Biomaterials Connect
ISSN: 3105-0387
2025, Article ID. 2025.0019, Cite as: https://doi.org/10.69709/BIOMATC.2025.188313

SCIFINITI PUBLISHING

Review Article

OPEN ACCESS

Integration of Nanotechnology and Nanomaterials in Biomaterials Research

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Article History
Submitted: March 12, 2025 Accepted: August 22, 2025 Published: October 23, 2025

Abstract
Nanotechnology has emerged as a transformative force in biomaterials research, significantly enhancing their functionality and versatility across medical applications, including tissue engineering, drug delivery, regenerative medicine, and medical implants. The integration of nanomaterials into biomaterials has improved biocompatibility, mechanical strength, drug release control, and bioactivity. The present review provides a comprehensive overview of the historical perspective, classification, and applications of nanomaterials in biomaterials research. It discusses how inorganic, organic, and hybrid nanomaterials are advancing biomedical applications, including their effects on scaffolds, nanoparticles for targeted drug delivery, and surface modifications for implants. The paper also addresses current challenges in the use of nanomaterials, including biocompatibility, toxicity, scalability, and regulatory considerations. Finally, future research directions are proposed to enhance the safety, functionality, and integration of nanotechnology in biomaterials, paving the way for next-generation biomedical applications. This review highlights 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; drug delivery system; nanocomposite scaffolds; stimuli-responsive nanomaterials; nano-enabled biosensors; osseointegration

1. Introduction

1.1. Overview of Biomaterials Research

From the late 19th century, the use of metals and their composites in biomaterials has increased significantly. Biomaterials, often synthetic but sometimes natural, have been extensively used to replace or repair various biological functions of human tissue. Since they are constantly exposed to body fluids, they play a vital role in supporting daily human activities. A global effort is underway to develop novel biomaterials that can further enhance these activities. Extensive research has led to the development of numerous biomaterials aimed at understanding the interactions between the human body and these materials [1]. These biomaterials exhibit exceptional properties applica-

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ble in a wide range of fields, from complex diagnostics to clinical treatments.

When designing biomaterials, it is essential to consider factors such as biocompatibility, as well as chemical, mechanical, and physical properties. In addition, their bioactivity and bioinertness should be evaluated [2]. Careful evaluation of these parameters enables the creation of more effective and biocompatible systems for medical use. For example, many bone substitutes act only as mechanical supports and do not facilitate processes such as hematopoiesis. They exhibit only basic functional properties within normal physiological systems. In contrast, pacemakers and neuromuscular stimulators perform specialized electrical functions. Specialized implants, such as oxygenators and dialyzers, can also perform essential chemical tasks like oxygenation and dialysis [3]. Further enhancement of biomaterials could enable the development of advanced implants with multiple functions.

One such biomaterial is smart polymers, which impart novel and innovative properties to inert polymers when interacting with peptides, proteins, cells, or DNA. A notable example is the use of biodegradable polymers in sutures and bone plates. These polymers are developed from natural or synthetic polyesters and 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. The biodegradability of such polymers has led to the development of various advanced drug delivery systems. Reconstituted collagen polymers are widely used in skin substitutes, heart valves, and arterial wall replacements, representing a major breakthrough in the field. Biological tissues are generally categorized as hard (e.g., bone, cartilage, teeth, nails) or soft (e.g., skin, ligaments, fibrous tissues, synovial membranes), irrespective of mineral content. Biomedical implants are engineered to support, repair, or restore the function of damaged or diseased tissues in both categories. These biomaterials are either natural or synthetic, designed to function properly in a biological setting. This growing demand for synthetic tissue has arisen from the limited availability of donor organs, driving research efforts toward developing methods to mimic or replicate biological tissues and organs [4].

1.2. Role of Nanotechnology

The integration of nanotechnology into the implant field has dramatically increased in recent years. Researchers are increasingly investigating nanomaterials with biomimetic properties to enhance the performance of conventional implants [5]. Nanomaterials offer increased surface area, tailored stiffness, and modified surface roughness and physicochemical properties, which collectively improve cell adhesion, proliferation, bone protein synthesis, and mineral deposition. Since the advent of nanotechnology, various nanophase materials (grain size less than 100 nm), including metals, polymers, ceramics, and composites, have emerged with unique surface properties; many of these materials exhibit enhanced capacity to promote osseointegration and new bone formation. For example, Serra et al. [6] produced a nanostructured Ti_6Al_4V alloy using severe plastic deformation techniques. 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. Due to these properties, nanoparticles (NPs) are ideal as drug carriers, thermal mediators in hyperthermia treatments, and contrast agents for computed tomography or magnetic resonance imaging (MRI). Therefore, the exposure of living organisms to natural, incidental, and engineered nanoparticles is rapidly increasing [7]. Metal oxide nanoparticles are particularly attractive as antibacterial agents due to their exceptionally large surface areas and unique crystalline morphologies, which feature numerous edges, corners, and other potentially reactive sites. The impact of iron-oxide nanoparticles on biofilms that developed on the surface of polymer-brush-coated biomaterials was assessed for this property.

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) matrices has been proposed to enhance the mechanical properties (in terms of tensile and compressive moduli) of the composite scaffolds. Carbon nanotubes (CNTs) serve as a safer alternative to traditional toxic fibers such as asbestos [8]. Incorporating single-walled carbon nanotubes (SWCNTs) into PLGA composites reduced polymer crystallinity by ~5%, increased tensile strength by ~12%, and slowed 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

2025, Vol. 2, Article ID. 2025.0019
https://doi.org/10.69709/BIOMATC.2025.188313

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

In recent decades, nanomaterials have significantly enhanced the properties and functions of biomaterials in biomedical research and healthcare applications [15]. Biomaterials are designed 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.

2.1. Historical Perspectives on Nanotechnology in Biomaterials

Nanomaterials possess a high surface-to-volume ratio, which enhances their chemical reactivity and enables precise interactions with biological systems at the molecular level, resulting in properties that can be effectively harnessed for biomedical applications. Advancements in nanotechnology have continuously driven the development of potentially biocompatible biomaterials ever since the concept of biocompatibility became integral to medical science [21,22]. Initially, nanoparticles, nanofibers, and nanostructured surfaces were introduced as biomaterials for the development of medical devices, tissue engineering, and drug delivery applications [23]. During the 1950s and 1960s, liposomes and polymeric carriers were developed as the first generation of biomaterials for targeted drug delivery, offering precision and efficiency [24]. They encapsulated drugs at the nanoscale and delivered them precisely to targeted tissues. This approach prevented drug degradation and allowed controlled release over time. This discovery helped overcome major issues such as poor bioavailability and non-specific targeting in conventional drug delivery.

