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REVIEW ARTICLE

Nanotechnology and Cartilage Regeneration: A Review

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Abstract

This review article covers the comprehensive incorporation of nanotechnology into cartilage tissue engineering. Specifically, nano-engineered scaffolds which replicate the hierarchical architecture of native cartilage, providing biomechanical support while promoting chondrocyte attachment and extracellular matrix deposition are highlighted. Nanoparticle-based systems which further enhance regeneration by enabling site-specific, sustained release of growth factors, anti-inflammatory agents, and gene therapies such as TGF-β and IL-1Ra, thereby improving therapeutic precision and efficacy are also discussed. Nanotopographical cues and surface functionalization techniques (e.g., RGD peptides) which guide mesenchymal stem cell behavior, influencing cell adhesion, proliferation, and differentiation pathways like FAK, MAPK, and Wnt signaling are also mentioned. Non-viral nanocarriers which offer a safer and effective route for localized gene delivery, minimizing immunogenic risks and providing sustained genetic modulation are also covered. In summary, this review provides promising information for how nanotechnology has aided in all aspects of cartilage tissue engineering.

Keywords: cartilage, nanomedicine, nanomaterials, regeneration, tissue engineering.

1 Introduction

Articular cartilage plays a critical role in maintaining joint function by providing a low-friction, load-distributing surface. However, due to its avascular, aneural, and hypocellular nature, cartilage has a limited intrinsic capacity for repair following injury or degeneration. Conditions such as osteoarthritis (OA), trauma-induced defects, and age-related wear collectively contribute to significant morbidity and loss of mobility in millions of individuals worldwide. Traditional treatment options—including microfracture, autologous chondrocyte implantation (ACI), and osteochondral grafting—often result in the formation of biomechanically inferior fibrocartilage and do not provide durable long-term outcomes. These clinical challenges have driven the exploration of regenerative medicine strategies aimed at restoring native hyaline cartilage structure and function (see Figure 1) [1].

Among the emerging technologies in regenerative medicine, nanotechnology stands out for its ability to precisely manipulate materials at the molecular

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and cellular scales. Nanomaterials, due to their high surface-area-to-volume ratio and tunable physicochemical properties, can closely mimic the structural and functional features of the native extracellular matrix (ECM), thereby improving cellular interactions and guiding tissue development. Moreover, the integration of nanotechnology with biomaterials, drug delivery systems, gene therapy, and 3D bioprinting has created new paradigms for treating cartilage defects. This review provides a comprehensive overview of how nanotechnology is being applied to cartilage regeneration, from scaffold design and nanoparticle-based therapeutics to gene-modulating systems and clinical translation [2].

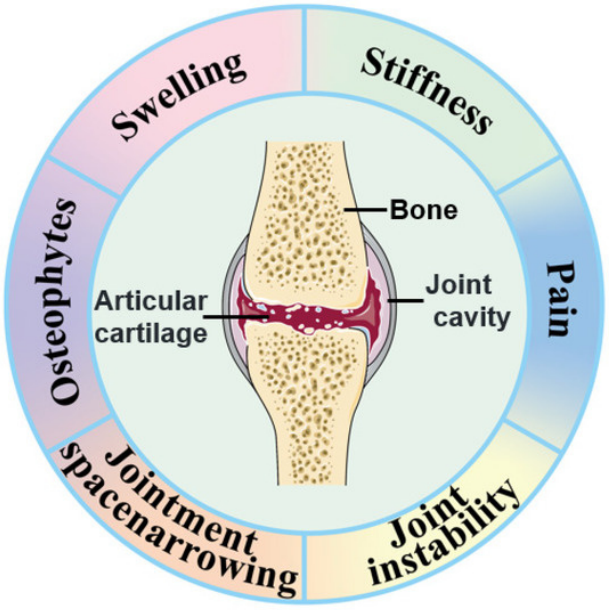

Figure 1. Clinical manifestation of degenerative joint disease [3].

2 Basics of Nanotechnology in Biomedicine

Nanotechnology in biomedicine leverages the unique physicochemical properties of materials at the nanoscale (1–100 nm) [4], where the surface-to-volume ratio, quantum effects, and tunable surface chemistry fundamentally alter interactions with biological systems. Nanomaterials—ranging from nanoparticles and nanofibers to nanocomposite scaffolds—are intentionally designed to mimic key aspects of the native extracellular matrix (ECM), promoting biocompatibility, biodegradability, and controlled bioactivity. For example, electrospun nanofibrous scaffolds made of natural (e.g., collagen, gelatin) or synthetic (e.g., polycaprolactone, PLGA) polymers can recreate the ECM's fibrous architecture, facilitating high porosity and large surface area that enhance cell adhesion, migration, proliferation, and even lineage-specific differentiation in applications like bone and cartilage tissue engineering [4].

