contemporary biology, NDDSs have emerged as a potent tool for optimising drug delivery and are now a popular area for research [52]. The EPR (enhanced permeability and retention) affect nanoscale molecules to gather largely in tumour tissue than in healthy tissue. This is due to the rapid development of blood vessels that are needed by speedily expanding tumours, which have a high oxygen requirement. Research has revealed that lung, breast, and ovarian tumours react positively and exhibit the EPR effect the most [53]. Another

area where the use of NDDSs has been successful is in the treatment of CAD (coronary artery disease), which is reported dangerous for people over the age of 35. Currently, there are primarily two ways to treat CAD: (a) non-invasive management through medication therapy, and (b) invasive therapy through mechanical revascularization (PCI or CABG). After PCI, the endothelium is almost entirely depleted. In a study, an endothelial cell-attracting nanofibrous matrix was employed. The development of endothelial cells, which is necessary for the good operation of the arteries and veins, significantly improved as a result of the study. Additionally reduced in vitro were platelet cell adhesion and smooth muscle cell growth. The patient's functional vascular transplant is employed during coronary artery bypass graft (CABG) surgery to bypass the constricting coronary arteries and re-establish cardiovascular circulatory system. In case the patient's natural blood vessels are not obtainable as they might be dysfunctional, TEVGs (tissue engineered vascular grafts) which are flexible like the regular arteries are a possible remedy to this difficulty [54]. The treatment of HIV (human immunodeficiency virus) and AIDS (acquired immune deficiency syndrome), two severe illnesses in which the immune response of the patient is essentially decimated, has also been greatly aided by nanotechnology. For those who have this condition, taking a huge number of tablets is necessary, but owing to TDDSs, this therapy can be made even more successful by synthesizing polymeric nanoparticles that carry antiretroviral (ARV) medications both intracellularly and to the brain. In order to prevent HIV infections, this technology can also be utilised in conjunction with immunizations. Numerous studies have shown that antiretroviral drug-loaded nanoparticles can specifically target monocytes and macrophages in vitro [55]. The discovery of quantum dots, which can be produced on demand in a wide variety of clearly distinct hues, was a significant advance in the field of nanotechnology. Quantum dot tagging has a number of benefits. Through the use of nanodots of a particular hue, this technique also enables the concurrent monitoring of numerous biological activities [56]. Theranostic nanoparticles, which can be used for both diagnosis and treatment, have received a lot of attention recently. It is conceivable to track the pathway and localization of these nanoparticles at the target region as well as drug action to evaluate therapeutic response by combining both a drug and an imaging agent in one ingenious combination [57]. Nanotechnology is thus able to transport medications for extended periods of time with less occasional dosage, as well as with more accuracy and depth in hard-to-access tissues, by manipulating molecular size and surface morphology. Considerable efforts have been made to learn more about the use of nanotechnology in foods, particularly in the encapsulation and delivery methods of food bioactives, in response to the growing attention in employing nanoparticles in the nutraceutical sector [58]. Due to the ease with which many of these bioactives can be quickly inactivated or degraded, encasing them helps to delay or stop the degradative processes until the bioactives are delivered to the target site(s) where their functions are needed. One area that has to be investigated in the future is the utilisation of this direct nanoparticle uptake, in particular for soluble but poorly absorbed chemicals, as well as the potential negative effects of these [59].

## 4. NANOTOXICOLOGY-RISK ASSESSMENT

The noteworthy organisations, including the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA),18 and national medicinal agencies in Europe, are concerned with patient safety, efficacy, and quality as a result of the use of nanomaterials in drug products [60,61]. The four main components of a risk assessment are hazard identification, toxicity assessment, exposure assessment, and risk characterization. Nanomaterials can have adverse effects, and determining their toxicity requires an understanding of their metabolism and dispersion in the body. A variety of techniques for determining the distribution of nanomedicine in a patient are currently available, such as radiolabeling, which can be used to evaluate distribution and uptake into specific cells and tissues. Distribution is determined by a number of factors, including the targeting mechanism. Cancer cells can be targeted using antibody