During the 1990s, biocompatible hydroxyapatite nanoparticles were extensively studied, playing a crucial role in the design of scaffolds for new bone formation and the regeneration of damaged bone tissue. Due to its high surface area and biocompatibility, hydroxyapatite also acts as a carrier for drugs and bioactive molecules. The development of these biomaterials laid the foundation for functionalizing nanoparticles with biological molecules to enhance biocompatibility and minimize immune responses associated with 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]. These advancements have enabled the development of nanocoatings and surface modifications that enhance medical implant performance by improving tissue integration and providing antimicrobial properties. Collectively, these innovations in biomaterials have significantly advanced medical science, enhancing treatment effectiveness and enabling patient-specific customization.

2.2. 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 progress in developing smart biomaterials that respond to environmental stimuli such as pH, temperature, or specific enzymes. These materials can be utilized in biological research and have applications in several fields, including tissue engineering [29], cell therapy [30], and gene transfection [31]. 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 enables the precise fabrication of complex, patient-specific structures at the nanoscale, opening new avenues for regenerative therapies and personalized 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].

2.3. Comparison of Traditional vs. Nanobiomaterials

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.

2.3.1. Biocompatibility and Tissue Integration

Conventional biomaterials often present biocompatibility challenges, potentially leading to immune reactions, 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]. Furthermore, implants with nanostructured surfaces can promote cell proliferation and adhesion, improve tissue integration, and reduce rejection rates.

2.3.2. 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].

2.3.3. Mechanical Properties and Functionality

Traditional biomaterials are often selected for their mechanical strength; however, they may fall short in meeting the flexibility and functional requirements necessary 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].

2.3.4. Antimicrobial Properties

Another advantage of nanotechnology-enhanced biomaterials is their ability to incorporate antimicrobial properties [34]. Traditional biomaterials are prone to bacterial colonization, which can lead to infections, particularly in implants. Nanomaterials, such as silver nanoparticles, have been incorporated into biomaterials to confer antimicrobial properties, thereby reducing the risk of infections and enhancing the safety of medical devices [41,42].

3. Types of Nanomaterials for Biomaterials Research

In biomaterials research, nanotechnology has introduced significant innovations that are highly relevant for medical applications. This section examines various types of nanomaterials used in biomaterials, with an emphasis on their properties and applications. Materials with at least one dimension in the range of 1–100 nm are termed nanomaterials. These materials possess unique physical, chemical, and biological properties that make them highly suitable for biomedical applications. Nanomaterials are generally categorized as 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. Ongoing research and development in this area are driving innovative healthcare solutions. The integration of nanoparticles and biomaterials is revolutionizing the development of advanced 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 promise 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].

2025, Vol. 2, Article ID. 2025.0019
https://doi.org/10.69709/BIOMATC.2025.188313

3.1. Inorganic Nanomaterials

3.1.1. 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 disrupts bacterial cell function by rupturing their 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].

3.1.2. Metal Oxide Nanoparticles

Metal oxide nanoparticles also play a key role as biomaterials in the research. A 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. These nanoparticles are also employed as efficient drug delivery vehicles, as they can enhance the bioavailability of encapsulated medications [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 used externally to deliver drugs, with the magnetic field directing the nanoparticle carrier to the target site [58–60].

Titanium Oxide Nanoparticles: Among various metal oxides, titanium dioxide (TiO_2) nanoparticles are recognized for their unique photocatalytic properties and have attracted widespread attention. 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 carried out as follows: In orthopedic and dental applications, TiO_2 nanoparticles are incorporated into implant coatings, promoting osseointegration and inhibiting bacterial colonization [61]. Tuned TiO_2 nanoparticles have been employed in photodynamic therapy and effectively function as photosensitizers under UV or visible light, generating reactive oxygen species (ROS) that selectively destroy 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 requires targeted and controlled drug release [63].

3.1.3. 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. Owing to its high surface area and functionalizability, graphene facilitates the development of highly sensitive and specific biosensors for detecting viruses and biomolecules [64,65]. In addition to its applications in biosensors, its exceptional strength and conductivity make it well-suited for drug delivery. Graphene functionalized with polyethylene glycol (PEG) or chitosan can be used in drug delivery, enhancing drug loading and enabling sustained release, particularly 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) enhance cell adhesion and proliferation in tissue scaffolds, particularly when incorporated into biodegradable polymers [68].

Carbon Quantum Dots: In the field of biosensing, nitrogen-doped carbon quantum dots functionalized with targeting ligands are highly selective and sensitive, enabling the detection of biomolecules for early diagnosis [69]. Modifications of carbon-based nanostructures are crucial for enhancing biofunctionality, while also ensuring biosafety, targeted delivery, and controlled degradation, making them a cornerstone of modern biomaterial systems.

3.2. Organic Nanomaterials

3.2.1. 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, featuring hydrophilic networks, swell in aqueous environments and respond to environmental stimuli such as pH, temperature, and ionic strength. Due to these properties, they are ideally suited for applications involving controlled drug delivery. 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: Dendrimers are highly branched structures that exhibit multifunctionality. They can be tailored for various applications, including 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].

3.2.2. Liposomes and Micelles

Liposomes: These are spherical vesicles composed of lipid bilayers. Liposomes are employed for drug encapsulation to improve the stability and bioavailability of therapeutic agents. These materials can be optimized for controlled and targeted drug delivery systems, enabling the release of medication in response to specific stimuli, such as changes in pH or enzyme activity [72].

Micelles: These self-assembling amphiphilic structures consist of hydrophilic shells and hydrophobic cores. Hydrophobic medications are delivered using micelles. These materials enhance drug solubility and improve system selectivity by functionalization with ligands targeting specific sites [73].

3.3. 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 extracellular matrix (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 such as 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 applications such as skin repair, nerve conduits, 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].

3.4. Hydrogel Nanomaterials

Hydrogels are valued for their excellent biocompatibility, softness, and tissue-like consistency. When combined with nanomaterials to form nano-hydrogels, these hydrogels acquire additional properties, including mechanical reinforcement, stimuli responsiveness, and enhanced drug delivery capabilities. These integrated nano-hydrogels can encapsulate cells, proteins, and nanoparticles, making them versatile materials for applications such as injectable therapies, 3D culture systems, and localized drug delivery [77]. These nano-hydrogels, composed of materials such as gelatin methacrylate (GelMA), alginate, cellulose nanofibrils, or chitosan, have shown promising results in treating burn wounds, osteoarthritis, ocular diseases, and tumor microenvironments. 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 highlighted the growing interest in multi-

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https://doi.org/10.69709/BIOMATC.2025.188313

component hydrogels that exhibit adaptive stiffness and tunable release profiles, which can be optimized for bone and cartilage regeneration; additionally, these hydrogels enable stem cell encapsulation. These materials can also be engineered to respond to physiological stimuli such as pH, temperature, or enzyme levels, making them promising candidates for personalized medicine [79]. Figure 1 illustrates various types of nanomaterials applicable in biomaterial research.

