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Review Article

# Integration of Nanotechnology and Nanomaterials in Biomaterials Research

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## Abstract

Nanotechnology has emerged as a revolutionizing element in biomaterials research, significantly enhancing their functionality and versatility in medical applications from tissue engineering, drug delivery, regenerative medicine, to medical implants. Integration of nanomaterials in biomaterials has led to an enormous enhancement in biocompatibility, mechanical strength, drug release control, and bioactivity. The present review provides an exhaustive overview of the historical perspective, classification, and applications of nanomaterials in biomaterials research. It talks about how inorganic, organic, and hybrid nanomaterials are contributing to advancing biomedical applications, including their impact on scaffolds, nanoparticles for targeted drug delivery, and surface modification for implants. The paper also considers the current challenges associated with the use of nanomaterials, including biocompatibility, toxicity, scalability, and regulation. Finally, future research directions are proposed to drive the safety, functionality, and integration of nanotechnology in biomaterials, with possibilities for next-generation biomedical applications. This review aims to highlight the profound influence of nanotechnology on biomaterials and its potential to revolutionize healthcare. It explores the transformative impact of nanomaterials on biological applications and focuses on specific applications such as tissue engineering, drug delivery systems, diagnostic instruments, and regenerative medicine.

**Keywords:** nanostructured biomaterials; nanoparticle drug delivery; nanocomposite scaffolds; surface nanoengineering; stimuli-responsive nanomaterials; nano-enabled biosensors; osseointegration.

## 1. Introduction

❖ Overview of Biomaterials Research

Since the late 19th century, the application of metals and their composites in biomaterials has significantly increased. Biomaterials are usually synthetic compounds that have been extensively used to replace or repair various biological functions of human tissue. Since they are continuously in contact with body fluids, they enhance everyday human activities. A global effort is underway to develop novel biomaterials that could enhance everyday human activities. Significant research has been done, and several biomaterials have been developed to understand the interaction between the human body and biomaterial [1]. Such biomaterials exhibit exceptional properties applicable in a wide range of fields, from complex diagnostics to clinical treatments.

While developing these materials, several crucial factors such as biocompatibility, their chemical, mechanical, and physical properties, should be considered; they should also be checked for their bioactivity and bio inertness [2]. Checking these parameters could help create much more effective and compatible systems for the body. For instance, current bone substitutes do not contribute to the creation of red blood cells; they just function as mechanical support. They have extremely basic functioning properties in terms of normal physiological systems. On the other hand, pacemakers perform electrical functions, and neuromuscular stimulators also do the same. There are some additional but basic chemical tasks—like oxygenation and dialysis that can be conducted by specialized implants such as oxygenators and dialyzers [3]. If the biomaterials are enhanced further, then advanced implants with multiple functions could be developed.

One such biomaterial is the smart polymers, which give new, unique, and innovative characteristics to the inert polymers when they interact with peptides, proteins, cells, and DNA. An example of such a polymer is the biodegradable polymer utilized in biodegradable sutures and bone plates today. These polymers are developed from natural or generated polyesters or polyamides, to temporarily scaffold or support tissues as they naturally regenerate [4]. Some biomolecules, such as liposomes, plasmid vectors, and enzymes, may be precipitated and dissolved in a switchable manner using stimuli-responsive polymers. As a result of polymers' biodegradability, several medication delivery techniques have been created. The reconstituted collagen polymers have found widespread applications in the replacement of skin, heart valves, and arterial walls, displaying a big breakthrough in this domain. Hard tissues (such as bone, cartilage, teeth, and nails) and soft tissues (such as skin, ligaments, fibrous tissues, and synovial membranes) are the two main categories into which biological tissues can be divided, regardless of whether they contain mineral components. Bio-implants have been developed to sustain, repair, or enhance the function of such types of damaged or diseased tissues. These biomaterials are either natural or synthetic, designed to function properly in a biological setting. This demand for synthetic tissue has progressed as a result of the limited availability of donor organs, which led research to develop methods for mimicking or replicating biological tissues and organs [4].

❖ Role of Nanotechnology:

The integration of nanotechnology into the implant field has dramatically increased in recent years. Researchers are being motivated by nanomaterials with biologically inspired properties to investigate their potential for enhancing the functionality of traditional implants [5]. To improve adhesion, proliferation, production of bone-related proteins, and deposition of calcium-containing minerals, the nanomaterials provide an increased surface area, effective stiffness, roughness, and changed physicochemical characteristics. Since the development of nanotechnology, a variety of nanophases (grained size less than 100 nm) materials, such as metals, polymers, ceramics, and composites, have appeared with unique surface characteristics; many of these materials have a greater capacity to promote osseointegration and to promote the formation of new bone. For example, Serra et al. [6] were able to produce nanostructured $Ti_6Al_4V$ alloy through severe plastic deformation of pure titanium. The nanostructured $Ti_6Al_4V$ alloy exhibited better mechanical properties over conventional titanium, including (i) an ultimate tensile strength of 1240 MPa over 700 MPa, (ii) a yield stress of 1200 MPa over 530 MPa, and (iii) an elongation of 12% over 25% of pure titanium.

A significant application is in diagnostics, where nanoparticles (NPs), such as gold NPs, functionalized with antibodies, can detect proteins associated with specific diseases. Iron oxide is regarded as a superparamagnetic NP, and other NPs have gained interest due to their magnetic characteristics. The regulated orientation and organization of these NPs in a strong magnetic field make them suitable for use as materials for drug delivery systems for cancer therapy. Because of these characteristics, NPs are perfect for use as drug vectors, thermal mediators in cases of hyperthermia, and contrast agents while patients are undergoing computed tomography or magnetic resonance imaging (MRI). Therefore, the exposure of living organisms to natural, incidental, and engineered nanoparticles is rapidly increasing [7]. Since metal oxide nanoparticles may be made with incredibly large surface areas and unique crystalline morphologies that include a lot of edges, corners, and other potentially reactive sites, they are particularly interesting as antibacterial agents. The impact of iron-oxide nanoparticles on biofilms that developed on the surface of polymer-brush-coated biomaterials was assessed.

Carbon nanotube (CNT)-based composites are also studied and used in this field. The incorporation of CNTs into polycaprolactone (PCL), polycarbonate-urethane (PCU), or polystyrene (PS) matrixes has been proposed to enhance the mechanical properties (in terms of tensile and compressive moduli) of the composite scaffolds. CNTs function as a safer alternative to the traditional toxic fibers like asbestos [8]. According to one study, adding single-walled carbon nanotubes (SWCNTs) to poly (lactide-co-glycolide)[PLGA] composites resulted in a ~5% drop in polymer crystallinity, a ~12% gain in tensile strength, and a decreased rate of degradation [9]. Traditional nanotoxicology assays have primarily focused on evaluating cytotoxicity and genotoxicity of nanoparticle uptake in cancer cell cultures (U251, IMR-90) [10]. Using cell lines such as HeLa, U937 [11], A549 [12], many articles have studied cytotoxicity and genotoxicity of Ag-nps. Similarly, ZnO and $TiO_2$ nps have been studied with Hep2 [13], and $TiO_2$ nps with PC-3M [14] to show more reproducible and homogeneous results, facilitating targeted studies of nanoparticle-cell interactions.

## 2. Historical Background and Evolution of Nanomaterials in Biomaterials Research

Over the past decades, nanomaterials have significantly enhanced the properties and functionalities of biomaterials in biomedical research and healthcare applications [15]. Biomaterials aim to interact with biological systems such as bioimaging [16], medical implants [17], biosensing [18], wound healing [19], tissue engineering, and drug delivery [20]. The integration of nanotechnology enables precise control at the molecular level, leading to significant improvements in the performance and functionality of these materials for medical applications.

❖ Historical Perspectives on Nanotechnology in Biomaterials

Nanomaterials have a high surface-to-volume ratio, which enables better chemical reactivity and makes them capable of interacting harmoniously with biological systems at the molecular level, leading to successful characteristics that can be utilized for biomedical applications. Progressive research in nanotechnology has been developing potentially biocompatible biomaterials since medical science has set foot in biocompatibility [21–22]. Initially, nanoparticles, nanofibers, and nanostructured surfaces were introduced as biomaterials to be incorporated in the development of medical devices, tissue engineering, and drug delivery applications, etc., that are suitable for medical applications [23]. During the 1950s and 1960s, liposomes and polymeric carriers were discovered, which were considered the first generation of biomaterials for targeted drug delivery, and were precise and efficient [24]. They could encapsulate the medicine at the nanoscale and carry it to the targeted part of the body or tissue precisely inside the body. This prevents loss of the drug by degradation and regulates the release of the drug over time. This discovery has significantly helped overcome serious issues such as poor bioavailability and non-specific targeting in the conventional medication system.

During the 1990s, biocompatible hydroxyapatite nanoparticles were studied, which played a significant role in designing the scaffold for new bone formation and in the regeneration of damaged bone tissues. Due to its high surface area and biocompatibility, hydroxyapatite also acts as a carrier for drugs and bioactive molecules. Development of the above-mentioned biomaterials functioned as groundwork for the emergence of functionalizing nanoparticles with biological molecules to improve biocompatibility and to reduce immune reactions of other biomaterials [25–26]. Similarly, nanofibers were produced via electrospinning and used to create scaffolds for tissue engineering that closely mimicked the extracellular matrix (ECM) of natural tissues. These nanofibrous scaffolds provided better cell attachment, proliferation, and differentiation compared to traditional biomaterials [27-28]. With the advancement, nano coatings were developed, and surface modifications were done, which enabled researchers to enhance the performance of medical implants by improving their integration with biological tissues and adding antimicrobial properties. Collectively, these innovations in the field of biomaterials have significantly advanced medical science, making the treatments more effective and may be tailored according to patient-specific needs.

❖ Key Milestones and Major Advancements in the Past Few Years

In recent years, the field of nanotechnology-enhanced biomaterials has witnessed several key milestones and major advancements. Researchers have made significant strides in developing smart biomaterials that can respond to environmental stimuli, such as pH, temperature, or specific enzymes. These materials can be utilized in biological research and rise in several fields, including tissue engineering [29], cell therapy [30], gene transfection [31], etc. A breakthrough in nanomaterials for biomaterials research was the development of a nano drug delivery system [32]. These nanoparticles can be programmed to release their therapeutic payloads in response to specific physiological conditions, such as the acidic environment of a tumor. Moreover, these materials can improve the poor water solubility of drugs, bioavailability, and reduce drug metabolism. This innovation has been particularly impactful in cancer treatment, where precise targeting is crucial to minimize damage to healthy tissues.

In tissue engineering, the evolution of nanomaterials has led to the creation of nanocomposite scaffolds that incorporate multiple nanomaterials to achieve superior mechanical, biological, and chemical properties. For example, graphene and carbon nanotubes have been integrated into polymeric scaffolds to enhance their electrical conductivity, making them suitable for tissue engineering applications that require electrical stimulation, such as bone and cartilage tissue engineering [33]. Recent advancements in nanotechnology-enhanced biomaterials have also focused on improving the biocompatibility and functionality of implantable devices. Nanoscale surface modifications, such as nanostructured coatings with anti-inflammatory or antibacterial properties, have contributed to reduced implant rejection and infection rates [34]. Nanoparticles are now being integrated with 3D printing technology to fabricate biomaterials. This makes it possible to precisely create intricate, patient-specific structures at the nanoscale, creating new opportunities for regenerative therapies and customized medicine. It is now simpler to construct tissues and organs for transplantation thanks to the development of scaffolds that can better support tissue growth, made possible by the combination of 3D printing and nanomaterials [35].