conjugation to a medication; direct targeting can be enabled so that the nanomedicine is taken up by specific cells; and nanomedicine can passively diffuse into tissues or cells, for example, by exploiting leaky endothelium in blood vessels surrounding some solid tumors. In each case, the medicine has the potential to reach a different population of unintended cells. This situation is complicated by the availability of numerous delivery options. The possibility of using a variety of delivery routes, such as oral, transdermal, intravenous, and inhalation, further complicates the situation. Furthermore, whether the nanomaterial remains localized or re-enters the circulatory system, as well as how it is used or metabolized, must be considered [62].

The greatest degree of unpredictability in any clinical area is in fact the "First in human" (FIH) trials of nanotechnology medical applications. Therefore, in spite of the advantages of nanoparticles in health science, risks and uncertainties are innate [63]. It is critical to perform a thorough morphological, physicochemical, in vitro, and in vivo biological characterization not only on manufactured nanomaterials but also on nanomaterials after contact with biological systems [64]. When the NM under investigation has unidentified toxicity, a Weight of Evidence (WoE) approach can be considered. Risk assessment is determined after careful hazard identification and prioritization, which takes into account and weights all available in vitro data. This could be done even without animal testing data [65].

In order to create new standards and encourage a coordinated strategy between Europe and the US, the European Nanomedicine Characterization Laboratory (EUNCL, euncl.eu) and the US National Cancer Institute Nanotechnology Characterization Laboratory (NCI-NCL) have backed nanomedicine developers in an unbiased manner. Unfortunately, despite their best efforts, there are currently only a handful of standard techniques for the characterization of nanomedicines due to the difficulty of standardising categorization approaches on numerous extremely specific nanomaterials. The absence of standardised methods to measure the following factors has been found to have significant gaps: (i) drug loading (free vs. encapsulated drug), (ii) particle stability in plasma, including drug release kinetics, (iii) surface properties and surface interactions with the biological environment, and (iv) particle interactions with the immune system [64-66]. Management of such risks is a systematic process, as well as risk communication, but they are also among the most difficult issues in nanomedicine clinical research [69].

The bioavailability, biodistribution, degradation, elimination, and biological activity of nanostructures can still be tough to predict in advance, despite the wealth of knowledge on nanotoxicity that has built up over the past ten years [70]. Since not all nanomaterials are created in the exact same manner, according to nanotoxicologists, discrepancies in the biological response may still take place even if the deviations from the materials' properties are negligible [71]. Computational toxicology assessment could be performed instead of laboratory based tests. These include structure–activity relationship models, physiologically based pharmacokinetic models, and molecular modeling based on a database created to effeiciently predict the behaviour of nanomedicine and its toxicity threshold. Thus, data integration and computational analysis can make the tedious and difficult method of toxicology risk assessment much simpler [72].

## 5. CHALLENGES AND REGULATORY CONCERNS

Nanomedicines possess greater efficiency and adaptability to deliver drugs at the target site [73]. However, only a handful of nano medicines have received approval for clinical usage as there are still several obstacles and regulatory concerns regarding their application [74,75]. Only 50 nano pharmaceuticals have been approved by the FDA and are presently accessible for clinical use between 1995 and 2017 [76]. In order to produce a reliable product with consistent physicochemical characteristics, biological behaviors, and pharmacological profiles, nanomedicine products require extensive design and engineering, stringent safety

characterization of physicochemical properties, and reproducible scale-up and manufacturing processes [77]. It is difficult to classify nanomedicines as their behavior changes with a slight tweak to one or more of their parameters. A crucial parameter that assesses the variability of particle size, shape, or mass is polydispersity (PD), for instance. When a nanomedicine product has a similar average size but a different PD, the secondary properties, such as targeting capabilities, drug release speed, biocompatibility, toxicity, and in vivo behaviours, may undergo significant shifts [78-82].