Nanotopographical cues—such as fiber alignment, nanoscale ridges, surface roughness, and charge—serve as potent regulators of cell fate by directing integrin clustering, cytoskeletal organization, and mechanotransduction pathways [5–10]. Numerous studies have shown that aligned nanofibers or nanogrooved surfaces direct mesenchymal stem cells (MSCs) to elongate and differentiate along specific lineages, activating signaling cascades like focal adhesion kinase (FAK), MAPK, Wnt, and YAP/TAZ. Similarly, functional motifs like RGD peptides or ECM proteins (e.g. laminin, fibronectin) covalently grafted onto fiber surfaces dramatically improve cell binding affinity through integrin-mediated adhesion.

Beyond structural mimicry, nanotechnology enables advanced scaffold functionalization and responsive delivery systems. Nanoparticles (e.g., gold, iron oxide) embedded in hydrogels or fiber matrices permit controlled release of growth factors, magnetic or electrical modulation of cell behavior, and real-time imaging capabilities. For instance, electro-conductive gold nanoparticle-infused hydrogels have been shown to enhance cardiomyocyte function via connexin-43 expression, while superparamagnetic iron-oxide nanoparticles (SPIONs) in magnetic scaffolds can be leveraged for mechanical stimulation and tracking transplanted cells.

However, optimizing nanomaterials for biomedicine also requires careful management of potential cytotoxicity, immune reactions, and degradation behaviors. Particle size, composition, and surface chemistry critically influence biocompatibility, and while biodegradable polymers like PLGA reduce long-term toxicity, their acidic degradation by-products can still alter local pH and cell responses [11].

2.1 Polymer-Based Nanomaterials

Polymer nanomaterials, both natural (such as collagen, gelatin, chitosan, and alginate) and synthetic (such as PLGA, PCL, PEG, and polyvinyl alcohol), enable fine control over mechanical properties, degradation rate, and bioactivity (see Figure 2). For instance, electrospun nanofiber scaffolds made of PLGA or PCL can closely resemble the fibrous

architecture of the native extracellular matrix (ECM), guiding cell attachment, migration, and eventual differentiation. Furthermore, the porous structure and high surface area enable efficient delivery of growth factors and nutrients directly to growing cells, fostering a regenerative microenvironment. Polymer nanoparticles can encapsulate and release signals in a sustained manner, reducing side effects and improving therapeutic outcomes [12, 13].

2.2 Inorganic Nanoparticles

Inorganic nanoparticles, including gold, iron oxide, silica, or carbon nanotubes, are frequently used due to their unique optical, magnetic, and structural properties (see Figure 2). Gold nanoparticles, for instance, can aid in drug delivery, imaging, and biosensing, while superparamagnetic iron oxide nanoparticles enable magnetic guidance and contrast enhancement in MRI. Silica nanoparticles can be functionalized to carry growth factors or genes, adding an additional layer of control over cellular responses. Furthermore, carbon nanotubes, with their high mechanical strength and conductive properties, can provide structural support and enable electrical stimulation, which is desirable for some regenerative applications [14].

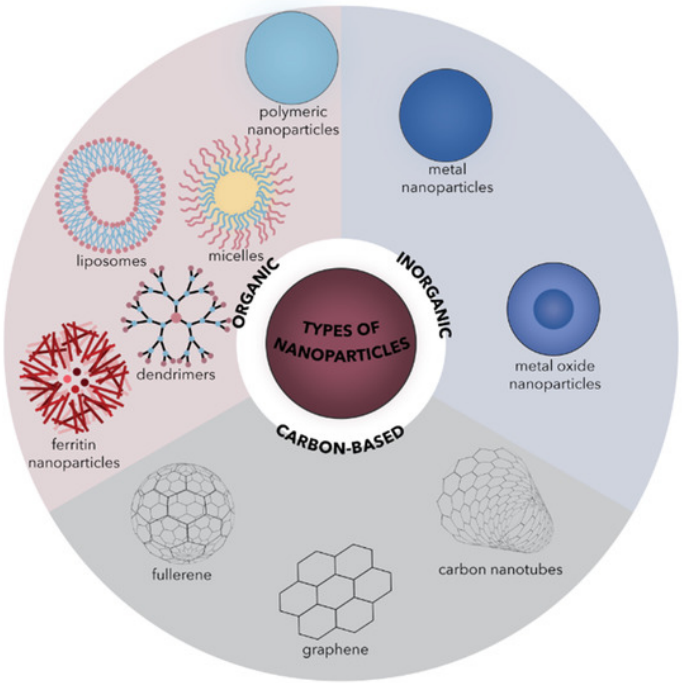

Figure 2. Organic and inorganic nanoparticles [15].