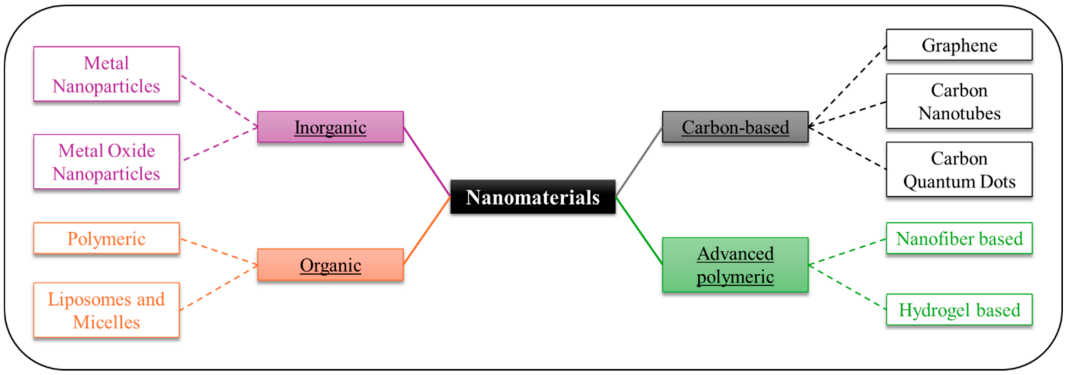


Figure 1: Types of nanomaterials relevant to biomaterial applications.

4. Various Strategies for Nanomaterial Modification

Nanomaterials are highly versatile, and various modification techniques can be employed to enhance their biocompatibility, physicochemical properties, and functional behavior, thereby improving their performance in biomedical applications. Hybrid nanomaterials and surface-functionalized nanoparticles are two of the most studied approaches for this purpose.

4.1. Hybrid Nanomaterials and Nanocomposites

Hybrid nanomaterials and nanocomposites combine organic and inorganic components, harnessing the advantages of both to achieve enhanced performance. One example is the coupling of polymers with carbon nanotubes to form a nanocomposite, yielding a material with enhanced 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]. Furthermore, silica–polymer composites possess adjustable porosity and degradability, which have shown promising results in controlled drug delivery systems. These hybrid materials are versatile and support applications across diverse fields, including tissue regeneration, targeted drug delivery, and biosensing technologies.

Recent advances in photodynamic and sonophotodynamic therapy have led to the use of TiO_2 composites. Yavaş et al. (2025) reported that TiO_2 nanoparticles, when combined with copper phthalocyanine (CuPc), exhibit potent, non-invasive anticancer activity, 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), which was further used to selectively suppress skin cancer cells in vitro as well as in vivo systems [82]. El-Bassyouni et al. (2025) reviewed that titanium and its alloys have been extensively modified using various techniques, including atomic layer deposition of TiO_2 thin films. This approach has been applied in long-term orthopedic and dental applications, as it enhances corrosion resistance, reduces implant degradation, and improves biocompatibility [83].

4.2. Functionalization and Surface Modification of Nanomaterials

Functionalization plays a key role in ensuring the 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 compo-

nents that can improve the body's ability to release chemicals [85]. State-of-the-art techniques, such as click chemistry, have facilitated the precise attachment of therapeutic drugs or biomolecules to nanoparticle surfaces. 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, such as those 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) and their favorable interactions with biological systems, stem cell-based regenerative strategies, and prospects for clinical translation [86].

5. Current Applications of Nanotechnology in Biomaterials

5.1. 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 μm) and microporosity (pore size < 20 μm); (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].

5.1.1. 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. The stiffness, swelling behavior, and molecular mobility of their architecture are influenced by the type of cross-linking and the degree of branching. The most prevalent types are polymeric gels, composed of bioinspired units linked by covalent bonds, and low-molecular-weight gelators (LMWGs), also called supramolecular gels, which self-assemble through weak non-covalent interactions [90]. The swelling capacity of nanostructured hydrogel scaffolds in liquid media aids cell entrapment and facilitates the transport of nutrients and oxygen 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. Due to their larger surface area, nanocrystalline hydroxyapatite (nHAp, $Ca_{10}(OH)_2(PO_4)_6$) powders have been shown to exhibit superior sintering behavior and enhanced densification, which can 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, due to 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] reported that the proliferation of MC3T3-E1 cells is sensitive to the nanoscale

roughness of polymeric materials. Additionally, modifications to both the bulk structure and surface of materials can influence 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].

5.1.2. 3D Bioprinting of Nanomaterials

Ceramics, metals, and polymers are among the materials proposed and employed as substitutes for natural bone and cartilage at damaged sites. Advancements in stem cell technology, 3D scaffold fabrication, and 3D printing for in vitro implant construction are anticipated to address current challenges in bone and cartilage repair. Scaffolds can be fabricated from natural polymers, which are highly biodegradable and exhibit 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 selective 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].

5.2. Drug Delivery Systems

5.2.1. 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 designed to administer biologically active agents via various routes, including oral, topical, intravenous, and intravaginal administration [106]. DDSs offer several advantages, including reduced systemic toxicity, improved efficacy, lower drug doses to achieve the same effect, shorter administration times, and more consistent drug levels. The primary application of DDSs lies in tissue engineering. Additionally, they are employed in the treatment of disorders such as osteomyelitis, osteoporosis, osteoarthritis, and osteosarcoma. [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 help overcome these challenges by enhancing the bioavailability, biodistribution, and accumulation of therapeutics. They enable targeted drug delivery to specific sites, increasing drug concentration where it is most needed while minimizing undesired 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, composed of biodegradable polymers such as PLGA (polylactic-co-glycolic acid), enable sustained drug release, whereas metallic nanoparticles (e.g., gold or silver) are employed for both drug delivery and diagnostic applications due to their distinctive optical properties [110].

Mechanisms of targeting (passive and active targeting): Nanoparticles can target diseased tissues through two main mechanisms: passive and active targeting. Passive targeting exploits the enhanced permeability and retention effect, particularly in cancerous tissues. Tumors frequently display leaky vasculature and compromised lymphatic drainage, which facilitates the accumulation of nanoparticles within the tumor microenvironment. This form of targeting does not require specific interactions between nanoparticles and cells but relies on the natural

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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].