Complex components, such as proteins or nucleic acids, are often included in proposed nanotherapeutics [83,84]. These components can be sensitive to the circumstances of the production process and, in some cases, change in composition [81]. Environmental safety is another such concern when producing nanoparticles. As airborne nanoparticles disperse as aerosols, handling dry materials with nanometer-scale requires extra vigilance [85,86]. Pulmonary toxicities from such nanoparticles can result from lung deposition. The skin barrier can also be breached by some nanoparticles. For this reason, professionals must be adequately protected [85].

Numerous nanomedicines connect with genetic material directly or with proteins necessary for cell proliferation and proper genome function, both of which have the potential to be genotoxic and mutagenic. The inflammatory response of neutrophils and macrophages, which induce oxidative and nitrosative stress, mediates this toxicity to nanomedicines [87]. There are certainly countless uncertainties for particles that cannot be traced after distribution, which could result in safety risks. The primary challenge for the regulation of nanomedicines is the utilisation of safety information from larger particles by regulatory organisations like the FDA, which do not exhibit the same pharmacologic and pharmacokinetic behaviour as nanomedicines [88]. Nanomaterial and nanomedicine sustainability is frequently interpreted in many different ways during scale-up and manufacturing processes. As a result, certain guidelines and guarantees are needed for approval. To better comprehend the production concept for nanomedicines, it is vital to assess and regulate manufacturing techniques at crucial details by developing Critical Quality Attributes (CQA) [89]. Some other difficulties authorities face are nanotoxicology and biological response. Before adequate regulatory advice is produced, new tests to assess the toxicity of nanomaterials and nanomedicines are needed, which is a problem that is seriously impeding headway. Another issue concerning the regulation of nanomedicines is the question of who should be in charge of developing nanomedicine guidelines. Due to the general newness of the technology and the diversity of nanomedicines' modes of action, key bodies frequently lack scientific expertise on the subject. When there is limited knowledge of nanomedicines, it is difficult to develop adequate regulations, and any regulations created may not be appropriate to preserve medication satisfaction and regulate the use of nanomedicines in a medical context [87,90].

## 6. CONCLUSION

We anticipate many more breakthroughs in the use of nanomedicine in therapeutics, ushering in a new era of advanced healthcare and pharmaceutical science. Nanomedicines will not only improve overall efficacy and success rates when compared to traditional medications, but they will also reduce toxicity, which is a common side effect of cancer treatments. Chemotherapy, hyperthermia, radiation therapy, gene or RNA interference (RNAi) therapy, and many other nanotechnology-enabled therapeutic modalities are being studied in clinical trials. Therapeutic nanoparticle (NP) mediums such as liposomes, albumin NPs, and polymeric micelles have been approved for cancer treatment, and many other nanotechnology-enabled therapeutic methods are under clinical investigation. To minimize any possible risks to human health and the environment, risk evaluations are necessary before new nano-based products are approved for clinical and commercial use, just as they are for any other product. In order to speed up the

approval procedure of nanomedicine drugs, it is essential for regulatory organizations to work collectively. Given the growing demand for precise medicines, we hope that the affordability of nanomedicines will also be addressed and researched upon.

## REFERENCES


[1] K. F. Smith et al., (2014) "Global rise in human infectious disease outbreaks," J. R. Soc. Interface, vol. 11, no. 101, p. 20140950.

[2] R. A. Freitas Jr, (2005) "What is nanomedicine?," Nanomedicine, vol. 1, no. 1, pp. 2–9.

[3] M. J. Mitchell, M. M. Billingsley, R. M. Haley, M. E. Wechsler, N. A. Peppas, and R. Langer, (2021) "Engineering precision nanoparticles for drug delivery," Nat. Rev. Drug Discov., vol. 20, no. 2, pp. 101–124.

[4] P. Boisseau and B. Loubaton, "Nanomedicine, nanotechnology in medicine, (2011)" C. R. Phys., vol. 12, no. 7, pp. 620–636.