❖ Comparison of traditional vs. Nano biomaterials

Performance and adaptability have significantly improved over traditional biomaterials because of the incorporation of nanotechnology into biomaterials research. Traditional biomaterials, such as metals, ceramics, and polymers, have been widely used in implants and medical devices due to their mechanical strength and durability [22, 36–37]. However, challenges remain regarding biocompatibility, integration with biological tissues, drug delivery, and tissue regeneration.

- Biocompatibility and Tissue Integration

Traditional biomaterials often raise biocompatibility concerns, potentially leading to immune responses, implant rejection, or inadequate tissue integration [38]. On the other hand, biomaterials augmented by nanotechnology can be designed with surface alterations at the nanoscale that replicate the composition and functionality of natural tissues [39]. Additionally, implants with nanostructured surfaces can encourage cell proliferation and adhesion, improve integration, and lower rejection rates.

- Drug Delivery Efficiency:

Traditional drug delivery methods usually depend on systemic administration, in which medications are dispersed throughout the body, which frequently results in side effects and non-specific targeting [40]. Nanotechnology-enhanced biomaterials offer more efficient drug delivery by targeting specific cells or tissues and controlling the release of the drug. This approach minimizes side effects and improves therapeutic outcomes, particularly in cancer treatment [32].

- Mechanical Properties and Functionality:

The traditional biomaterials are chosen due to their mechanical strength, but they may lack in providing the flexibility and functionality requirements for biomedical applications [37]. In contrast, nanomaterials can be tailored to achieve a balance between strength and flexibility, as seen in nanocomposite materials. For instance, the incorporation of carbon nanotubes into polymer matrices can enhance the mechanical properties of scaffolds while providing electrical conductivity, which is essential for applications like nerve or muscle tissue engineering [15].

- Antimicrobial Properties:

Another advantage of nanotechnology-enhanced biomaterials is their ability to incorporate antimicrobial properties [34]. Traditional biomaterials are susceptible to bacterial colonization, leading to infections, especially in implants. Nanomaterials like silver nanoparticles have been integrated into biomaterials to provide antimicrobial properties, reducing the risk of infections and improving the safety of medical devices [41–42].

## 3. Types of Nanomaterials Used in Biomaterials Research

In the biomaterial domain, nanotechnology has brought significant changes, providing innovations beneficial for medical applications. This section explores several types of nanomaterials used as biomaterials, providing an analysis of their properties and applications. Materials with a minimum one dimension in the range of 1-100 nm are termed nanomaterials. These materials have typical physical, chemical, and biological properties that can create highly suitable materials for biomedical applications. Nanomaterials can be categorized into one of the following: inorganic, organic, hybrid, or nanocomposites [43]. Nanoscale biomaterials hold immense potential to advance medical research and improve therapeutic outcomes. Nanomaterials' characteristics make them perfect for a variety of medicinal and diagnostic applications. Current research and development in this area point towards innovative healthcare solutions. The integration of nanoparticles and biomaterials is revolutionizing the development of innovative treatment approaches [44].

Inorganic and organic nanomaterials possess unique properties that enhance drug delivery, improve biocompatibility, and facilitate the development of innovative medical devices. Future research in this field holds great promises for improving patient outcomes and developing innovative treatments for various diseases. Continued advancements in nanotechnology will serve as the foundation for future medical breakthroughs [45].

❖ Inorganic Nanomaterials

- Metal Nanoparticles

Gold Nanoparticles: Gold nanoparticles (AuNPs) are widely recognized for their biocompatibility and ease of functionalization. They are suitable for application in photothermal therapy, targeted medication delivery, and diagnostic imaging due to their unique optical properties, including surface plasmon resonance. Studies have demonstrated that conjugating AuNPs with antibodies, peptides, or drugs to target specific cells or tissues can enhance the efficacy and specificity of therapies [46]. To mitigate potential liver toxicity associated with AuNP accumulation, gold core-shell nanoparticles are preferred for cancer therapy [47–50].

Silver Nanoparticles: Silver nanoparticles (AgNPs) are widely recognized for their potent antibacterial properties. They are typically utilized as antibacterial agents, dressings, and antimicrobial coatings for medical equipment [51]. The antibacterial properties of nano silver stem from their capacity to release silver ions and generate reactive oxygen species (ROS). This interferes with the bacterial cells' ability to function by rupturing their cell membranes [52]. Research has also focused on drug delivery systems, cancer treatments, and toxicity, confirming AgNPs as novel nanoparticles in the field of biomaterials [53-54].

Titanium Nanoparticles: Titanium nanoparticles (TiNPs) are used in dental and orthopedic implants due to their good biocompatibility and favorable mechanical properties. Titanium dioxide ($TiO_2$) nanoparticles are also frequently utilized as photocatalysts and as UV-blocking ingredients in sunscreens [55].

- Metal Oxide Nanoparticles

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Metal oxide nanoparticles also play a key role as biomaterials in the research. Few of them are discussed below.

Zinc Oxide Nanoparticles: Zinc oxide nanoparticles (ZnO NPs) are used in sunscreen, antimicrobial coatings, and wound healing applications due to their antibacterial and UV-blocking properties. Because these nanoparticles can increase the bioavailability of encapsulated medications, they are also utilized as efficient drug delivery vehicles [56-57].

Iron Oxide Nanoparticles: Iron oxide nanoparticles ($Fe_3O_4$) exhibit superparamagnetic properties, making them excellent contrast agents for magnetic resonance imaging (MRI). Additionally, they serve as vehicles for targeted therapy, employing magnetic fields to transport drugs precisely or as targeted drug delivery systems. They are also employed externally to administer drugs, as the magnetic field guides the vehicle nanoparticle to the intended location [58-60].

Titanium Oxide Nanoparticles: Among various metal oxides, titanium dioxide ($TiO_2$) nanoparticles are known for their unique photocatalytic properties and have received attention from all over. They are less toxic and are chemically stable. Recently, studies have underlined the use of $TiO_2$ nanoparticles as antibacterial coatings, cancer photodynamic therapy, and bone tissue engineering. The application has been conducted by following ways: For prevention of their use in orthopedical and dental applications, $TiO_2$ nanoparticles are combined with the implant coatings, which have promoted osseointegration and prevented bacterial colonization, making them valuable in this application [61]. Tuned $TiO_2$ nanoparticles were used for Photodynamic therapy and were observed to perform effectively as photosensitizers under UV or visible light for the generation of reactive oxygen species (ROS) and selectively destroyed the tumor cells [62]. $TiO_2$ nanocomposites can be made by doping other materials into it; these doped $TiO_2$ are explored for drug delivery. It possesses a large surface area and controlled release properties, especially in cancer treatment, which require targeted and controlled drug release [63].

- Carbon-Based Nanomaterials

Graphene: Graphene, a single layer of carbon atoms arranged in a hexagonal lattice, possesses remarkable mechanical, thermal, and electrical properties. It is utilized in the same form or as a derivative in the fields of drug delivery systems, tissue scaffolds, and biosensors. Because of its high surface area and functionalizability, graphene has made it possible to create biosensors that are both very sensitive and specific for identifying viruses and biomolecules [64-65]. In addition to uses in biosensors, its exceptional strength and conductivity make it excellent for use in medication delivery. Graphene, when functionalized with polyethylene glycol (PEG) or chitosan, can be used in drug delivery as it enhances drug loading and sustained release, especially in cancer therapies. Apart from this, it also improves the material's biocompatibility and dispersibility in aqueous media [66].

Carbon Nanotubes (CNTs): CNTs are cylindrical structures composed of carbon atoms arranged in a hexagonal lattice. They are being investigated in the fields of biosensing, tissue engineering, and medication delivery [67]. They are incredibly strong, electrically conductive, and chemically stable. These are adaptable, and their unique qualities enable the creation of innovative materials and gadgets with excellent functionality and performance. Carbon nanotubes (CNTs) improve the adhesion of cells and their proliferation in tissue scaffolds, mainly when they are blended with biodegradable polymers [68].

Carbon Quantum Dots: In the field of biosensing, carbon quantum dots doped with nitrogen and functionalized with targeting ligands, which enable the detection of biomolecules for early diagnosis as they are highly selective and sensitive [69]. The modifications mentioned in carbon-based nanostructures are very important for enhancing biofunctionality, and they also ensure biosafety, targeted delivery, and controlled degradation, and thus they have become a basis of modern biomaterial systems.

❖ Organic Nanomaterials

- Polymer-Based Nanoparticles

Polymeric nanogels and dendrimers are prominent polymer-based nanoparticles used in biomaterials research. Additionally, micelles and liposomes are significant organic nanomaterials.

Polymeric Nanogels: Polymeric nanogels, with their hydrophilic networks, swell in aqueous environments and respond to environmental stimuli such as pH, temperature, and ionic strength. Because of these properties, they are perfect for applications involving controlled drug administration. They can also contain the medicine and release it in a regulated manner. Additionally, polymeric nanogels can be tailored to provide materials with improved efficacy, safety, and a favorable responsiveness to specific physiological situations [70].

Dendrimers: These are highly branched structures and possess multifunctionality. The dendrimers can be tuned for several functionalities, such as drug delivery and gene therapy. Their three-like structured polymers have a very high density of functional groups with unique structures. The formation of dendrimers makes them an effective material for application in drug delivery and imaging techniques. This is made possible as it can encapsulate the drug as well as contrast it. They can also be modified and improved by functionalization with ligands for the drug delivery mechanism, particular cells, or tissues [71].

- Liposomes and Micelles

Liposomes: These are spherical-shaped bladder which is made up of lipid bilayers. Liposomes are utilized for drug encapsulation, to enhance the stability and bioavailability of the drugs. These materials could be improved and used for regulated and targeted drug delivery systems, to achieve a system that can release the medication in response to certain stimuli like a change in pH or enzyme activity [72].

Micelles: The self-assembling amphiphilic molecular structure, which has hydrophilic shells and hydrophobic cores, is termed micelles. Medications that are hydrophobic are delivered using micelles. These materials increase the drug's solubility and enhance the selectivity of the system by functionalizing with ligands having specific targets [73].

**Nanofiber-Based Biomaterials**

Nanofiber biomaterials, particularly those fabricated using electrospinning, have gained considerable attention due to their ability to replicate the fibrillar architecture of the ECM. These fibers provide large surface area, high porosity, and interconnected pore networks, which are vital for cell attachment, nutrient diffusion, and biological signalling [74]. They can be made from a wide range of organic polymers like gelatin, silk fibroin, polycaprolactone, or synthetic copolymers, and are often enhanced with carbon-based nanomaterials (e.g., graphene oxide, carbon nanotubes) or metallic nanoparticles (e.g., silver, gold) for added functionality. Nanofiber mats can be functionalized with growth factors, antibacterial agents, or drugs for site-specific delivery and can be designed to support specific cell lineages, such as neuronal or musculoskeletal stem cells. These systems are particularly valuable in skin regeneration, nerve conduits, vascular grafts, and muscle regeneration. Nanofiber-based platforms have also been adapted into wound dressings that respond to environmental cues such as pH or enzymatic activity for on-demand drug release [75]. A study by Arbade et al. highlighted that nanofiber systems loaded with antibacterial agents like silver nanoparticles provided excellent microbial resistance while maintaining biocompatibility, making them ideal for chronic wound treatment and post-operative healing environments [76].