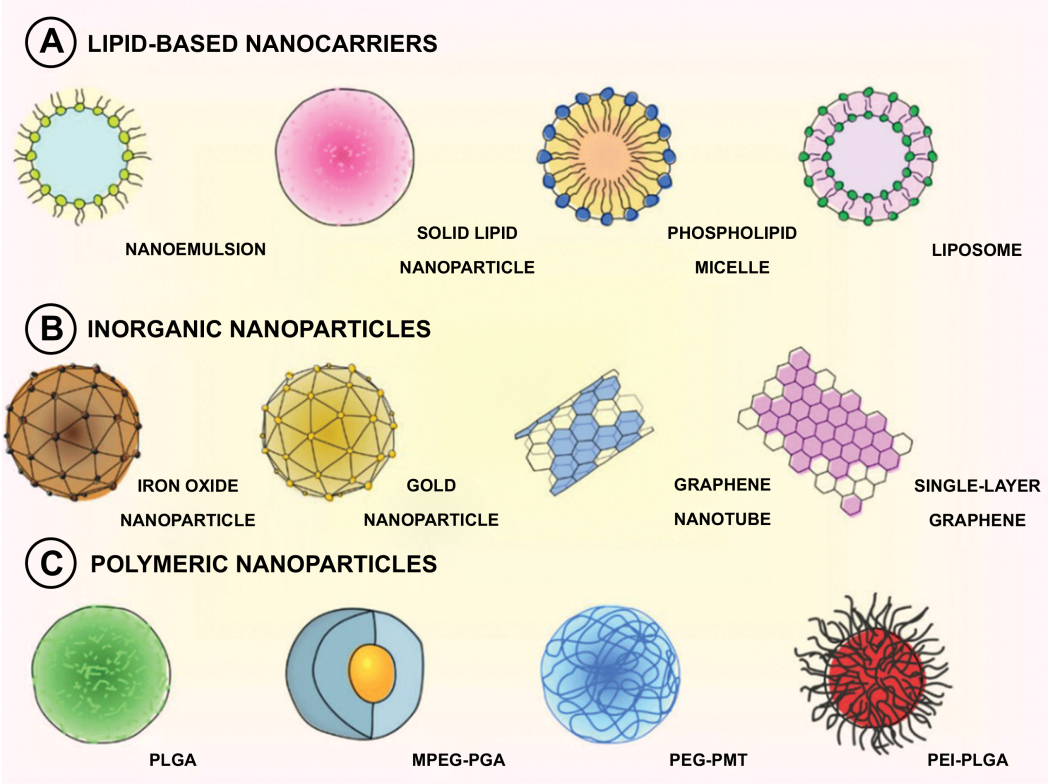


Figure 2: Primary categories of nanocarriers used in cancer drug delivery: (**A**) lipid-based, (**B**) inorganic, and (**C**) polymeric nanoparticles (adapted from [109], Copyright © 2021 by the authors).

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, can be conjugated to nanoparticle surfaces to specifically recognize and bind target 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 crucial for targeted drug delivery, enabling site-specific therapies in cancer and inflammatory conditions. 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 selectively bind to receptors or overexpressed antigens in target tissues, thereby facilitating 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, identifying predisposed patients extends beyond basic genetic profiling [117].

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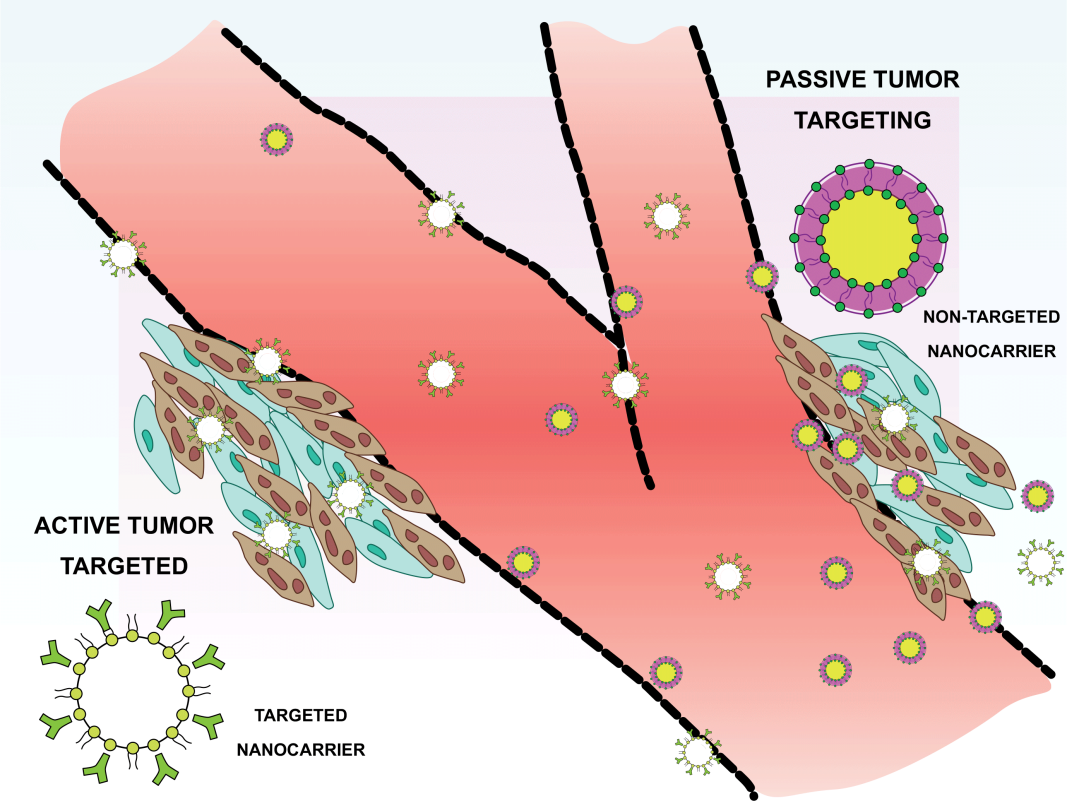


Figure 3: Comparison of passive and active nanoparticle targeting to tumors. Passive targeting relies on the Enhanced Permeability and Retention (EPR) effect, while active targeting employs molecules that specifically bind to tumor cells (adapted from [109], Copyright © 2021 by the authors).

5.2.2. 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 designed to provide personalized release profiles, tailored to the severity of the disease. 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 using alternating magnetic fields to trigger drug release, providing a non-invasive approach for controlled drug delivery [119].

5.2.3. 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 de-

livery systems: (a) Active targeted drug delivery (smart drug delivery) is based on ligand-receptor interactions. It is based on a method that delivers a precise amount of a therapeutic or diagnostic agent specifically to diseased areas within the organ [121]. Drug-loaded nanoparticles (NPs) functionalized with ligands recognize specific receptors or antigens on target cells, enabling controlled drug distribution that reduces side effects on healthy tissues, which is not achievable with traditional chemotherapy [122], and (b) passive targeted delivery exploits the enhanced permeability and retention (EPR) effect. Rapid tumor growth leads to improperly formed blood vessels and junctions, making them loose and leaky. Due to their unique size, nanoparticles can pass through these loose junctions, leading to preferential accumulation at the tumor site over time. These phenomena are known as enhanced permeation and retention [123]. The behavior of drugs and their specific affinity for the intratumoral environment must be considered individually when designing passively targeted nanoparticles, and the optimal drug release profiles should be determined on a case-by-case basis [117].