[5] X. Li, L. Wang, Y. Fan, Q. Feng, and F.-Z. Cui, (2012) "Biocompatibility and toxicity of nanoparticles and nanotubes," J. Nanomater., vol. 2012, pp. 1–19.

[6] X.-Q. Zhang, X. Xu, N. Bertrand, E. Pridgen, A. Swami, and O. C. Farokhzad, (2012) "Interactions of nanomaterials and biological systems: Implications to personalized nanomedicine," Adv. Drug Deliv. Rev., vol. 64, no. 13, pp. 1363–1384.

[7] N. Singh et al., (2009) "NanoGenotoxicology: the DNA damaging potential of engineered nanomaterials," Biomaterials, vol. 30, no. 23–24, pp. 3891–3914.

[8] R. Foulkes, E. Man, J. Thind, S. Yeung, A. Joy, and C. Hoskins, (2020) "The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives," Biomater. Sci., vol. 8, no. 17, pp. 4653–4664.

[9] A. Baun and S. F. Hansen, (2008) "Environmental challenges for nanomedicine," Nanomedicine (Lond.), vol. 3, no. 5, pp. 605–608.

[10] D. J. Irvine and E. L. Dane, (2020) "Enhancing cancer immunotherapy with nanomedicine," Nature Reviews Immunology, vol. 20, no. 5, pp. 321–334.

[11] J. K. Patra et al., (2018) "Nano based drug delivery systems: recent developments and future prospects," Journal of Nanobiotechnology, vol. 16, no. 1.

[12] B. Xu, R. Watkins, L. Wu, C. Zhang, and R. Davis, (2015) "Natural product-based nanomedicine: recent advances and issues," International Journal of Nanomedicine, p. 6055.

[13] P.-L. Lam, W.-Y. Wong, Z. Bian, C.-H. Chui, and R. Gambari, (2017) "Recent advances in green nanoparticulate systems for drug delivery: efficient delivery and safety concern," Nanomedicine, vol. 12, no. 4, pp. 357–385.

[14] de Jong, (2008) "Drug delivery and nanoparticles: Applications and hazards," International Journal of Nanomedicine, vol. 3, no. 2, p. 133.

[15] A. K. Gupta and M. Gupta, (2005) "Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications," Biomaterials, vol. 26, no. 18, pp. 3995–4021.

[16] M. Mahkam, "Modified Chitosan Cross-linked Starch Polymers for Oral Insulin Delivery," Journal of Bioactive and Compatible Polymers, vol. 25, no. 4, pp. 406–418, May 2010, doi: 10.1177/0883911510369038.

[17] M. O. Emeje and I. C. Obidike, "Nanotechnology in Drug Delivery," Oct. 31, 2012.

[18] M. S. Erdal, G. Özhan, M. C. Mat, Y. Özsoy, and S. Güngör, (2016) "Colloidal nanocarriers for the enhanced cutaneous delivery of naftifine: characterization studies and in vitro and in vivo evaluations," International Journal of Nanomedicine, vol. 11, pp. 1027–1037.

[19] H. Jahangirian, E. G. Lemraski, T. J. Webster, R. Rafiee-Moghaddam, and Y. Abdollahi, (2017) "A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine," International Journal of Nanomedicine, vol. 12, pp. 2957–2978.

[20] S. Sengupta et al., (2005) "Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system," Nature, vol. 436, no. 7050, pp. 568–572.

[21] J. Shi, A. R. Votruba, O. C. Farokhzad, and R. Langer, (2010) "Nanotechnology in Drug Delivery and Tissue Engineering: From Discovery to Applications," Nano Letters, vol. 10, no. 9, pp. 3223–3230.

[22] F Yang et al., (2010) "Genetic Engineering of human cells human stem cells for enhanced angiogenesis using biodegradable polymeric nanoparticles", Proc. Natl. Acad. Sci. U.S.A.; vol. 107, no. 8, pp. 3317–3322.