**Hydrogel Nanomaterials**

Hydrogels have been considered for their very good biocompatibility; they are soft and have consistency like the tissues. When these hydrogels are combined with nanomaterials to form nano-hydrogels, they acquire extra characteristics such as mechanical reinforcement, stimuli responsiveness, and unique drug delivery abilities. These integrated nano-hydrogels are capable of encapsulating cells, proteins, and nanoparticles, which ultimately transforms them into versatile materials for use in injectable treatments, systems of 3D culture, and localized drug delivery systems [77]. These nano-hydrogels and made up of materials like gelatin methacrylate (GelMA), alginate, cellulose nanofibrils, or chitosan and have shown remarkable results in burn wound treatment, osteoarthritis, ocular diseases, tumor microenvironments, etc. Including materials such as metal–organic frameworks (MOFs), nano-silica, gold nanoparticles, etc., in hydrogels has diversified its applications and made it usable for controlled photothermal treatment, biosensing, and angiogenesis stimulation [78]. Arbade et al. have displayed increased focus on hydrogels with multiple components that show adaptive stiffness and release profiles, can be improvised for bone and cartilage regeneration, also stem cell encapsulation has been made possible. These materials can also be engineered according to the usage in responding to physiological stimuli such as pH, temperature, or enzyme levels, etc., and make them highly suitable for personalized

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medicine [79]. Figure 1 showcases various types of nanomaterials that can be used for biomaterials applications.

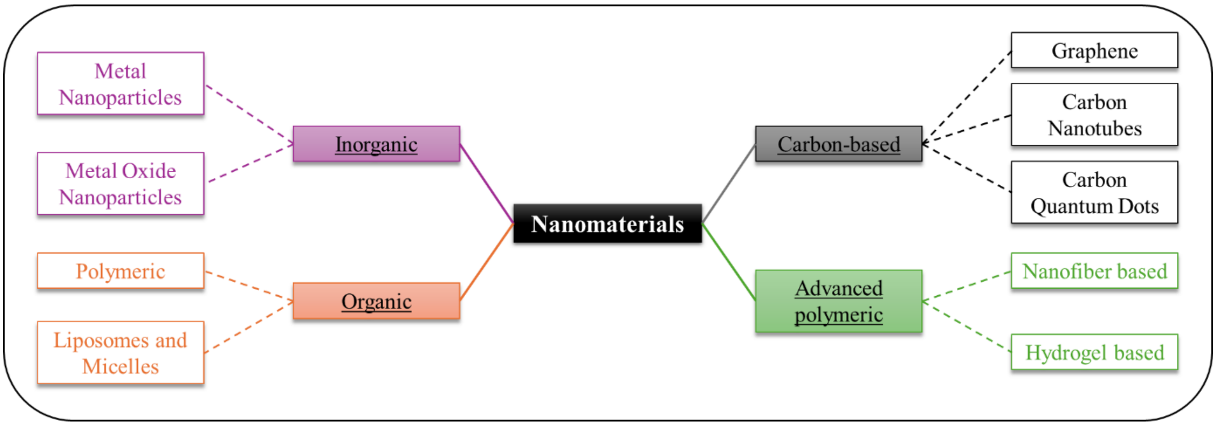


Figure 1. Several types of nanomaterials which can be used for biomaterials applications.

## 4. Various Strategies for Nanomaterial Modification

Nanomaterials are too versatile, and different modification techniques could be used to improve their biocompatibility, physicochemical properties, functional behavior, etc., and increase their performance for biomedical applications. Hybrid nanomaterials and surface functionalized nanoparticles are two of the most studied approaches for this purpose.

❖

❖ Hybrid Nanomaterials and Nanocomposites

Hybrid nanomaterials and nanocomposites combine the properties of organic and inorganic materials, offering enhanced properties such that they can function exceptionally well and demonstrate the advantages of both materials. One example is the coupling of polymers and carbon nanotubes to form a nanocomposite, producing a material with good electrical conductivity and mechanical strength. There are various applications for these materials where they can be used. Some of them are tissue engineering, medication delivery, and biosensing [80]. Further, silica–polymer composites possess adjustable porosity and degradability, due to which it has shown promising results in the field of controlled drug delivery systems. These hybrid materials are versatile and possess functionalities that enable them to be used in broad fields such as tissue regeneration, targeted drug delivery, and biosensing technologies, etc.

Recent progress in photodynamic and sonophotodynamic therapy has brought forth the use of composites of $TiO_2$. Yavaş et al. (2025) have studied that $TiO_2$ nanoparticles, when integrated with copper phthalocyanine (CuPc), have demonstrated potent and non-invasive treatment by inducing up to 83.8% apoptosis in HepG2 liver cancer cells under sonophotodynamic activation [81]. Similarly, Abd El-Kaream et al. (2025) also synthesized microwave-activated $TiO_2$/rose bengal@chitosan nanoparticles, which increased the production of reactive oxygen species (ROS) production which was further used to selectively suppress skin cancer cells *in vitro* as well as *in vivo* systems [82]. El-Bassyouni et al. (2025) have reviewed that titanium and its alloys have been modified extensively by various techniques such as atomic layer deposition of $TiO_2$ thin films, which was used for long-term orthopedic and dental applications as it enhanced corrosion resistance, reduced the implant degradation, and also improved their biocompatibility [83].

❖ Functionalization and Surface Modification of Nanomaterials

Functionalization plays a key role and ensures effective utilization of nanoparticles. The surface functionalization/modifications are crucial for improved biocompatibility and enhanced targeting capabilities. Various methods, such as coating nanoparticles with biocompatible polymers, attaching ligands, and altering surface charge, are employed to enhance interactions between nanomaterials and biological systems [84]. Functionalization facilitates the attachment of targeted ligands for selective medication delivery or the incorporation of biodegradable components that can improve the body's ability to release chemicals [85]. Techniques, such as click chemistry, are state-of-the-art techniques that have facilitated the attachment of therapeutic drugs or biomolecules on the surface of nanoparticles accurately. These advancements have enhanced the efficiency of treatment and have minimized effects on the off-target areas.

These successful discoveries were later backed by recent broad reviews, like by Kulwade et al. (2025), which have put forth the application of Carbon-based nanostructures in tissue engineering, such as skin, bone, cartilage, neural, cardiac, muscle, and hepatic tissues. This review emphasized the versatility of carbon nanomaterials (including nano-diamonds, CNTs, graphene, and fullerenes) along with their superb interactions with biological systems, stem cell-based regenerative strategies, and prospects for clinical translation [86].

## 5. Current Applications of Nanotechnology in Biomaterials

❖ Tissue Engineering

Nanoscale material design and development improve material properties and functionalities, revolutionizing biomaterial applications in drug delivery, tissue engineering, and diagnostics. In tissue engineering, extracellular matrix (ECM) components and cell-cell/cell-ECM interactions, including osteoprogenitor cell migration, recruitment, proliferation, differentiation, matrix formation, and bone remodeling, are observed under standard 2D culture conditions. Researchers have manipulated mechanical properties (e.g., scaffold stiffness, strength, and toughness) by creating nanostructures (e.g., incorporating nanoparticles or nanofibers into polymer matrices) to mimic the natural nanocomposite structure of bone [87]. In 2002, Hutmacher et al. first reported the processing of bioresorbable scaffolds for tissue engineering applications using FDM (Fused Deposition Modeling) [88]. The key factors for an ideal scaffold for bone tissue engineering are: (i) macro- (pore size > 100 lm) and microporosity (pore size < 20 lm); (ii) interconnected open porosity for *in vivo* tissue in-growth; (iii) sufficient mechanical strength and controlled degradation kinetics for proper load transfer to the adjacent host tissue; (iv) initial strength for safe handling during sterilizing, packaging, transportation to surgery, as well as survival through physical forces *in vivo*; and (v) sterile environment for cell seeding [89].

- Nanostructured Scaffolds

With the advent of technology, the design of a scaffold that meets the requirements of a reproducible 3D culture was brought to life. Hydrogels can be designed as soft scaffolds for cell culture. Their architecture's stiffness, swelling characteristics, and molecular mobility are influenced by cross-linking type and branching degree. Both polymeric gels, which are made of bioinspired units connected by covalent bonds, and low-molecular-weight gelators (LMWG), known as supramolecular gels because of their units that self-assemble through weak interactions, are the most prevalent [90]. The swelling ability of nanostructured hydrogel scaffolds in liquid media aids in cell entrapment and facilitates nutrient and oxygen flow within the scaffolds. As a result, these scaffolds can also give cells the support they need to remain differentiated and proliferate [91]. Recent studies, such as that by Sudheesh Kumar et al., have shown that chitin can form hydrogen bonds with ceramics and polymers, creating enhanced composites. Using freeze-drying, they created 90-chitin hydrogel/nano-hydroxyapatite (nHAp) nanocomposite scaffolds with interconnected pores and 70-80% porosity [92].

Resorbable ceramic scaffolds can be biphasic (containing hydroxyapatite (HA) and tricalcium phosphate (TCP)) or composed of HA or TCP alone. Such as, Due to their larger surface area, nanocrystalline HAp (nHAp) [ having formula $Ca_{10}(OH)_2(PO_4)_6$] powders have been shown in studies to have better sintering ability and enhanced densification, which may improve fracture toughness and other mechanical properties. The mechanical and biocompatibility of bone-grafting materials may be enhanced by specially created nHAp composites [93]. For instance, because of their larger surface area for cell adhesion and reduced crystallinity, HA nanoparticles coated on glasses showed greater MG-63 cell attachment and proliferation than micro-sized HA particles [94]. In a similar vein, HA nanoparticles embedded in 3D PCL (polycaprolactone) scaffolds have demonstrated increased calcium deposition, alkaline phosphatase activity, attachment, and proliferation (i.e., mineralization of MSCs, or mesenchymal stem cells [95].

CNTs and nanofibers, with their electrical and mechanical properties, are promising for bone tissue engineering. High porosity is essential for cell ingrowth and nutrient/waste distribution, and electrical conductivity is crucial for tissue regeneration. For example, an 80%/20% (w/w) PLA/CNT composite showed optimal electrical conductivity for bone formation, despite PLA's insulating properties [96]. Cellular processes like adhesion, proliferation, migration, and differentiation are sensitive to material surface characteristics. Raffa et al. [97] showed that PC12 cells adhered to nanometer-scale topography. Conversely, Washburn et al. [98] found MC3T3-E1 cell proliferation was sensitive to nanoscale polymeric material roughness. Additionally, changing the materials' bulk structure as well as their surface can have an impact on the differentiation process. According to some studies, the differentiation of H9c2 cells, their cytocompatibility, proliferation, and adhesion are impacted by the surface roughness of nanofilms with varying MNP concentrations [99]. Adding MNPs to the nanofilms enhances the proliferation and cells' adhesion without compromising their viability [100].