2.3 Hybrid Nanocomposites

Hybrid nanocomposites combine organic and inorganic components to achieve desirable mechanical properties alongside high biocompatibility and functionality (see Figure 3). For instance, graphene oxide-reinforced nanofiber scaffolds exhibit enhanced stiffness, toughness, and cellular attachment, making them a powerful platform for cartilage regeneration. Such composite materials can be tailored to provide both physical guidance and biochemical signals, while retaining desirable degradation profiles, thereby delivering a biomimetic microenvironment for chondrogenesis. This synergy helps foster proper cell proliferation, matrix deposition, and eventual formation of functional cartilage-like tissue in injured sites [16].

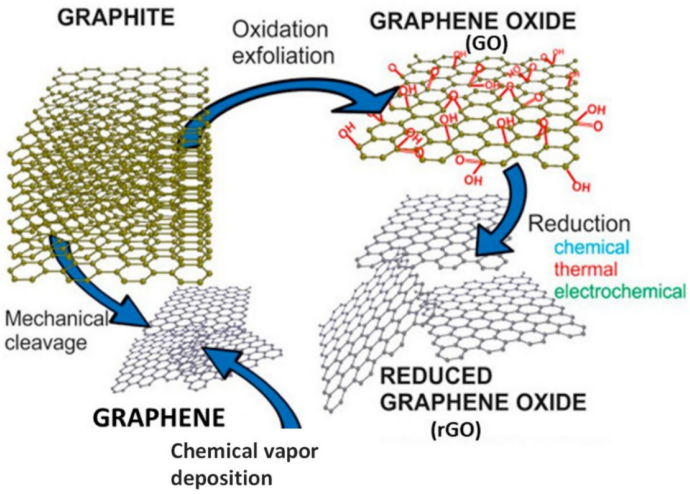

Figure 3. Hybrid nanocomposites [17].

2.4 Surface Functionalization and Bioconjugation

Functionalization involves adding biomolecular motifs (such as RGD, growth factors, or peptides) or altering surface properties to enable targeted delivery, strong cell adhesion, and control over cellular behavior (see Figure 4) [18]. This approach can be used to incorporate signaling molecules directly into the nanomaterials' surface, thereby influencing cell fate, differentiation, and metabolic activity. Furthermore, bioconjugation strategies enable the delivery of therapeutic genes, small interfering RNAs (siRNA), or microRNAs alongside growth factors, adding a powerful dimension to regenerative therapy. The result is a sophisticated platform that can respond to cellular signals, release desirable biomolecules in a sustained manner, and enable a regenerative process that closely resembles the native healing mechanisms [19].

3 Pathophysiology of Cartilage and Challenges in Regeneration

Articular cartilage is a highly specialized connective tissue that covers the surfaces of diarthrodial joints,

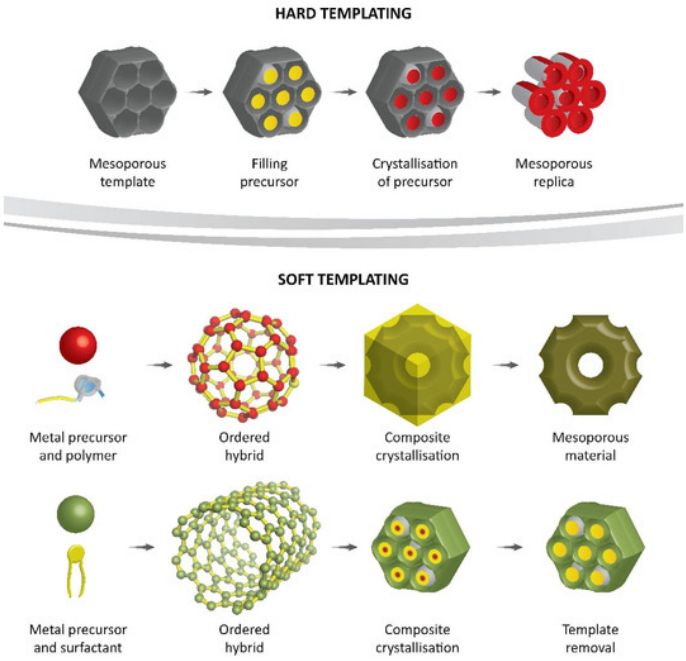

Figure 4. Example of surface functionalization and bioconjugation [20].