[23] W. Lin, (2015) "Introduction: Nanoparticles in Medicine," Chemical Reviews, vol. 115, no. 19, pp. 10407–10409.
[24] J.-C. Leroux, E. Allémann, F. De Jaeghere, E. Doelker, and R. Gurny, (1996) "Biodegradable nanoparticles — From sustained release formulations to improved site specific drug delivery," Journal of Controlled Release, vol. 39, no. 2–3, pp. 339–350.
[25] A. Mangraviti et al., (2015) "Polymeric Nanoparticles for Nonviral Gene Therapy Extend Brain Tumor Survival in Vivo," ACS Nano, vol. 9, no. 2, pp. 1236–1249.
[26] K. MG, K. V, and H. F, (20150 "History and Possible Uses of Nanomedicine Based on Nanoparticles and Nanotechnological Progress," Journal of Nanomedicine & Nanotechnology, vol. 06, no. 06.
[27] E. P. Stater, A. Y. Sonay, C. Hart, and J. Grimm, (2021) "The ancillary effects of nanoparticles and their implications for nanomedicine," Nature Nanotechnology, vol. 16, no. 11, pp. 1180–1194.
[28] R. Sinha, (2006) "Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery," Molecular Cancer Therapeutics, vol. 5, no. 8, pp. 1909–1917.
[29] L. Zhang et al., (2020) "Microfluidic-assisted polymer-protein assembly to fabricate homogeneous functionalnanoparticles," Materials Science & Engineering. C, Materials for Biological Applications, vol. 111, p. 110768.
[30] M. Caldorera-Moore, J. E. Vela Ramirez, and N. A. Peppas, (2019) "Transport and delivery of interferon-α through epithelial tight junctions via pH-responsive poly(methacrylic acid-grafted-ethylene glycol) nanoparticles," Journal of Drug Targeting, vol. 27, no. 5–6, pp. 582–589.
[31] F. C. Knight et al., (2019) "Mucosal Immunization with a pH-Responsive Nanoparticle Vaccine Induces Protective CD8+ Lung-Resident Memory T Cells," ACS Nano, vol. 13, no. 10, pp. 10939–10960.
[32] M. S. Strand et al., (2019) "Precision delivery of RAS-inhibiting siRNA to KRAS driven cancer via peptide-based nanoparticles," Oncotarget, vol. 10, no. 46, pp. 4761–4775.
[33] Jose et al., (2019) "Transferrin-Conjugated Docetaxel–PLGA Nanoparticles for Tumor Targeting: Influence on MCF-7 Cell Cycle," Polymers, vol. 11, no. 11, p. 1905.