- 3D Bioprinting of Nanomaterials

Ceramics, metals, and polymers are among some of the materials that have been suggested and utilized to replace natural bone and cartilage tissue at damaged locations. It is expected that stem cells, 3D scaffold fabrication advancement, and 3D printing for *in vitro* implant construction are expected to address challenges in bone tissue and cartilage repair. Scaffolds can be created using natural polymers that have high chances of biodegradability and have low immunogenicity. A useful 3D macroporous nanofibrous (MNF) scaffold, for instance, was created by Cai et al. for use in bone tissue regeneration [101]. They observed hESC-MSC morphology on the MNF scaffold, not spindle-like shapes, and improved attachment. They also assessed *in vivo* bone formation over six weeks. 3D bioprinting, an additive manufacturing process, deposits bioinks and biomaterials layer-by-layer [102]. This technology is further separated into elective laser sintering, stereolithography (SLA), powder-based printing (3DP), fused deposition modeling, and robocasting. Nanotechnology has applications in biotechnology and medicine across various tissues. Bioactive glasses and nHA enhance bone regeneration. Nano-HA's biocompatibility, bioactivity, and osteoconductivity make it valuable for orthopedic implants. A study also showed nHA supports bone repair without inflammation [103]. Cheng et al. found ZA had higher binding to nHA (92%) than micro-HA (43%) [104].

❖ Drug Delivery Systems

- Role of Nanoparticles in Targeted Drug Delivery

Nanotechnology has revolutionized drug delivery systems, offering innovative approaches to target diseases with precision and efficiency. Nanoparticles, as key components in these systems, provide numerous advantages over traditional drug delivery methods. They can be engineered for controlled release, targeting specific cells or tissues, and overcoming biological barriers. In this section, we will explore the role of nanoparticles in targeted drug delivery, mechanisms of targeting, functionalization techniques, and examples of nanomaterials used in drug delivery systems [105]. Drug delivery systems (DDSs) are developed to deliver biologically active agents to patients through oral, topical, intravenous, and intravaginal, etc. administration routes [106]. DDSs provide several advantages, such as lower systemic toxicity, better efficiency, reduced drug dosage for the same effect, shorter times of administration, a more constant level of the drug, etc. The major scope of DDs is in tissue engineering. Moreover, DDSs are used in disorders like osteomyelitis, osteoporosis, osteoarthritis, and osteosarcoma, etc. [107]. Nanoparticles have revolutionized drug delivery systems due to their small size, high surface area, and modifiable surfaces, and are ideal carriers for targeted drug delivery. Traditional drug administration often results in drugs being distributed non-specifically throughout the body, leading to side effects and reduced therapeutic efficacy. Nanoparticles address these challenges and improve the bioavailability, biodistribution, and accumulation of therapeutics by allowing the delivery of drugs in preferentially targeted sites, increasing drug concentration where it is needed most, and reducing unwanted systemic exposure [107].

Nanocarriers for Targeted Drug Delivery: Nanocarriers, including liposomes, polymeric nanoparticles, and metallic nanoparticles, are widely used for delivering therapeutic agents. These nanocarriers can encapsulate drugs, protecting them from degradation and controlling their release over time. The surface of these nanocarriers can be modified to enhance their ability to recognize and bind to specific target cells, such as cancer cells or inflamed tissues [108]. Figure 2 illustrates the primary categories of nanocarriers utilized in cancer drug delivery, specifically lipid-based, inorganic, and polymeric nanoparticles [109]. Liposomes, for instance, are spherical vesicles made of lipid bilayers that can carry both hydrophilic and hydrophobic drugs. Polymeric nanoparticles, made from biodegradable polymers like PLGA (polylactic-co-glycolic acid), allow for sustained drug release, while metallic nanoparticles (e.g., gold or silver) are used for both drug delivery and diagnostic purposes due to their unique optical properties [110].

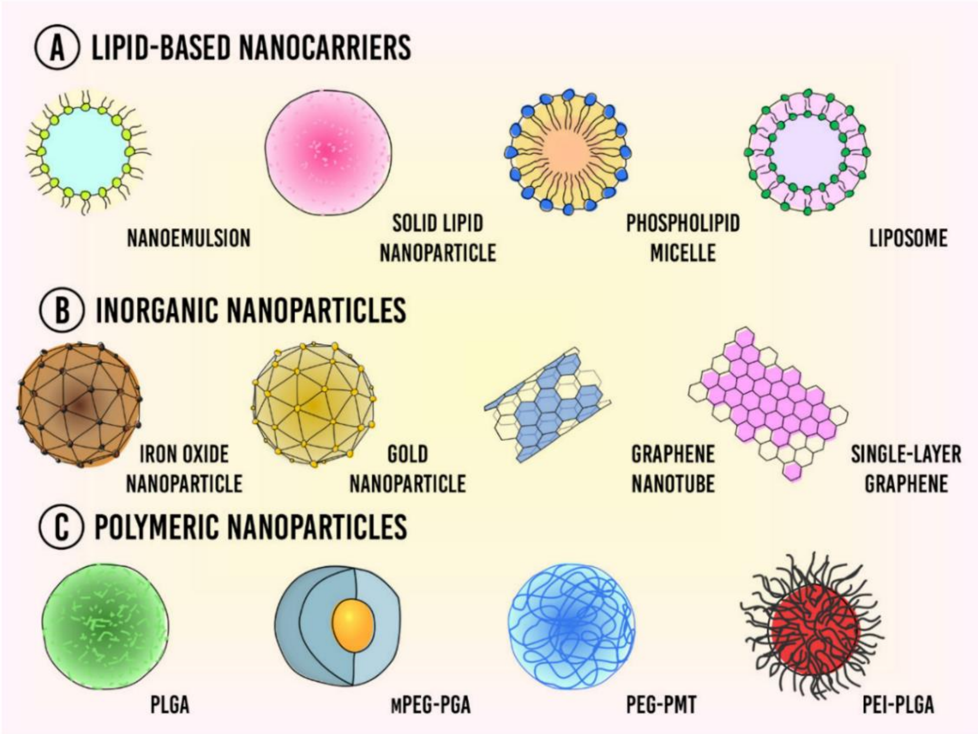


Figure 2. The image outlines the primary categories of nanocarriers utilized in cancer drug delivery, specifically: (A) lipid-based, (B) inorganic, and (C) polymeric nanoparticles. (Adapted from reference [109], Copyright © 2021 by the authors.)

Mechanisms of targeting (passive and active targeting): Nanoparticles can target diseased tissues through two main mechanisms: passive and active targeting. Passive targeting exploits enhanced permeability and retention effect, particularly in cancerous tissues. Tumors often exhibit leaky vasculature and impaired lymphatic drainage, enabling nanoparticle accumulation in the tumor microenvironment. This form of targeting does not require specific interactions between nanoparticles and cells but relies on the natural characteristics of the tumor [111]. Active targeting involves functionalizing the surface of nanoparticles with ligands, such as antibodies, peptides, or small molecules, which can specifically bind to receptors overexpressed on the surface of target cells (e.g., cancer cells or inflamed tissues). Active targeting enhances the precision of drug delivery, ensuring that nanoparticles specifically interact with diseased cells while sparing healthy cells [111]. Figure 3 illustrates and compares passive and active methods for delivering nanoparticles to tumors, highlighting how passive targeting leverages the Enhanced Permeability and Retention (EPR) effect, while active targeting relies on specific molecular binding [109].

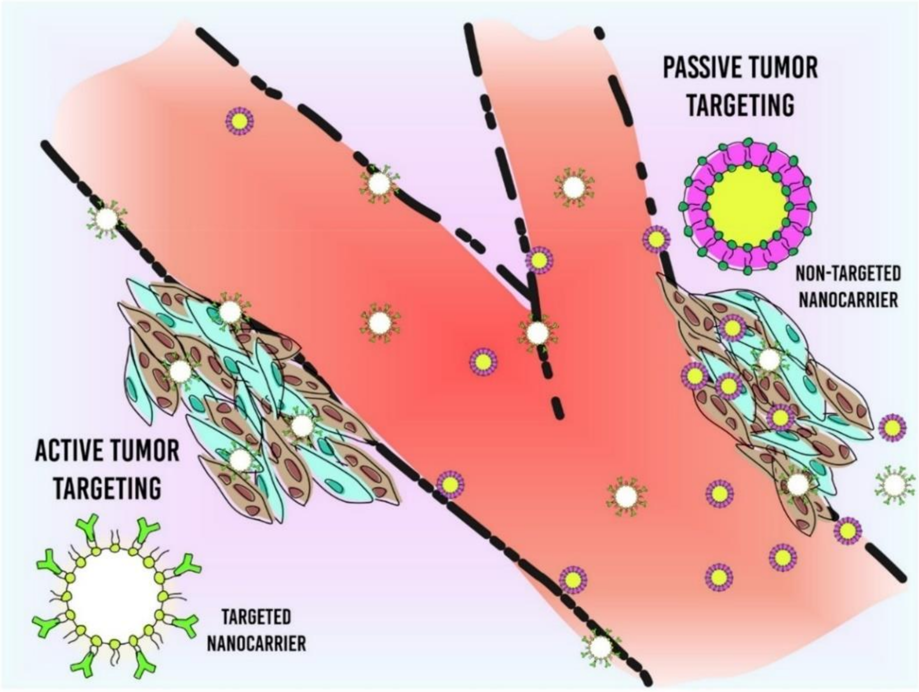


Figure 3. The illustration compares passive and active methods for delivering nanoparticles to tumors. Passive targeting exploits the Enhanced Permeability and Retention (EPR) effect, where nanoparticles leak through the abnormally permeable tumor blood vessels and are retained due to poor lymphatic drainage. Active targeting involves attaching molecules to the nanoparticles that specifically bind to tumor cells. (Adapted from reference [109], Copyright © 2021 by the authors.)

Functionalization of nanoparticles with ligands for site-specific delivery: Functionalization of nanoparticles with ligands is a critical strategy in active targeting. Ligands, such as antibodies, peptides, or aptamers, are attached to nanoparticle surfaces to recognize and bind to specific cell surface receptors. In cancer therapy, nanoparticles can be functionalized with antibodies targeting receptors like HER2 in breast cancer [112] or EGFR in lung cancer, ensuring that the drug is delivered directly to tumor cells [113]. Similarly, nanoparticles that function with ligands that recognize inflamed tissues can be used for diseases like rheumatoid arthritis. Ligand-based targeting enables site-specific delivery, reducing off-target effects and increasing the drug's therapeutic index [114]. Ligand-functionalized nanoparticles are pivotal for targeted drug delivery, enabling site-specific therapies for cancer and inflammation. By attaching ligands to nanoparticles, therapeutic agents can be directed precisely to diseased tissues, enhancing efficacy while minimizing systemic side effects. Nanoparticles are functionalized through covalent or non-covalent binding of ligands, such as small molecules, antibodies, or peptides [115]. These ligands particularly bind to receptors or over-expressed antigens in target tissues; they facilitate enhanced drug uptake by the target cells [116]. The actively targeted NPs, therefore, display an increased degree of complexity. To potentially benefit from the active targeting strategy, it is imperative that the specific antigen be present and accessible on the targeted cells to bind the NPs. It is also important that antigen localization and expression remain adequate throughout the treatment. In this context, identification of predisposed patients goes beyond relatively simple genetic profiling [117].

- Controlled Release Mechanisms

One of the most important aspects of nanotechnology-based drug delivery is the ability to control when and where drugs are released. Nanoparticles can be engineered to release their payload in response to a specific stimulus, ensuring that the drug is released at the right time and in the right place.