It becomes evident that passive targeting of nanoparticles to diseased cells is more complex than it appears, as therapeutics developed solely through passive pathways may not realize the full potential benefits of nanoparticle-based therapies. Patients who are inherently more responsive to nanoparticles may receive more effective treatment [124]. Although active targeting can significantly enhance drug selectivity, challenges remain in identifying suitable biomarkers for various diseases. In addition, the biological complexity of receptor-mediated internalization can have a decisive impact, particularly if the target ligand binds to receptors expressed on 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 a 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 such as EGFR (Epidermal Growth Factor Receptor), HER2 (Human Epidermal Growth Factor Receptor 2), folate receptors, and transferrin 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 primary advantage of ligand-functionalized nanoparticles is their ability to enhance the specificity and selectivity of drug delivery, thereby minimizing off-target effects and improving 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].

5.3. 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 employed to deliver genetic material for tissue regeneration, enhance stem cell activity, and modify the cellular microenvironment [130].

5.3.1. Stem Cell Engineering with Nanomaterials

Stem cell therapy holds potential for treating a variety of diseases, but controlling stem cell differentiation and ensuring proper tissue regeneration remain challenging. Nanomaterials enable the creation of 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 can direct their differentiation into specific lineages, including bone, cartilage, or vascular tissues [131–134].

Role of nanomaterials in creating niche environments for stem cells in regenerative medicine: Nanomaterials can mimic the extracellular matrix (ECM) to create niche environments that support stem cell proliferation and differentiation. For instance, nanofibrous scaffolds enhance tissue regeneration by providing both physical support and pharmacological cues that influence cell behavior. Nanotechnology has also been utilized in gene therapy,

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enabling the delivery of genetic material, such as CRISPR/Cas9 or siRNA, to target cells for gene editing [135]. Nanocarriers, including lipid and polymeric nanoparticles, deliver these systems to target tissues, enabling gene modification for conditions such as cancer, genetic disorders, and viral infections. By leveraging the surface topography and chemical composition of biomaterials, researchers can influence cell behavior to promote 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].

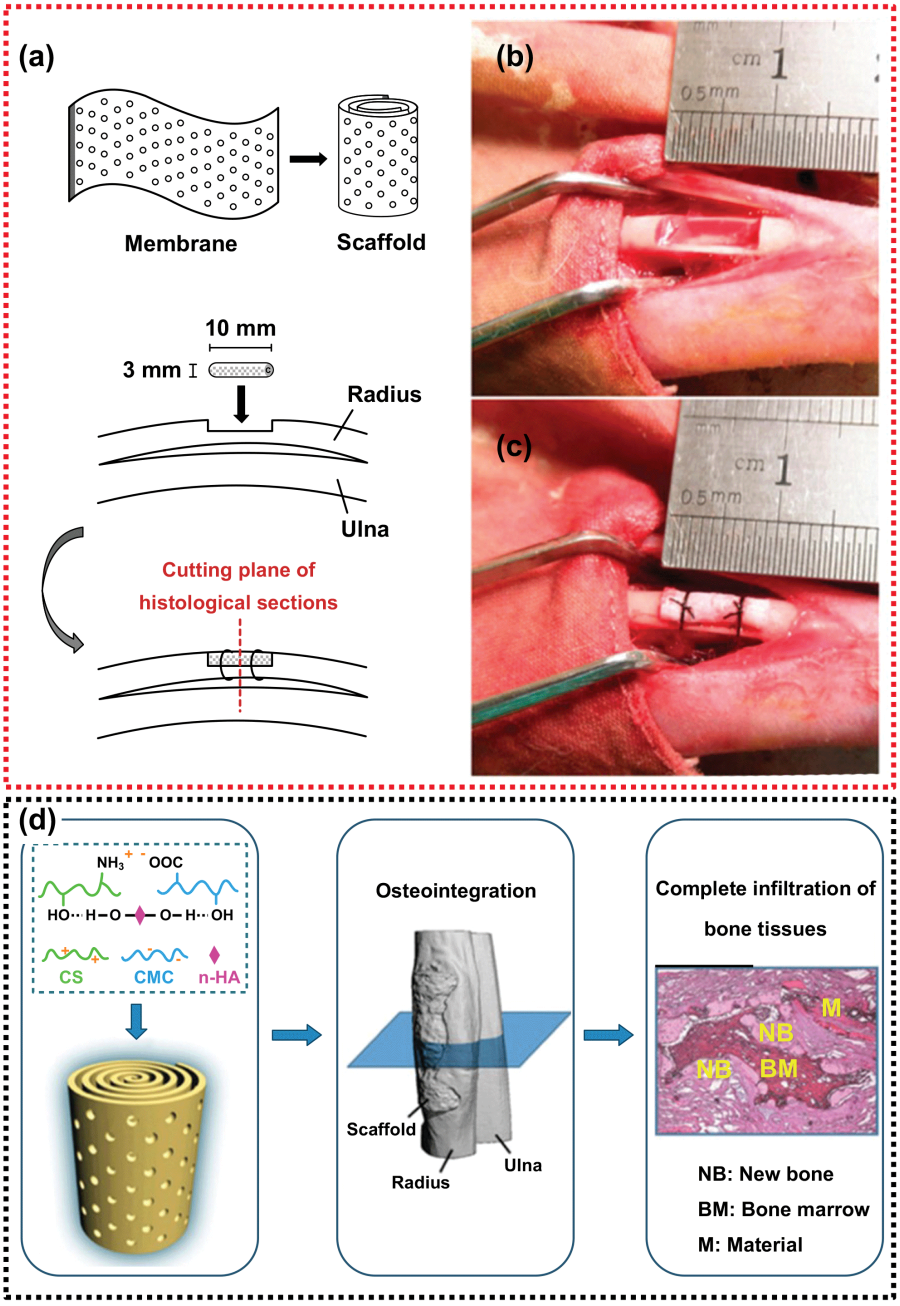


Figure 4: Surgical procedure for scaffold implantation: (**a**) the general procedure, (**b**) bone defect in a rabbit's radius, (**c**) scaffold insertion and fixation, and (**d**) spiral-shaped scaffold composed of chitosan, cellulose, and nano-hydroxyapatite, mimicking natural tissue architecture (reprinted with permission from [137], Copyright © 2013 ACS).

5.4. Biosensing and Diagnostics

5.4.1. Fundamental and Diverse Applications of Nanomaterial-Enhanced Biosensors

Biosensors are innovative engineering instruments with a wide range of technological uses. Additionally, biosensors are used to monitor environmental pollution, detect toxic elements, identify biohazardous bacteria or viruses in organic matter, and measure 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 sensors and biosensors, particularly those utilizing nanomaterials, involves combining the detection sample with bioreceptors conjugated to nanomaterials, resulting in a signal response, as illustrated 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].