[34] X. Liu et al., (2020)"Glucose and H2O2 Dual-Responsive Polymeric Micelles for the Self-Regulated Release of Insulin," ACS Applied Bio Materials, vol. 3, no. 3, pp. 1598–1606, Feb. 2020, doi: 10.1021/acsabm.9b01185.
[35] M. J. Mitchell, M. M. Billingsley, R. M. Haley, M. E. Wechsler, N. A. Peppas, and R. Langer, (2020) "Engineering precision nanoparticles for drug delivery," Nature Reviews Drug Discovery, vol. 20, pp. 1–24.
[36] W. Yang, H. Liang, S. Ma, D. Wang, and J. Huang, (2019) "Gold nanoparticle based photothermal therapy: Development and application for effective cancer treatment," Sustainable Materials and Technologies, vol. 22, p. e00109.
[37] L. Arias, J. Pessan, A. Vieira, T. Lima, A. Delbem, and D. Monteiro, (2018) "Iron Oxide Nanoparticles for Biomedical Applications: A Perspective on Synthesis, Drugs, Antimicrobial Activity, and Toxicity," Antibiotics, vol. 7, no. 2, p. 46.
[38] B. B. Manshian, J. Jiménez, U. Himmelreich, and S. J. Soenen, (2017) "Personalized medicine and follow-up of therapeutic delivery through exploitation of quantum dot toxicity," Biomaterials, vol. 127, pp. 1–12,.
[39] A. C. Anselmo and S. Mitragotri, (2019) "Nanoparticles in the clinic: An update," Bioengineering & Translational Medicine, vol. 4, no. 3.
[40] O. S. Fenton, K. N. Olafson, P. S. Pillai, M. J. Mitchell, and R. Langer, (2018) "Advances in Biomaterials for Drug Delivery," Advanced Materials, vol. 30, no. 29, p. 1705328.
[41] M. Sarfraz et al., (2018) "Development of Dual Drug Loaded Nanosized Liposomal Formulation by A Reengineered Ethanolic Injection Method and Its Pre-Clinical Pharmacokinetic Studies," Pharmaceutics, vol. 10, no. 3, p. 151.
[42] M. F. Attia, N. Anton, J. Wallyn, Z. Omran, and T. F. Vandamme, (2019) "An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites," Journal of Pharmacy and Pharmacology, vol. 71, no. 8, pp. 1185–1198.
[43] S. Sagnella and C. Drummond, (1970) "Drug Delivery: A nanomedicine approach",Australian Biochemist, vol. 43, no.3, pp. 5-8.
[44] L. E. van Vlerken, T. K. Vyas, and M. M. Amiji, (2007) "Poly(ethylene glycol)-modified nanocarriers for tumor-targeted and intracellular delivery," Pharm. Res., vol. 24, no. 8, pp. 1405–1414.