Nanomaterial-Based Smart Drug Release Mechanisms: Smart drug delivery systems are engineered for personalized release, tailored to disease severity. Increased release in severe infections ensures effective antimicrobial activity. These nanocarriers remain inactive during circulation, releasing their payload only at the target site, enhancing drug efficacy and reducing side effects [105, 107]. For example, pH-sensitive nanoparticles release their drug load in response to the acidic environment found in tumors or inflamed tissues. This ensures that the drug is not prematurely released in normal tissues but only at the target site [107].

Nanocarriers respond to stimuli for controlled and sustained drug release: Nanocarriers can be designed to respond to various stimuli, enabling targeted and controlled drug delivery. pH-sensitive nanocarriers, for example, release drugs in acidic environments, such as those found in tumors or inflamed areas, where even a slight pH difference between healthy and diseased tissues can trigger the drug release [108]. Temperature-sensitive nanocarriers, on the other hand, release drugs when exposed to hyperthermic conditions, which can be induced externally through local heating or occur naturally in inflamed or cancerous tissues [118]. Additionally, magnetic field-responsive nanocarriers, such as those made from iron oxide nanoparticles, can be directed to specific locations using external magnetic fields. Once localized, these nanoparticles can be heated through alternating magnetic fields to trigger drug release, offering a non-invasive method to control drug delivery [119].

- Targeting mechanisms

Chemotherapeutic drug delivery is widely used, but the toxicity of these drugs can cause severe side effects. Selective tissue targeting is employed to mitigate these effects. The unique size of nanoparticles enables distinction of cancer pathology and molecular biology, resulting in preferential therapeutic targeting compared to traditional treatments [120]. There are two kinds of targeted drug delivery systems: (a) Active targeted drug delivery (smart drug delivery) is based on ligand-receptor interactions. It is based on a method that delivers a certain amount of a therapeutic or diagnostic agent that is targeted to diseased areas of the organ in the body [121]. The drug-loaded Nanoparticles (NPs) mixed with ligands used for recognition by receptors/antigens on target cells for controlled distribution of the drug decreases side effects of drugs on healthy cells and organs which is impossible in traditional chemotherapy [122] and (b) Passive targeted drug delivery is based on the enhanced permeability and retention (EPR) effect. Due to the fast growth of tumors, the blood vessels and junctions are not formed properly, so they become loose and leaky. Because of the unique size of nanoparticles, they can pass through these loose junctions, resulting in preferential accumulations at the tumor site over time. These phenomena are known as enhanced permeation and retention [123]. The behavior of drugs and their other affinity for the intratumoral environment needs to be considered individually while designing passively targeted NPs, and the optimal drug release profiles should be optimized case by case [117].
It becomes apparent that passive targeted NPs to diseased cells may be more complex than it seems, because the development of future therapeutics solely based on passive pathways might not achieve the full potential benefits of Therapeutics NPs. The patients who are naturally more responsive to NPs might receive effective treatment [124]. While achieving an active goal can significantly improve the selectivity of the drug, there are still challenges in identifying biomarkers in various diseases. In

addition, the biological complexity of the internal elimination effect of the receptor sometimes has a decisive effect, especially if the target link binds to the receptor associated with normal tissues or immune cells [125]. Both active and passive targeting mechanisms have their advantages regarding the design of novel drug delivery systems. Passive targeting-essentially through the EPR effect-is a relatively simple and efficient approach, especially in the case of tumor targeting. However, it is often less specific, with changes in drug distribution. On the other hand, active targeting has greater specificity due to the use of ligand-receptor interactions, thus allowing more precise delivery to target tissues. However, it requires very careful selection of appropriate targeting ligands and consideration of off-target effects. Both mechanisms offer more effective and less toxic treatments, and ongoing research is focused on optimizing these strategies for additional clinical applications [126].

Cancer targeting: Cancer cells often display unique surface markers, making them ideal targets for ligand-functionalized nanoparticles. Common targets include receptors like EGFR (Epidermal Growth Factor Receptor), HER2 (Human Epidermal Growth Factor Receptor 2), folate, and transferring receptors. For example, folate receptor-targeted nanoparticles have shown promise in delivering chemotherapeutic agents to ovarian and breast cancers [127].

Inflammatory Tissue Targeting: Ligand-functionalized nanoparticles targeting inflammation-specific markers, such as integrins and selectins, benefit inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease [128]. The main advantage of ligand-functionalized nanoparticles is their ability to improve the specificity and selectivity of drug delivery, minimizing off-target effects and enhancing therapeutic outcomes. However, challenges remain in the conjugation process, including the need for precise control over ligand density and orientation, and potential immune responses that may hinder nanoparticles' efficacy [129].

❖ Regenerative Medicine

The use of nanotechnology in regenerative medicine, which aims to replace or repair damaged tissues and organs, has been extremely beneficial. Nanomaterials can be used to transfer genetic material for tissue regeneration, improve stem cell activity, and modify cellular surroundings [130].

- Stem Cell Engineering with Nanomaterials

Stem cell therapy has the potential to treat a variety of diseases, but controlling stem cell differentiation and ensuring proper tissue regeneration is a challenge. Nanomaterials provide a way to create controlled microenvironments that promote stem cell differentiation. While regulating stem cell development and ensuring tissue regeneration are challenging, stem cell therapy holds promise for treating various diseases.

Gene delivery by nanoparticles encourages stem cell differentiation: Nanoparticles can be used as carriers to deliver genes or growth factors that promote stem cell differentiation. By introducing genes like BMP (bone morphogenetic protein) or VEGF (vascular endothelial growth factor) into stem cells, nanoparticles help guide stem cells to differentiate into specific lineages, such as bone, cartilage, or vascular tissues [131-134].

Role of nanomaterials in creating niche environments for stem cells in regenerative medicine: The extracellular matrix (ECM) can be mimicked by nanomaterials to create niche environments that promote the proliferation and differentiation of stem cells. For instance, nanofibrous scaffolds increase tissue regeneration results by offering both physical support and pharmacological cues that affect cell behavior. Nanotechnology has also been utilized in gene therapy, enabling the delivery of genetic material, such as CRISPR/Cas9 or siRNA, to target cells for gene editing [135]. Nanocarriers such as lipid or polymeric nanoparticles deliver this system to target tissues, which allows gene modification for diseases like cancer, genetic abnormalities, and viral infections. By using the properties of surface topography and chemical composition of biomaterials, researchers can find the cell behavior to support tissue regeneration. Additionally, nanostructured biomaterials are particularly effective in promoting the regenerating tissues like bone, cartilage, and nerves, leading to applications in regenerative medicine [136]. Figure 4 provides a detailed illustration of a surgical process involving the insertion and securing of a spiral-shaped scaffold, composed of chitosan, cellulose, and nano-hydroxyapatite, designed to mimic natural tissue for bone defect repair [137].

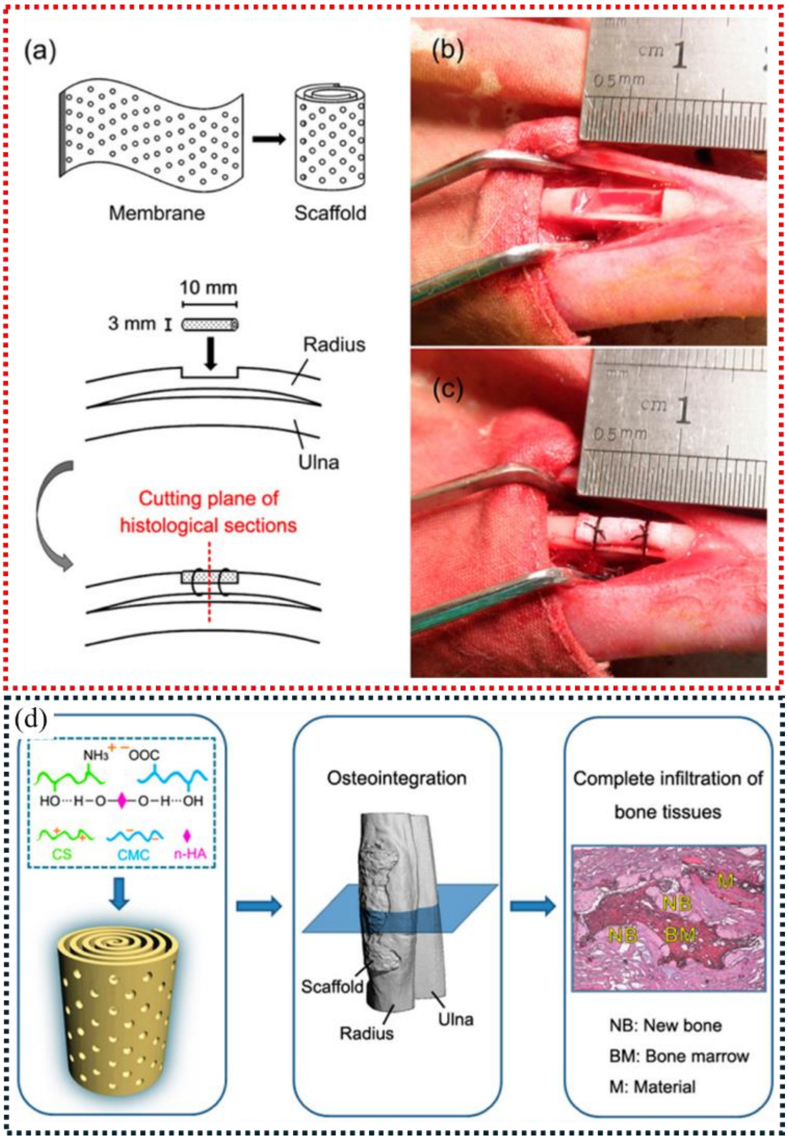


Figure 4. This image shows the surgical process: (a) the general procedure, (b) the created bone defect in a rabbit's radius, and (c) the scaffold being inserted and secured. (d) A spiral-shaped scaffold mimicking natural tissue, made from a blend of chitosan, cellulose, and nano-hydroxyapatite. (Reprinted with permission from [137], Copyright © 2013 ACS Publishing Group.)

❖ Biosensing and Diagnostics

- Fundamental and Diverse Applications of Nanomaterial-Enhanced Biosensors

Biosensors are innovative engineering instruments with a wide range of technological uses. Additionally, biosensors are specifically employed in the monitoring of environmental pollution, the detection of toxic elements, the detection of bio-hazardous bacteria or viruses in organic matter, and the detection of biomolecules in clinical diagnostics [138-139]. The high specificity of biological recognition processes and the sensitivity of electrochemical transducers, as demonstrated by low detection limits, are combined in electrochemical biosensors, a subclass of chemical sensors [140-141]. A biological recognition element found in these devices selectively reacts with the target analyte to generate an electrical signal correlated with the analyte's concentration under study [142-144]. The general workflow for constructing such sensors and biosensors, especially those leveraging nanomaterials, involves the combination of a detection sample with bioreceptors conjugated with nanomaterials, leading to a signal response, as depicted in Figure 5 [145]. Many studies have investigated using transducers that are physically similar to the target species to create sensitive biosensors [146]. As a result, pathogen detection has been studied using electrodes that range in size from micrometers to nanometers. The creation of nanoscale structures of conducting and semiconducting materials through a variety of bottom-up and top-down nanomanufacturing techniques, including nanowires, has prompted research into nanostructured electrodes for pathogen detection, even though nanoscale planar electrodes are among the most frequently studied for this purpose [146-147].