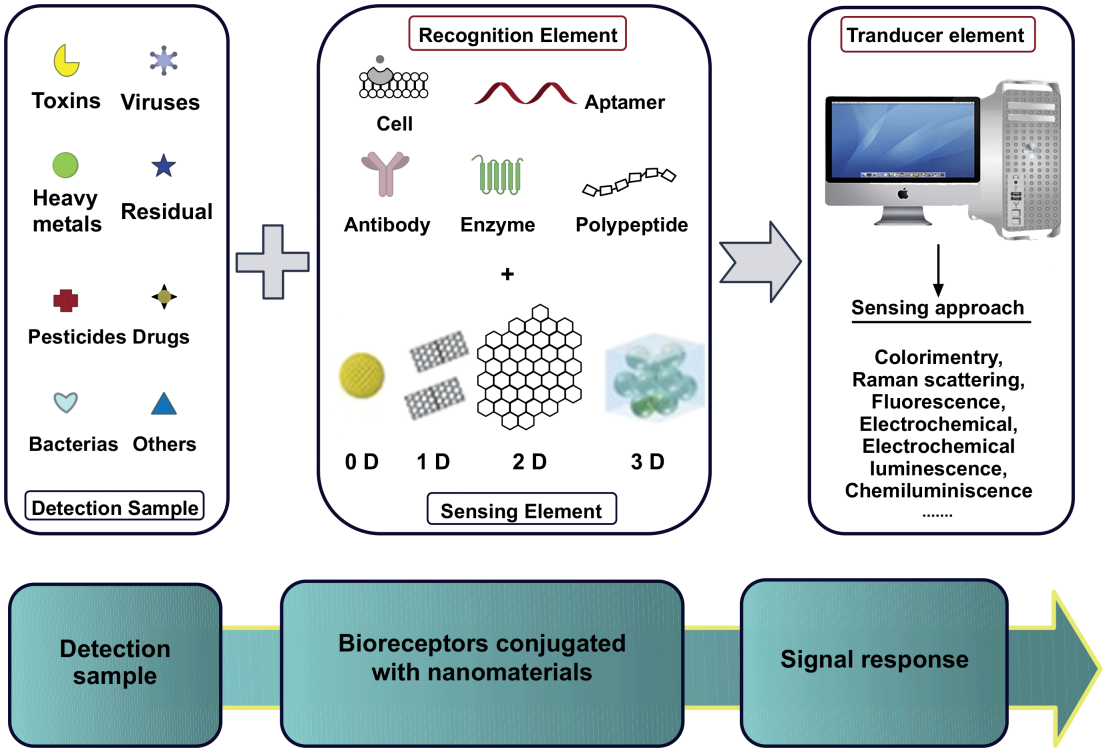


Figure 5: Schematic representation of the steps in constructing sensors and biosensors that utilize nanomaterials (adapted from [145], Copyright © 2022 by the authors).

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 application of optical nanosensors in biological measurements is the development of calcium ion-sensitive nanosensors, which have been used to monitor calcium ion fluctuations

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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.

5.4.2. 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 developed by Wang's research group enables the quantification of platelet-derived growth factor BB (PDGF-BB), a specific protein associated with cancer that is often measured only 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. developed a novel aptasensor by immobilizing graphene/dual-labeled aptamers onto a glassy carbon-modified electrode [155]. The linear range was from 3.16 $\times 10^{-16}$ M to 3.16 $\times 10^{-12}$ 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 (ε-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]

Table 1: *Cont.*

Material	Fabrication Technique	Properties	Outcomes	Ref
PLGA/MWCNT	Electrospinning	Composite fiber	Compared to the PLGA control, there was an increase in BMSC attachment after 24 h 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 nanoscale HA crystals	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]
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, 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]

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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].

6.1. 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 are considered excellent candidates for controlled drug delivery due to their ability to achieve targeted drug release, protect the encapsulated payload, and prolong circulation time [169,170]. The toxicity of nanomaterials can adversely disrupt the normal physiology of human and animal organs and tissues. 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].

6.2. Challenges in Manufacturing and Scalability

6.2.1. 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]. Scalability and cost-effectiveness of nanobiomaterial production are critical challenges that must be addressed to ensure widespread accessibility.

6.2.2. 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.

6.2.3. 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.

6.2.4. Unclear Regulatory Pathways

Traditional frameworks are inadequate to address nanomaterial complexities. For instance, the behavior of nanomaterials in biological systems differs significantly from that of 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.

6.2.5. Safety Concerns

Long-term safety is a major concern for nanomaterials. Regulatory agencies require comprehensive data on their potential toxicity, biodistribution, and degradation prior to approval for medical applications. 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].

6.3. 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.

6.3.1. 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 environmental behavior of nanomaterials, including their interactions with ecosystems, degradation, and bioaccumulation, remains incompletely 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].

6.3.2. 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

7.1. Breakthroughs in Nanomaterials for 3D Bioprinting

Recent advances in nanomaterials, especially in bioink development, have greatly enhanced 3D bioprinting technologies. To improve the mechanical properties, biocompatibility, and functionality of bioinks, nanomaterials such as 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]. The integration of 3D bioprinting and nanotechnology has enabled the development of smart bioinks that respond to environmental cues and have also been applied in 4D bioprinting [178]. The integration of nanotechnology has advanced bioprinting by enhancing the mechanical and biological properties of printed scaffolds and enabling the creation of dynamic tissue architectures capable of post-printing transformations [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 introduced transformative changes in tissue engineering when incorporated into 3D bioprinting and have opened up to advanced approaches for the development of regenerative medicine.

7.2. Smart and Stimuli-Responsive Nanomaterials

Nanomaterials are increasingly developed as smart, stimuli-responsive systems, capable of responding to external stimuli such as light, pH, and temperature. Advances in this field include polymeric micelles for stimuli-responsive drug delivery, which can release therapeutic agents in a controlled manner and have significantly improved drug delivery and cancer therapy [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].