[45] T. D. Clemons, R. Singh, A. Sorolla, N. Chaudhari, A. Hubbard, and K. S. Iyer, (2018) "Distinction between active and passive targeting of nanoparticles dictate their overall therapeutic efficacy," Langmuir, vol. 34, no. 50, pp. 15343–15349.
[46] L. D. Leserman, J. Barbet, F. Kourilsky, and J. N. Weinstein, (1980) "Targeting to cells of fluorescent liposomes covalently coupled with monoclonal antibody or protein A," Nature, vol. 288, no. 5791, pp. 602–604.
[47] N. Kamaly, Z. Xiao, P. M. Valencia, A. F. Radovic-Moreno, and O. C. Farokhzad, (2012)"Targeted polymeric therapeutic nanoparticles: design, development and clinical translation," Chem. Soc. Rev., vol. 41, no. 7, pp. 2971–3010.
[48] W. Arap, R. Pasqualini, and E. Ruoslahti, (1998) "Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model," Science, vol. 279, no. 5349, pp. 377–380.
[49] J. P. Balthasar and H. L. Fung, (1996) "Inverse targeting of peritoneal tumors: selective alteration of the disposition of methotrexate through the use of anti-methotrexate antibodies and antibody fragments," J. Pharm. Sci., vol. 85, no. 10, pp. 1035–1043.
[50] S. P. Dunuweera, R. M. S. I. Rajapakse, R. B. S. D. Rajapakshe, S. H. D. P. Wijekoon, M. G. G. S. Nirodha Thilakarathna, and R. M. G. Rajapakse, (2019) "Review on targeted drug delivery carriers used in nanobiomedical applications," Curr. Nanosci., vol. 15, no. 4, pp. 382–397.
[51] N. AlSawaftah, W. G. Pitt, and G. A. Husseini, (2021) "Dual-targeting and stimuli-triggered liposomal drug delivery in cancer treatment," ACS Pharmacol. Transl. Sci., vol. 4, no. 3, pp. 1028–1049.
[52] J. Silva, A. R. Fernandes, and P. V. Baptista, (2014) "Application of nanotechnology in drug delivery," in Application of Nanotechnology in Drug Delivery, A. D. Sezer, Ed. London, England: InTech.
[53] Rajora, D. Ravishankar, H. Osborn, and F. Greco, (2014) "Impact of the enhanced permeability and retention (EPR) effect and cathepsins levels on the activity of polymer-drug conjugates," Polymers (Basel), vol. 6, no. 8, pp. 2186–2220.
[54] P. Ambesh et al., (2017) "Nanomedicine in coronary artery disease," Indian Heart J., vol. 69, no. 2, pp. 244–251.
[55] S. A. A. Rizvi and A. M. Saleh, (2018) "Applications of nanoparticle systems in drug delivery technology," Saudi Pharm. J., vol. 26, no. 1, pp. 64–70.
[56] R. Datta and S. S. Jaitawat, (2006) "Nanotechnology - the new frontier of medicine," Med J. Armed Forces India, vol. 62, no. 3, pp. 263–268.
[57] M. S. Bhojani, M. Van Dort, A. Rehemtulla, and B. D. Ross, (2010) "Targeted imaging and therapy of brain cancer using theranostic nanoparticles," Mol. Pharm., vol. 7, no. 6, pp. 1921–1929.
[58] D. J. McClements and J. Rao, (2011) "Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity," Crit. Rev. Food Sci. Nutr., vol. 51, no. 4, pp. 285–330.
[59] K. A. Ishak, M. S. Mohamad Annuar, and N. Ahmad, (2017) "Nano-delivery Systems for Nutraceutical Application," in Nanotechnology Applications in Food, Elsevier, pp. 179–202.
[60] B. S. Zolnik and N. Sadrieh, (2009) "Regulatory perspective on the importance of ADME assessment of nanoscale material containing drugs," Advanced Drug Delivery Reviews, vol. 61, no. 6, pp. 422–427.
[61] F. Ehmann et al., (2013) "Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines," Nanomedicine, vol. 8, no. 5, pp. 849–856.
[62] I. Linkov, F. K. Satterstrom, and L. M. Corey, (2008) "Nanotoxicology and nanomedicine: making hard decisions," Nanomedicine: Nanotechnology, Biology and Medicine, vol. 4, no. 2, pp. 167–171, 001.
[63] J. Kimmelman and A. J. London, (2011) "Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty," PLoS Medicine, vol. 8, no. 3, p. e1001010.
[64] L. Accomasso, C. Cristallini, and C. Giachino, (2018) "Risk Assessment and Risk Minimization in Nanomedicine: A Need for Predictive, Alternative, and 3Rs Strategies," Frontiers in Pharmacology, vol. 9.
[65] D. R. Hristozov et al., (2012) "A weight of evidence approach for hazard screening of engineered nanomaterials," Nanotoxicology, vol. 8, no. 1, pp. 72–87.
[66] "Global Summit on Regulatory Science 1 (GSRS16) Nanotechnology Standards and Applications," 2016.