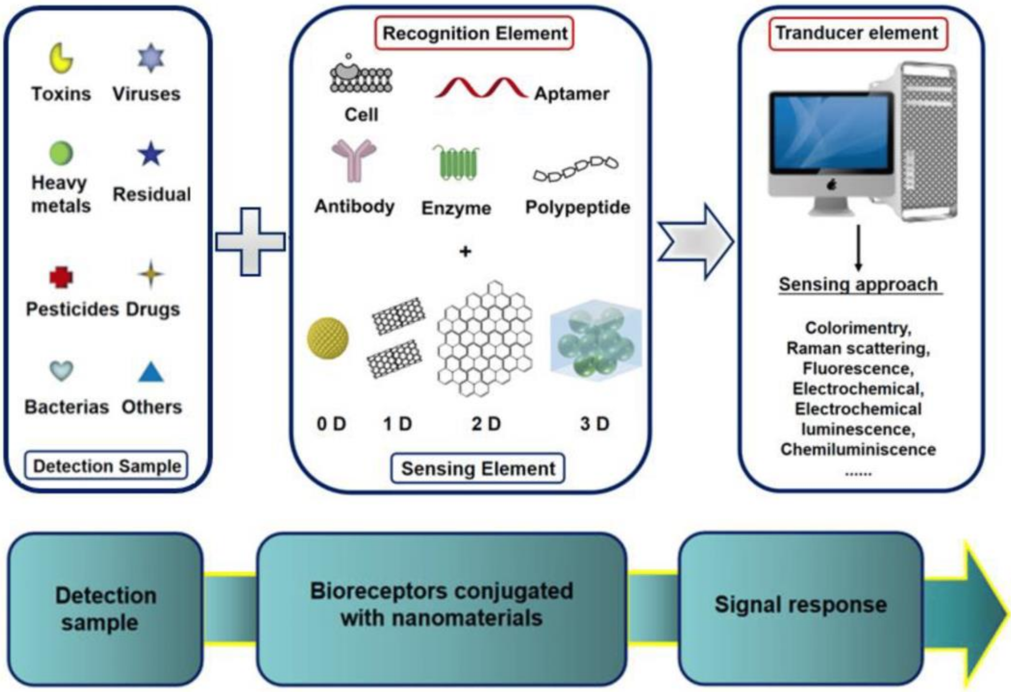


Figure 5. This schematic illustrates the steps involved in constructing sensors and biosensors that utilize nanomaterials. (adapted from reference [145], Copyright © 2022 by the authors)

A wide range of measurements is described by optical transduction (e.g., Raman, surface enhanced Raman, refraction, dispersion spectrometry, fluorescence, phosphorescence, absorption, etc.). A wide range of optical characteristics can be measured using any of these spectroscopic methods. Amplitude, energy, polarization, decay time, and/or phase are some of these characteristics [148]. For example, changes in the local environment surrounding the analyte, its intramolecular atomic vibrations (i.e., the energy of the electromagnetic radiation measured), can frequently be inferred from their energy. Another use of optical nanosensors for biological measurements was the development of calcium ion-sensitive nanosensors, which were used to measure calcium ion fluctuations in smooth vascular muscle cells during stimulation [149]. Despite their luminescence potential, dendrimers are rarely used for sensing. For instance, Lebedev et al, created luminescent dendrimers with a porphyrin core (either as a metal complex or as a free base). The fluorescence of a metal-free porphyrin (pKa = 6.3) and the phosphorescence of a metalloporphyrin (pH = 0–100 percent air saturation) demonstrated their suitability for measuring pH and oxygen [150]. However, a high degree of non-specific binding and the fact that many substances can function as quenchers can compromise the use of QDs in optical sensors.

- Nanomaterial-Based Biosensors in Specific Diagnostic Applications

There is an urgent need for highly sensitive techniques to measure cancer diagnosis markers that are present at extremely low levels in the preliminary stages of the disease. Current diagnostic procedures (e.g., G. ELISA) are insufficiently sensitive and identify proteins at concentrations indicative of more advanced disease stages [151-152]. Various detection techniques, including oligonucleotide microarrays, nanoparticle probes, microfluidic protein chips and arrays, and nanobio chips, have been reported, even though they involve numerous biomarkers [153]. The development of biosensors has historically focused primarily on electrochemical devices. Only a small percentage of biosensors and aptasensors among cancer detection tools are capable of quantitative analysis. An aptasensor created by the Wang's research group could be used to quantify platelet-derived growth factor BB (PDGF-BB), a unique protein linked to cancer that is frequently assessed qualitatively [154]. This portable, sensitive nano-based aptasensor offered quick detection for early cancer diagnosis. A very low LOD of roughly 0–11 fM was produced by the large amount of loading aptamers on magnetic nanoparticles, the CX reaction that released zinc ions, and the fragments of disported DNA. Similarly, Zhao et al. created a novel aptasensor with graphene/dual-labeled aptamers immobilized onto a glassy carbon modified electrode [155]. The linear range was from $3.16\times10^{-16}$ M to $3.16\times10^{-12}$ Mdot. Carcinoembryonic antigen (CEA), a glycoprotein with an aberrant amount, is a significant tumor marker that is closely related to cancer detection. A nano-based electrochemical CEA biosensor was constructed using one-pot synthesis in a study conducted by Jang and colleagues [156]. In this work, multidimensional polymer nanotubes with conductive qualities were prepared using 3-carboxylate polypyrrole. A quick reaction (less than 1 s) with ultrasensitive detection was seen by binding between CEA aptamers and the amid groups of multidimensional polymer nanotubes immobilized on the electrode surface.

For a summary of recent advancements and specific examples of nanomaterials and their applications in biomedical research, refer to Table 1.

Table 1: A Few recent works on nanomaterials used in biomedical research.

| Material | Fabrication Technique | Properties | Outcomes | Ref |
| --- | --- | --- | --- | --- |
| Nanocomposite of poly(e caprolactone) (PCL) and silica | Solvent casting | Composite nanoparticle scaffold | When compared to pure PCL, silica improved the mechanical characteristics of mesenchymal stem cells or marrow stromal cells (MSCs) grown on PCL composites without sacrificing their biocompatibility. | [157] |
| PLGA/nHA | Solvent casting/particulate leaching | Composite scaffolds with nHA crystal | When compared to PLGA controls, osteoblasts grown on PLGA/nHA composites produced more bone. | [158] |

| | | | | |
|---|---|---|---|---|
| Chitosan/nHA | To induce HA growth, freeze dry followed by a change in pH | Composite scaffold contacting nHA crystal | MG-63 adhesion, spreading, and proliferation on chitosan/nHA composites were higher after 21 days compared to chitosan controls. | [159] |
| PLGA/MWCNT | Electrospinning | Composite fiber | Compared to the PLGA control, there was an increase in BMSC attachment after 24 hours and proliferation after 5 days of culture on composite scaffolds. | [160] |
| PPF/PF-DA/CNT composite | Particulate leaching/thermal crosslinking | CNT homogeneously distributed into porous material | At 4 and 12 weeks, nanocomposite scaffolds showed positive soft and hard tissue responses. A three-fold increase in bone tissue ingrowth at 12 weeks appeared in flaws that included nanocomposite scaffolds, in contrast to scaffolds made of control polymers. Furthermore, the 12-week samples revealed decreased density of inflammatory cells and elevated connective organization of tissues. | [161] |
| Polyamide HA composite | Particle leaching and phase separation | Allogenic BMSCs coupled with porous scaffolds containing | In the early post-implantation phase, the composite with BMSCs demonstrated improved osteogenesis, osteoconductivity, and high biocompatibility. At the late stage following implantation, the effects of the composite with or without BMSCs on osteogenesis were comparable. | [162] |

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| | | nanoscale HA crystals | | |
| Ti alloy | Anodization process | Nanotube/ nanorods | High osseointegration and corrosion resistance | [163] |
| Co-Cr-Mo alloys tantalum | Microemulsion technique and heat treatments | Nanostructure and nanoparticle | Excellent biocompatibility and anticorrosive behavior, as well as high resistance to wear and corrosion. | [164] |
| CNF/polycaprolactone/mineralized HA | Electrochemical deposition | Nanofibrous scaffolds | High cell viability, good adhesion strength and elastic modulus, and suitability for load-bearing applications | [165] |
| CNT/alumina ceramic composites | Stirring | Ceramics and nanotubes | It improves the mechanical characteristics, and in bone implantation testing, the composite showed good bone tissue compatibility and connected directly to new bone | [166] |
| Graphene/HA composites | Spark plasma sintering | Nanosheets reinforced composites | Improvements in apatite mineralization, osteoblast adhesion, and fracture toughness of about 80% as compared to pure HA | [167] |
| Aluminum oxide-coated Ti alloy | Oxide magnetron sputtered coating | *In vivo* and *in vitro* systems | High corrosion resistance and the hydrophilic nature of the coated surface contribute to good biocompatibility. | [168] |

## 6. Challenges and Limitations of Nanomaterials in Biomaterials

Although nanomaterials have significantly advanced biomaterials research, particularly in drug delivery and regenerative medicine, their use presents several challenges and limitations. These challenges span multiple areas, including biocompatibility, manufacturing, regulatory frameworks, and environmental considerations. Understanding and addressing these issues is critical to fully realizing the potential of nanomaterials in biomedical applications [169].

❖ Issues Related to Biocompatibility and Toxicity

One of the most significant challenges in using nanomaterials with biomaterials is ensuring their biocompatibility and minimizing toxicity. Due to their interactions with biological systems at cellular and molecular levels, the small size and high surface reactivity of nanomaterials can sometimes lead to unintended biological effects [169]. Biocompatibility of nanomaterials refers to their ability to perform their intended function within the body without eliciting undesirable responses, such as immune reactions, inflammation, or other adverse effects. Polymeric nanomaterials are used in nanomedicine due to their biocompatibility and biodegradability. These nanoparticles have been categorized as a great candidate for controlled drug delivery, as they have the capability of targeted drug release and protection of the encapsulated payload, and prolonged circulation time [169-170]. The toxicity of the nanomaterials adversely interrupts the physiology of normal organs and tissues of humans and animals. The interaction between nanomaterials and biological matter is complex due to a lack of understanding of the intracellular mechanisms and pathways. Furthermore, accumulating knowledge of nanoparticle-cell interactions indicates that cells uptake nanoparticles via active or passive mechanisms. All metallic nanomaterials (NMs) can induce an inflammatory response, depending on their composition, size, and shape [170].

❖ Challenges in Manufacturing and Scalability

- Precision and Consistency

Achieving desired therapeutic effects with nanomaterials requires precise control over their size, shape, surface properties, and composition. Precise targeting of infected or cancerous cells is another challenge, as the biodistribution of nanoparticles within the body may not always align with therapeutic objectives, leading to off-target effects. Small variations in these parameters can lead to significant performance differences, hindering consistent large-scale production [171]. The scalability and cost-effectiveness of nanobiomaterial production are practical challenges that must be addressed for widespread accessibility.

- Scalability

Many nanoparticle synthesis methods, such as chemical vapor deposition or electrospinning for nanofibers, are difficult to scale up for industrial production. Batch-to-batch variability, high production costs, and low yields are common issues when attempting to produce nanomaterials in larger quantities for clinical or commercial use. This presents a barrier to the widespread adoption of nanomaterial-based biomaterials, particularly in cost-sensitive markets like healthcare.