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 expanded the potential of drug delivery systems and bioanalysis by enabling the selective recognition of specific biomolecules using smart

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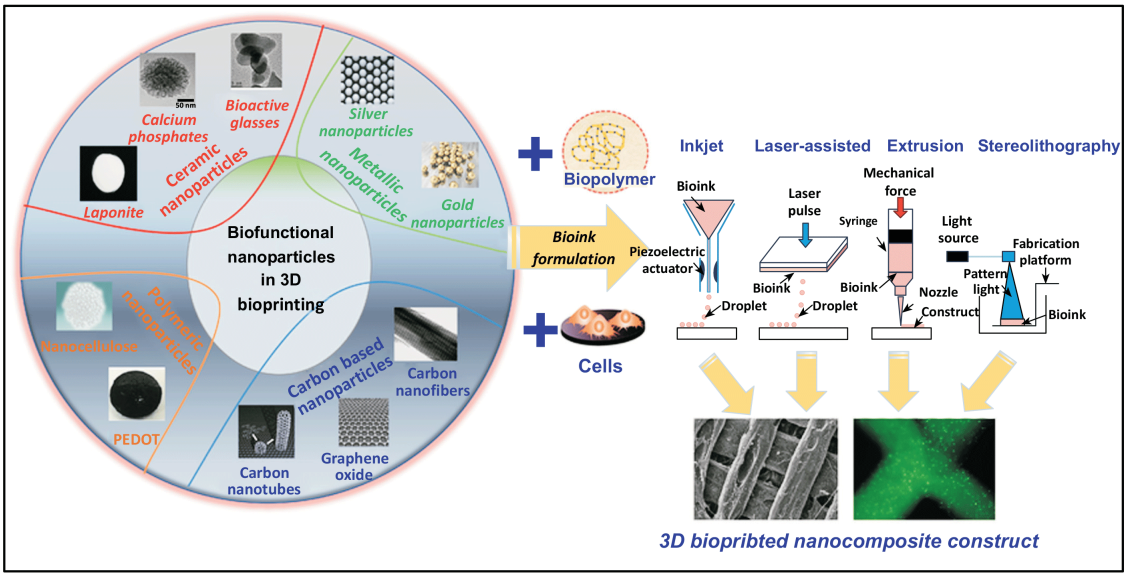


Figure 6: Schematic of 3D bioprinting of nanocomposite structures using ceramic, metallic, polymeric, or carbon-based nanomaterials combined with biopolymers and cells via inkjet, laser-assisted, extrusion-based, or stereolithography methods (adapted from [180], Copyright © 2023 by the authors).

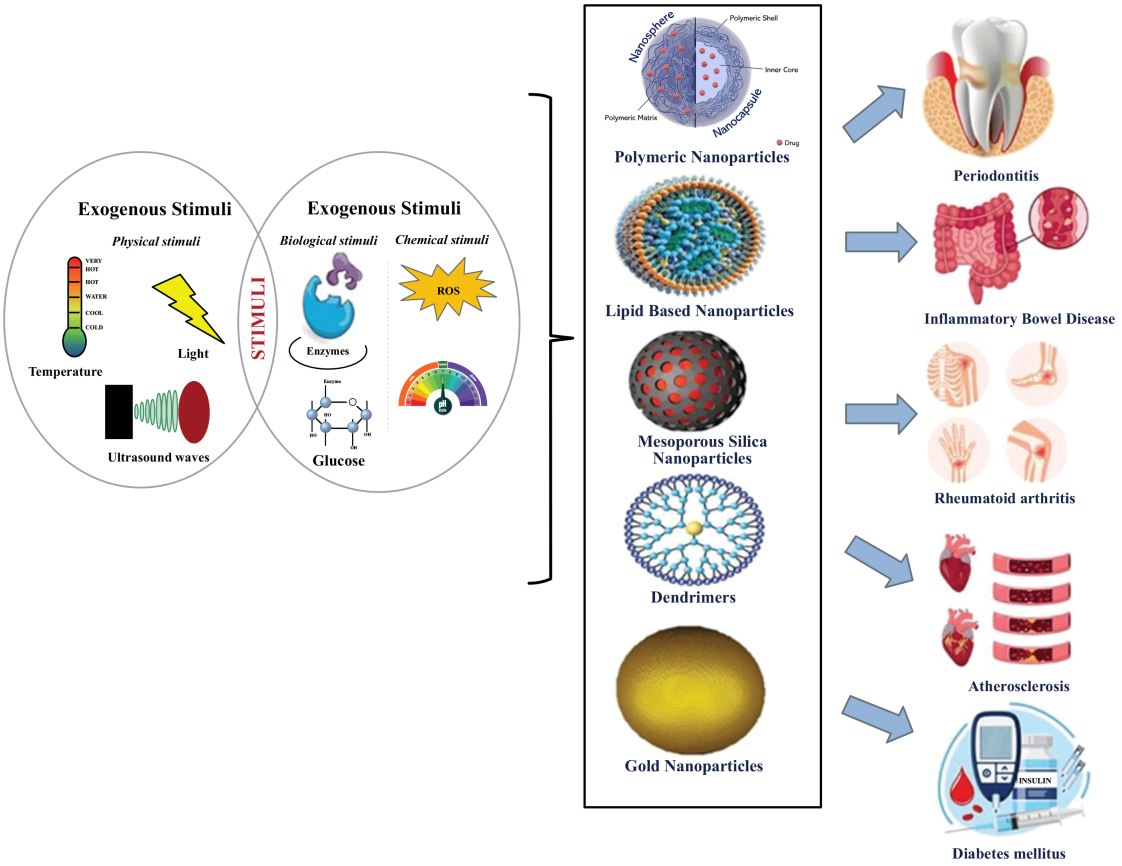


Figure 7: Application of stimuli-responsive nanoparticles in the treatment of various ailments (reprinted with permission from [183], Copyright © 2024 Wiley-VCH GmbH).

systems [185,186]. All of these developments have contributed to the creation of smart nanomaterials, enabling novel approaches in therapeutic interventions, drug delivery systems, and diagnostic technologies.

7.3. Nanomaterial-Based Immunomodulation

Today, immunomodulation strategies have greatly benefited from the use of nanomaterials. These materials enhance the effectiveness of immunotherapy for diseases such as autoimmune disorders and cancer. Recent research highlights the applications of nanosystems for immunomodulatory purposes, which have potential for targeted immune response for specific immune cells and modification in the tumor microenvironment [187]. Advances in the delivery of immunotherapeutic agents have enhanced these systems, addressing challenges such as insufficient immune stimulation and off-target effects [188]. Nanomaterials designed to target lymphoid organs are engineered to efficiently enhance immune responses and enable targeted therapy for the treatment of inflammation and cancer [189]. Advancements in treatment outcomes require extensively studied and improved nanomaterials that can modulate immune responses while simultaneously evading immune detection [190]. The incorporation of nanomaterials into current immunotherapeutic strategies has improved the efficacy of checkpoint inhibitors and cancer vaccines [191]. Thus, the use of nanomaterials offers new opportunities for targeted therapies and may enable breakthrough advancements in precision medicine when integrated into immunomodulation strategies.

7.4. Emerging Nanocomposite Designs

Recent research and developments in nanocomposites have demonstrated transformative applications in fields such as 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]. The primary focus of current research is the ability to tune the electrical and mechanical properties of nanocomposites through modified production methods. Lanthanide-doped nanoparticles have been incorporated into nanocomposites, enabling the design of diverse materials and opening innovative approaches for cancer treatment and bioimaging [194]. The architectural development of nanocomposites has opened a way to create versatile materials having a wide range of multisector usage.