[67] K. B. Halamoda et al., (2019) "Anticipation of regulatory needs for nanotechnology-enabled health products," JRC Publications Repository.
[68] S. Bremer-Hoffmann, B. Halamoda-Kenzaoui, and S. E. Borgos, (2018) "Identification of regulatory needs for nanomedicines," Journal of Interdisciplinary Nanomedicine, vol. 3, no. 1, pp. 4–15.
[69] D. B. Resnik and S. S. Tinkle, (2007) "Ethics in nanomedicine," Nanomedicine, vol. 2, no. 3, pp. 345–350.
[70] M. Zhou et al., (2019) "The Bioavailability, Biodistribution, and Toxic Effects of Silica-Coated Upconversion Nanoparticles in vivo," Frontiers in Chemistry, vol. 7, p. 218.
[71] P. M. Costa and B. Fadeel, (2016) "Emerging systems biology approaches in nanotoxicology: Towards a mechanism-based understanding of nanomaterial hazard and risk," Toxicology and Applied Pharmacology, vol. 299, pp. 101–111.
[72] N. L. von Ranke et al., (2022) "Applying in silico approaches to nanotoxicology: Current status and future potential," Computational Toxicology, vol. 22, p. 100225.
[73] K. A. Howard, (2016) "Nanomedicine: Working Towards Defining the Field," Advances in Delivery Science and Technology, pp. 1–12.
[74] R. Gaspar and R. Duncan, (2009) "Polymeric carriers: Preclinical safety and the regulatory implications for design and development of polymer therapeutics," Advanced Drug Delivery Reviews, vol. 61, no. 13, pp. 1220–1231.
[75] W. R. Sanhai, J. H. Sakamoto, R. Canady, and M. Ferrari, (2008) "Seven challenges for nanomedicine," Nature Nanotechnology, vol. 3, no. 5, pp. 242–244.
[76] C. L. Ventola, (2017) "Progress in Nanomedicine: Approved and Investigational Nanodrugs," P & T : a peer-reviewed journal for formulary management, vol. 42, no. 12, pp. 742–755.
[77] L.-P. Wu, D. Wang, and Z. Li, (2020) "Grand challenges in nanomedicine," Materials Science and Engineering: C, vol. 106, p. 110302.
[78] K. L. Aillon, Y. Xie, N. El-Gendy, C. J. Berkland, and M. L. Forrest, (2009) "Effects of nanomaterial physicochemical properties on in vivo toxicity," Advanced Drug Delivery Reviews, vol. 61, no. 6, pp. 457–466.
[79] M. A. Dobrovolskaia and S. E. McNeil, (2007) "Immunological properties of engineered nanomaterials," Nature Nanotechnology, vol. 2, no. 8, pp. 469–478.
[80] A. E. Nel et al., (2009) "Understanding biophysicochemical interactions at the nano–bio interface," Nature Materials, vol. 8, no. 7, pp. 543–557.
[81] G. F. Paciotti et al., (2004) "Colloidal Gold: A Novel Nanoparticle Vector for Tumor Directed Drug Delivery," Drug Delivery, vol. 11, no. 3, pp. 169–183.
[82] L. Li et al., (2004) "A novel antiangiogenesis therapy using an integrin antagonist or anti-Flk-1 antibody coated 90Y-labeled nanoparticles," International Journal of Radiation Oncology, Biology, Physics, vol. 58, no. 4, pp. 1215–1227.
[83] O. C. Farokhzad et al., (2006) "Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo," Proceedings of the National Academy of Sciences of the United States of America, vol. 103, no. 16, pp. 6315–6320.
[84] N. Desai, (2012) "Challenges in Development of Nanoparticle-Based Therapeutics," The AAPS Journal, vol. 14, no. 2, pp. 282–295.
[85] A. Nel, (2006) "Toxic Potential of Materials at the Nanolevel," Science, vol. 311, no. 5761, pp. 622–627.
[86] Y. Song, X. Li, and X. Du, (2009) "Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma," European Respiratory Journal, vol. 34, no. 3, pp. 559–567.
[87] R. Foulkes, E. Man, J. Thind, S. Yeung, A. Joy, and C. Hoskins, (2020) "The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives," Biomater. Sci., vol. 8, no. 17, pp. 4653–4664.
[88] B. Raj, A. G. F., and R. Brian, (2016) "Handbook of clinical nanomedicine: Law, business, regulation, safety, and risk, 1st ed. Singapore", Singapore: Pan Stanford Publishing.
[89] M. S. Muthu and B. Wilson, (2012) "Challenges posed by the scale-up of nanomedicines," Nanomedicine (Lond.), vol. 7, no. 3, pp. 307–309.
[90] V. Limaye, G. Fortwengel, and D. Limaye, (2018) "Regulatory roadmap for nanotechnology based medicines," Int. J. Drug Regul. Aff., vol. 2, no. 4, pp. 33–41.

## AUTHORS

**Rusha Chatterjee** is currently pursuing her B.Tech in Chemical Engineering Department of University of Calcutta. She may be contacted at rushachatterjee20@gmail.com.

**Mahima Banerjee** is currently pursuing her B.Tech in Chemical Engineering Department of University of Calcutta. She may be contacted at mahimabanerjee1@gmail.com.