- Regulatory Hurdles and Safety Concerns

The introduction of nanomaterials into the medical field also faces substantial regulatory challenges. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have stringent guidelines for the approval of new medical products, and nanomaterials present unique regulatory hurdles due to their novel properties.

- Unclear Regulatory Pathways

Traditional regulatory frameworks are often insufficient to address the complexities of nanomaterials. For instance, the behavior of nanomaterials in biological systems differs significantly from bulk materials, and there is currently no standardized testing methodology for assessing the safety and efficacy of nanoparticles. This can slow down the approval process for nanomaterial-based products, as companies and regulators must navigate uncharted territory to establish the safety of these materials.

- Safety Concerns

Long-term safety is a significant concern for nanomaterials. Regulatory agencies require comprehensive data on their potential toxicity, biodistribution, and degradation before approval for medical use. The long-term effects of nanomaterials in the body remain largely unknown, especially for non-biodegradable materials or those that accumulate over time. Ensuring nanomaterials do not interfere with the immune system, cause unintended tissue damage, or accumulate in non-target organs further complicates regulatory approval [172].

❖ Environmental Impact and Long-Term Stability

Nanomaterials, particularly those used in medical devices and drug delivery systems, also raise concerns about their environmental impact and long-term stability, both within the body and in the external environment.

- Environmental Impact

The manufacturing, use, and disposal of nanomaterials can have unintended environmental consequences. Nanoparticles can enter the environment through wastewater, manufacturing runoff, or medical waste, potentially leading to environmental contamination. The behavior of nanomaterials in the environment, such as their interaction with ecosystems, degradation, and bioaccumulation, is still not fully understood. For example, metallic nanoparticles, such as silver or titanium dioxide, widely used for their antimicrobial properties, may pose risks to aquatic life or disrupt microbial ecosystems if released into water supplies [173].

- Long-Term Stability

In biomedical applications, the long-term stability of nanomaterials is essential for their safety and efficacy. Some nanomaterials, such as biodegradable polymers, are designed to break down over time, while others, like metallic nanoparticles, are intended to remain stable. However, non-biodegradable nanomaterials can accumulate in tissues or organs over time, leading to potential long-term toxicity. The degradation products of some nanomaterials, such as metal ions released from metallic nanoparticles, can have toxic effects [173-174].

## 7. Recent Innovations, advances, and challenges

❖ Breakthroughs in Nanomaterials for 3D Bioprinting

Recent nanomaterial developments, particularly in bioink creation, have significantly improved 3D bioprinting technologies. To enhance the mechanical characteristics, biocompatibility, and functioning of bioinks, nanomaterials like graphene, nanosilicates, and carbon nanotubes have been incorporated. For example, nanocellulose-based inks have emerged as viable substitutes due to their structural similarity to extracellular matrices, which support cell survival and proliferation [175–176]. Furthermore, it has been demonstrated that adding nanoparticles improves the hydrogels' printability and structural stability, enabling the production of intricate tissue architectures [177]. Integrating 3D bioprinting techniques and nanotechnology helped develop smart bioinks that have responded to environmental cues and have also been applied for 4D bioprinting [178]. The integration of nanotechnology has enhanced bioprinting by improving the mechanical and biological characteristics of scaffolds that are printed, along with facilitating the creation of dynamic tissue architectures that are capable of changing after printing [179]. The diverse range of biofunctional nanoparticles, including ceramic, metallic, polymeric, and carbon-based types, along with their integration into biopolymers and cells for various 3D bioprinting methods (such as inkjet, laser-assisted, extrusion-based, and stereolithography) to create nanocomposite structures, is comprehensively illustrated in Figure 6 [180]. Furthermore, it is noticeable that nanomaterials have brought about revolutionary change in tissue engineering when incorporated into 3D bioprinting and have opened up to advanced approaches for the development of regenerative medicine.

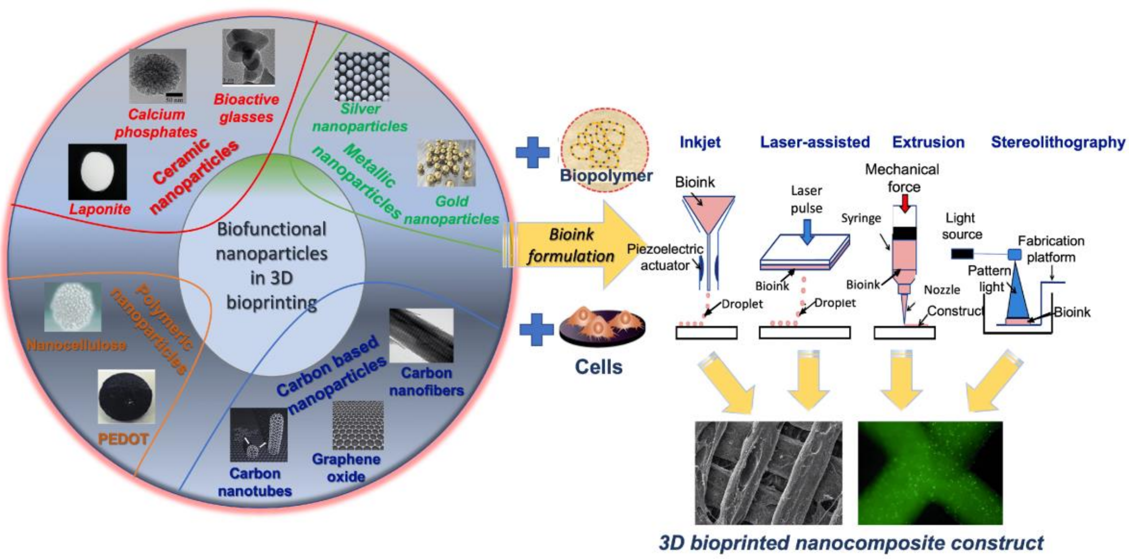


Figure 6. The schematic demonstrates the process of creating 3D bioprinted nanocomposite structures by combining ceramic, metallic, polymeric, or carbon-based nanomaterials with biopolymers and

cells, utilizing printing methods such as inkjet, laser-assisted, extrusion-based, and stereolithography. (adapted from reference [180], Copyright © 2023 by the authors)

❖ Smart and Stimuli-Responsive Nanomaterials

Nanomaterials have also gathered attraction for their use as Smart and Stimuli-Responsive materials as they show potential changes when exposed to external stimuli, namely, light, pH, and temperature. Advances in this field have included polymeric micelles for stimuli-responsive, which are capable of releasing therapeutic agents in a regulated way, which have improved drug delivery and cancer therapy significantly [181]. These nanocarriers can be designed to respond to specific biological triggers, enhancing their effectiveness and minimizing adverse effects [182]. Figure 7 further elaborates on this, demonstrating how various stimuli (exogenous like temperature, light, and ultrasound, and endogenous like enzymes, ROS, and glucose) are leveraged with different types of nanoparticles (polymeric, lipid-based, mesoporous silica, dendrimers, and gold nanoparticles) for therapeutic drug delivery in diverse ailments such as periodontitis, inflammatory bowel diseases, rheumatoid arthritis, atherosclerosis, and diabetes mellitus [183].

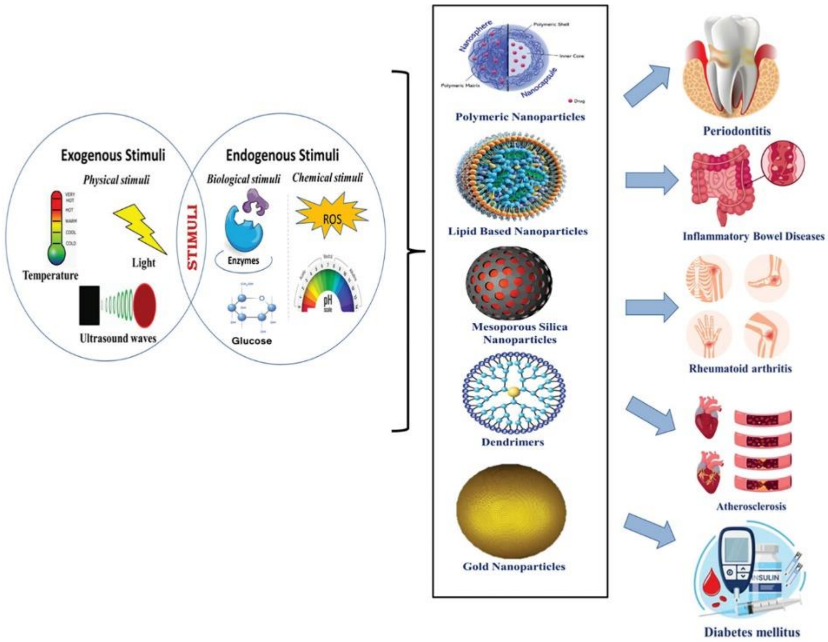


Figure 7. The image demonstrates the application of stimuli-responsive nanoparticles in the treatment of diverse ailments. (Reprinted with permission from [183], Copyright © 2024 Wiley-VCH GmbH)

Self-assembled peptide nanoparticles have demonstrated significant potential in biological applications, serving as versatile platforms for targeted imaging and therapy [181]. The potential of graphene-based nanomaterials to improve treatment outcomes through controlled drug release in response to various stimuli has also been reported [184]. The development of molecularly imprinted nanomaterials has widened the potential of drug delivery systems and bioanalysis by enabling recognition of specific biomolecules with the use of smart systems [185-186]. All of these lead to the invention of smart nanomaterials and lead to novel approaches towards therapeutic interventions, drug delivery systems, and diagnostic systems.

❖ Nanomaterial-Based Immunomodulation

Today, immunomodulation tools have also greatly benefited from the use of nanomaterials. Nanomaterials enhance the effectiveness of immunotherapy for diseases like autoimmune disorders, cancer, etc. The present research lights up the applications of nano systems for immunomodulatory which have potential for targeted immune response for specific immune cells and modification in the tumor microenvironment [187]. Improvement in the delivery of immunotherapeutic agents has improved these systems and has been capable of addressing issues of inadequate stimulation of the immune system and the off-target effects [188]. Nanomaterials that are developed to target lymphoid organs are designed in a way that can efficiently improve immune responses and provide a system of targeted therapy in the treatment of inflammation and cancer [189]. Development in the results of the treatment needs much studied and improved nanomaterials which are capable of modulation as per the immune responses and also avoid immune detection at the same instance [190]. Nanomaterials' incorporation with the current immunotherapeutic techniques has enhanced the efficiency of checkpoint inhibitors and cancer vaccines [191]. Hence, using nanomaterials opens up various new possibilities for specific treatment and can lead to breakthrough developments for precision medication when incorporated in immunomodulation.

❖ Emerging Nanocomposite Designs

The current research and developments in nanocomposites have shown transformation in applications, such as in medicine, electronics, and energy storage. Recent developments include ceramic-polymer nanocomposites that combine the flexibility of polymer matrices with the high permittivity of ceramic fillers, making them suitable for energy storage applications [192]. The improved dielectric qualities of these composites are essential for the creation of sophisticated capacitors and electrical devices. Thermally drawn elastomer nanocomposites, developed for soft mechanical sensors, have shown significant potential in robotics and health monitoring [193]. One of the primary areas of current research is the ability to tune the electrical and mechanical properties of such nanocomposites by use of modified methods for production. Lanthanide-doped nanoparticles have been included in nanocomposites, which gives the capability of designing various nanocomposites, which opens innovative approaches to treat cancer and also for bioimaging [194]. The architectural development of nanocomposites has opened a way to create versatile materials having a wide range of multisector usage.