7.5. 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 highly significant in reducing the time and cost associated with conventional material discovery approaches. One computational approach for materials optimization is a Bayesian optimization-based, data-driven design framework, developed to simultaneously determine the composition and microstructure of nanocomposites, thereby enhancing performance across 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, known for its precise control over the properties of synthesized materials, is further enhanced through machine learning algorithms and in-line characterization tools [197]. Today, the design and application of nanomaterials across various domains have become more innovative and efficient through the integration of nanotechnology with digital and computational technologies. Several challenges remain in integrating AI into nanomaterials research, including the scarcity of consistent, high-quality datasets for training AI models. In some cases, there is also a complete lack of datasets in the case of many nanomaterial investigations, leading to misclassification or inaccurate material prediction [198].

7.6. 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 the transparent interpretation of AI models and the potential for model bias. AI models can be influenced by training data bias and may not fully capture the diversity of nanomaterials, potentially affecting prediction accuracy. Moreover, AI algorithms are complex and generally show difficulty in inter-

2025, Vol. 2, Article ID. 2025.0019
https://doi.org/10.69709/BIOMATC.2025.188313

pretation, and complicate the result validation [199]. Another challenge arises when integrating AI with existing research workflows, as incorporating AI into conventional nanomaterial development methods can be difficult, limiting the effective application of this technology [200]. The incorporation of AI in nanotechnology raises several regulatory and ethical concerns. Specifically, 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, the computational demands for advancing AI can be substantial and require readily available resources for research [201]. Although AI and machine learning hold significant potential in nanomaterials research, addressing challenges through collaboration, the development of standardized datasets, and computational advancements is essential to fully harness this technology.

8. Proposed Future Advancements and Research Directions

8.1. 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 at the forefront of development for photothermal therapy and have also demonstrated effectiveness in stimuli-responsive designs, enhancing their therapeutic potential [203]. Moreover, hollow nanostructures have gained popularity in drug delivery due to their high drug-loading capacity and versatility, making them well-suited for biomedical applications [204]. Future research should explore 2D nanomaterials for cellular-level applications, leveraging their unique properties to develop innovative cellular constructs [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 remain fundamental challenges for these materials, making their resolution critical for the commercialization of advanced nanomaterials.

8.2. Enhancing Safety Profiles and Reducing Toxicity

As the applications of nanomaterials continue to expand, safety has become an increasingly important concern. Recent research emphasizes the need for safer-by-design methodologies that integrate safety assessments into the design process to mitigate potential risks [206]. 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 [207]. Novel approaches, such as machine learning, are being used to enhance risk assessment and safety profiling of nanomaterials and to improve predictions of their interactions with biological systems [208,209]. Furthermore, advancements in solid-state batteries utilizing nanomaterials highlight the importance of improving safety through 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.

8.2.1. 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 development of cephalopod-inspired nanomaterials for thermal and optical control demonstrates the adaptability of bioinspired material designs, which are versatile for applications in both medical technology and sensing [213]. Research should focus on exploring bio-inspired, multifunctional nanomaterials capable of addressing global challenges in environmental sustainability and healthcare [214,215].

9. Conclusions and Future Outlook

Nanotechnology has become a cornerstone of recent advances in materials science in recent times. It has revolutionized research on biomaterials, with unprecedented

progress in material properties, their applications, biological interactions, and therapeutic applications. The incorporation of nanomaterials has enhanced properties across various domains, including biosensors, medical implants, tissue engineering scaffolds, and drug delivery systems. Despite numerous breakthroughs, several challenges persist for nanomaterials, including toxicity, long-term biocompatibility, large-scale manufacturing, and regulatory concerns. 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. In the coming years, research in nanotechnology and biomaterials will focus on developing intelligent, multifunctional nanomaterials with precise monitoring of biological interactions. Advanced and emerging technologies in computer science, such as machine learning and artificial intelligence, can play a pivotal role in the development of novel biomaterials. They can support the design of biomaterials tailored 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, enhancing the biocompatibility and antibacterial properties of medical implants can reduce complications and improve long-term success. 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.

List of Abbreviations

AgNPs	Silver Nanoparticles
AI	Artificial Intelligence
AuNPs	Gold Nanoparticles
BaP	Benzo[a]pyrene
BMP	Bone Morphogenetic Protein
BPT	Benzopyrene Tetrol
$Ca_{10}(OH)_2(PO_4)_6$	Hydroxyapatite Chemical Formula
CEA	Carcinoembryonic Antigen
CMNHs	Carbon-Metal Nanohybrids
CNPs	Carbon Nanoparticles
CNF	Carbon Nanofiber
CNTs	Carbon Nanotubes
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DDSs	Drug Delivery Systems
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EPR	Enhanced Permeability and Retention
FDA	Food and Drug Administration
FDM	Fused Deposition Modeling
Fe_3O_4	Iron Oxide Nanoparticles
fM	Femtomolar
HAp	Hydroxyapatite
HER2	Human Epidermal Growth Factor Receptor 2
hESC-MSC	Human Embryonic Stem Cell-Derived Mesenchymal Stem Cell
HIV	Human Immunodeficiency Virus
LMWG	Low-Molecular-Weight Gelators
LOD	Limit of Detection
MC3T3-E1	Mouse Pre-Osteoblast Cell Line
MNP	Magnetic Nanoparticles
MNF	Macroporous Nanofibrous
MPa	Megapascal
MRI	Magnetic Resonance Imaging
MSCs	Mesenchymal Stem Cells
nHAp	Nano-Hydroxyapatite
nm	Nanometer
NMs	Nanomaterials
NPs	Nanoparticles
PCL	Polycaprolactone
PCU	Polycarbonate-Urethane
PDGF-BB	Platelet-Derived Growth Factor BB
PLA	Polylactic Acid
PLGA	Polylactic-co-Glycolic Acid
PLLA	Poly-L-Lactic Acid
PS	Polystyrene
QDs	Quantum Dots
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
siRNA	Small Interfering Ribonucleic Acid
SLA	Stereolithography
SWCNT	Single-Walled Carbon Nanotube
TCP	Tricalcium Phosphate
Ti_6Al_4V	Titanium-Aluminum-Vanadium Alloy
TiNPs	Titanium Nanoparticles
TiO_2	Titanium Dioxide
VEGF	Vascular Endothelial Growth Factor
ZA	Zoledronic Acid
ZnO	Zinc Oxide

Author Contributions

Conceptualization: T.K.D., R.K.; Validation, formal analysis: S.K., M.P.; Investigation, resources, writing—original draft preparation: A.K.S., R.S., V.S.K., A.K., writing—review and editing: T.K.D., R.K., S.K., visualization, supervision, project administration: T.K.D., M.P., V.S.K. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding this manuscript.

Funding

The study did not receive any external funding and was conducted using only institutional resources.

Acknowledgments

ChatGPT (version 4) and Co-pilot AI tools were used to assist with rephrasing, editing, and conceptual understanding in parts of this manuscript.

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