❖ Integration of nanomaterials with Digital and Computational Technologies

Integrating digital and computational technologies, mainly machine learning and artificial intelligence (AI), into nanomaterials development has shown significant advancement. Ongoing research has shown that algorithms of AI are capable of optimizing designs for nanocomposites and have been identifying materials with desired properties very quickly [195]. This has been very significant in lowering time and cost related to the conventional approaches for material discovery. One such computation-based materials optimization technique is a Bayesian optimization-based data-driven design framework, which is created to determine the composition of nanocomposites and also the microstructures, simultaneously, thus improving performance in a wide range of applications [196]. There has been growth in the production of nanomaterials and also in their characterization by using machine learning, which highlights the relation between material characterization and processing parameters. Microfluidic technology, which is known to have precise control over the properties of materials that are synthesized using this technique, is also enhanced using algorithms of machine learning and the in-line characterization tools [197]. Today, the designing of nanomaterials and their usage in different domains has become both innovative and efficient due to the integration of nanotechnology with digital and computational technology. There are also many challenges associated with the integration of AI into nanomaterials research, which are faced today, including the lack of datasets with consistency and high quality for training of AI models. In some cases, there is also a complete lack of datasets in the case of many nanomaterial investigations, which results in incorrect material identification [198].

### ❖ Challenges in Integrating Advanced Technologies such as AI into Nanomaterials Research

There are several challenges in the integration of AI in the research and development of nanomaterials that need a proper solution for successful results.

One of the challenges is clear interpretation and model bias. AI models can show bias due to the data used for training, and hence cannot fully portray diverse nanomaterials, which may affect the accuracy of predictions by AI. Moreover, AI algorithms are complex and generally show difficulty in interpretation and complicate the result validation [199]. Another issue is faced while integrating AI with existing research processes, and hence, research can face problems while incorporating AI into conventional methods for nanomaterial development, which can limit the effective application of this technology [200]. There are also some regulatory and ethical concerns that give rise to many issues while incorporating AI in nanotechnology. Specifically, when it is related to potential impact on environmental safety, sustainability, and self-learning abilities. Ensuring responsible development in this field is important to address [198]. Moreover, demands in computation for advancement in AI could be substantial, and need resources that are readily available for research [201]. Regardless of the potential involvement of AI and machine learning in the research of nanomaterials is very large, overcoming the challenges through collaboration, standardized datasets development, and computational advancements is important to use the potential of this technology.

## 8. Proposed Future Advancements and Research Directions

❖ Designing Next-Generation Multifunctional Nanomaterials

The advancements today in the field of nanomaterials with multifunctionalities are focused greatly on combining several different properties to challenge the complex problems in the biomedicine sector, environmental science application, energy sector etc. there have been cutting edge development in Carbon-metal nanohybrids (CMNHs), which exhibit improved electrical and optical properties which are termed very critical for energy harvesting and environmental remediation technologies [202]. Polymer-based nanoparticles are also at the forefront and have significantly developed for photothermal therapy; they also show the effectiveness in stimuli-responsive designs for effective therapeutic value [203]. Moreover, nanostructures that are hollow show popularity in drug delivery as they show high drug-carrying capacity and adaptability, making them appropriate for usability in biomedical research [204]. The prospect research should explore 2D nanomaterials for applications at the cellular level, using their unique characteristics to create cellular constructs that would be innovative [205]. Furthermore, integration of artificial intelligence (AI) into designing nanomaterials would bring about a significant increase in the development of new materials, which also enhance their properties and can be used for application in clean energy [206]. Scalability and reproducibility are the basic problems related to this material, and therefore, resolving this issue is crucial for the commercialization of advanced nanomaterials.

❖ Enhancing Safety Profiles and Reducing Toxicity

Applications for nanomaterials are growing, and with that, safety has become a prominent problem. Recent research emphasizes the need for safer-by-design methodologies that integrate safety assessments into the design process to mitigate potential risks [207]. While functionalized silver and gold nanoparticles have shown promise in biomedical applications, further research is necessary to fully elucidate their toxicity mechanisms and enhance biocompatibility [208]. Novel techniques, such as machine learning, are being employed to enhance risk assessment and safety profiling of nanomaterials and improve predictions of their interactions with biological systems [209]. Furthermore, developments in solid-state batteries employing nanomaterials underscore the significance of augmenting safety via enhanced mechanical and thermal stability [210]. Future studies should focus on developing comprehensive frameworks for assessing nanomaterial safety to ensure their responsible use in consumer products and medical applications.

❖ Application of Bioinspired and Biomimetic Nanomaterials

Bioinspired nanomaterials, which leverage natural processes for innovative applications, are emerging as a transformative concept in nanotechnology. Recent advancements in biomolecular self-assembly have facilitated the creation of hierarchical nanomaterials with specific functionalities for energy and environmental applications [211]. Enhancing biocompatibility and multifunctionality, the incorporation of bioinspired nanomaterials into micro/nanodevices has demonstrated considerable promise in biomedical domains [212]. Research on protein-guided biomimetic nanomaterials, with a focus on drug delivery and disease therapy, is expanding. In addition, the creation of nanomaterials inspired by cephalopods used in thermal and optical control applications exhibits adaptability of bioinspired material designs, which are versatile in usage, i.e., either medical technology or sensing application [213]. The research should importantly include exploration of different bio-inspired multifunctional nanomaterials that are capable of addressing challenges globally in environmental sustainability and health [214-215].

## 9. Conclusion and Future Outlook

Nanotechnology has become a cornerstone in the latest advances in material science in recent times. It has revolutionized research on biomaterials, with unprecedented progress in material properties, their applications, biological interactions, as well as therapeutic applications. The incorporation of nanomaterials has improved properties in various domains such as biosensors and medical implants, tissue engineering scaffolding, as well as medication administration vehicles. Despite many good breakthroughs, several issues still persist for nanomaterials, such as toxicity, long-term biocompatibility, large-scale manufacturing, and regulatory issues. These issues require the establishment of standardized test protocols to increase safety profiles, optimize manufacturing strategies, and ensure the efficiency and reliability of nanomaterial-based biomaterials. Some work in this regard has already started in the European Union, but it is still in the initial stages before an industry-wide regulation can become a norm. Over the next few years, research in the field of nanotechnology and biomaterials will pay attention to the development of intellectual and multifunctional nanomaterials with accurate monitoring of biological interactions. Advanced and upcoming technologies in the computer science domain, like Machine learning and artificial intelligence, can play a critical role in the development of new biomaterials. They can help design biomaterials with individual properties for specific medical applications. Similarly, biomimetic nanomaterials can also help in regenerative medicine. The adoption of green synthesis strategies for nanomaterials and biodegradable nanocomposites synthesis will further reduce the environmental impact and improve the long-term stability of these materials. Similarly, by improving the biocompatibility and antibacterial properties of medical implants, complications can be reduced, and long-term success can be increased. Nano-enabled point-of-care testing and wearable biosensors can enable early disease detection and real-time health monitoring. This will promote preventive health care practices. With each innovation, nanotechnology is going to drive advances in medicine and shape the future of biomaterials.

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## Graphical Abstract


## List of Abbreviations

| S. No. | Abbreviation | Full form |
|---|---|---|
| 1 | AgNPs | Silver Nanoparticles |
| 2 | AI | Artificial Intelligence |
| 3 | AuNPs | Gold Nanoparticles |
| 4 | BaP | Benzo[a]pyrene |
| 5 | BMP | Bone Morphogenetic Protein |
| 6 | BPT | Benzopyrene Tetrol |
| 7 | Ca10(OH)2(PO4)6 | Hydroxyapatite Chemical Formula |
| 8 | CEA | Carcinoembryonic Antigen |
| 9 | CMNHs | Carbon-Metal Nanohybrids |
| 10 | CNPs | Carbon Nanoparticles |
| 11 | CNF | Carbon Nanofiber |
| 12 | CNTs | Carbon Nanotubes |
| 13 | CRISPR | Clustered Regularly Interspaced Short Palindromic Repeats |
| 14 | DDSs | Drug Delivery Systems |
| 15 | DNA | Deoxyribonucleic Acid |
| 16 | ECM | Extracellular Matrix |
| 17 | EGFR | Epidermal Growth Factor Receptor |
| 18 | ELISA | Enzyme-Linked Immunosorbent Assay |
| 19 | EMA | European Medicines Agency |
| 20 | EPR | Enhanced Permeability and Retention |
| 21 | FDA | Food and Drug Administration |
| 22 | FDM | Fused Deposition Modeling |
| 23 | Fe3O4 | Iron Oxide Nanoparticles |
| 24 | fM | Femtomolar |
| 25 | HAp | Hydroxyapatite |
| 26 | HER2 | Human Epidermal Growth Factor Receptor 2 |
| 27 | hESC-MSC | Human Embryonic Stem Cell-Derived Mesenchymal Stem Cell |
| 28 | HIV | Human Immunodeficiency Virus |
| 29 | LMWG | Low-Molecular-Weight Gelators |
| 30 | LOD | Limit of Detection |
| 31 | MC3T3-E1 | Mouse Pre-Osteoblast Cell Line |
| 32 | MNP | Magnetic Nanoparticles |
| 33 | MNF | Macroporous Nanofibrous |

| | | |
|---|---|---|
| 34 | MPa | Megapascal |
| 35 | MRI | Magnetic Resonance Imaging |
| 36 | MSCs | Mesenchymal Stem Cells |
| 37 | nHAp | Nano-Hydroxyapatite |
| 38 | nm | Nanometer |
| 39 | NMs | Nanomaterials |
| 40 | NPs | Nanoparticles |
| 41 | PCL | Polycaprolactone |
| 42 | PCU | Polycarbonate-Urethane |
| 43 | PDGF-BB | Platelet-Derived Growth Factor BB |
| 44 | PLA | Polylactic Acid |
| 45 | PLGA | Polylactic-co-Glycolic Acid |
| 46 | PLLA | Poly-L-Lactic Acid |
| 47 | PS | Polystyrene |
| 48 | QDs | Quantum Dots |
| 49 | RNA | Ribonucleic Acid |
| 50 | ROS | Reactive Oxygen Species |
| 51 | SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| 52 | siRNA | Small Interfering Ribonucleic Acid |
| 53 | SLA | Stereolithography |
| 54 | SWCNT | Single-Walled Carbon Nanotube |
| 55 | TCP | Tricalcium Phosphate |
| 56 | Ti6Al4V | Titanium-Aluminum-Vanadium Alloy |
| 57 | TiNPs | Titanium Nanoparticles |
| 58 | $TiO_2$ | Titanium Dioxide |
| 59 | VEGF | Vascular Endothelial Growth Factor |
| 60 | ZA | Zoledronic Acid |
| 61 | ZnO | Zinc Oxide |

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Conceptualization: TKS, RK.; Validation, formal analysis: SK, MP; Investigation, resources, data curation, writing—original draft preparation: AKS, RS, VSK, AK, writing—review and editing: TKD, RK, SK, visualization, supervision, project administration: TKD, MP, VSK.

## Conflicts of Interest

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