providing shock absorption and enabling smooth, near-frictionless motion under repetitive loading. Structurally, it is characterized by its avascularity, aneurality, and alymphatic nature, composed primarily of a sparse population of chondrocytes embedded within a dense extracellular matrix (ECM) rich in type II collagen and proteoglycans such as aggrecan. The unique zonal organization of cartilage—from the superficial tangential zone to the deep calcified layer—contributes to its anisotropic mechanical properties and functional resilience during physiological movement.

However, this highly specialized architecture comes at a cost: cartilage possesses a very limited intrinsic capacity for self-repair. The lack of vasculature and low cellular turnover mean that injured or degenerated cartilage often fails to regenerate spontaneously. Instead of regenerating native hyaline cartilage, the tissue typically heals with fibrocartilage, which lacks the same biomechanical strength and durability, predisposing the joint to further degeneration and pain.

Cartilage damage can result from acute trauma, repetitive overloading, congenital joint disorders, or chronic inflammatory conditions such as osteoarthritis (OA). OA is particularly prevalent, affecting over 595 million people globally as of 2020, and is a leading cause of disability among the aging population. Conventional surgical interventions—such as microfracture, mosaicplasty, and autologous chondrocyte implantation (ACI)—are commonly used to treat focal cartilage defects. However, these techniques often lead to the formation of fibrocartilaginous tissue or incomplete integration with surrounding native cartilage, resulting in limited long-term functional improvement.

From a tissue engineering perspective, the ideal strategy for cartilage regeneration must overcome multiple physiological and engineering hurdles. Moreover, it must address the complex mechanical gradients of the osteochondral unit and allow for proper zonal matrix organization.

These challenges highlight the need for advanced, multifunctional biomaterials—such as those derived from nanotechnology—that can simultaneously recapitulate the structural, mechanical, and biochemical cues of native cartilage and drive functional regeneration [1].

4 Applications for Nanotechnology in Cartilage Regeneration

4.1 Nanomaterials for Scaffolds

Nanofibrous and nanocomposite scaffolds produced by electrospinning, freeze-drying, or 3D printing can closely mimic cartilage ECM architecture and facilitate stem cell attachment and differentiation. Naturally derived polymers (e.g., collagen, gelatin) or synthetics like PCL/PLGA, sometimes reinforced with graphene oxide or nanoclays, improve mechanical strength and bioactivity, boosting chondrogenesis in preclinical models.

Nanofibrous and nanocomposite scaffolds produced by advanced techniques such as electrospinning, freeze-drying, and 3D bioprinting have emerged as powerful platforms for cartilage regeneration. These scaffolds aim to replicate the hierarchical structure of native articular cartilage, particularly its zonal ECM architecture, and to provide a biomimetic microenvironment that supports cellular infiltration, proliferation, and differentiation.

Electrospun nanofibers, typically made from natural polymers (e.g., collagen, gelatin, silk fibroin) or synthetic polymers (e.g., polycaprolactone [PCL], polylactic-co-glycolic acid [PLGA]), offer high surface-area-to-volume ratios, adjustable porosity, and customizable mechanical properties. They not only provide physical support for cell adhesion but also guide cellular alignment and organization, which is

particularly beneficial for recapitulating the superficial zone of cartilage where chondrocytes are aligned parallel to the surface.

Hybrid nanoscaffolds further enhance functionality by incorporating bioactive nanofillers such as graphene oxide (GO), hydroxyapatite (HA), or nanoclays. These additives can significantly improve the scaffold's mechanical stiffness, compressive strength, and osteochondral integration capacity. For instance, GO-loaded PCL scaffolds have been shown to enhance chondrocyte viability and upregulate expression of cartilage-specific markers such as COL2A1 and aggrecan.

Moreover, 3D bioprinting technologies enable spatially controlled deposition of nanocomposite bioinks, allowing for the fabrication of gradient or zonal scaffolds that mimic the multi-layered nature of osteochondral tissues. When nanomaterials are embedded in hydrogel-based bioinks (e.g., GelMA, alginate), they improve cell retention, matrix deposition, and mechanical resistance under physiological loading [21].

To further support chondrogenesis, many nanofiber scaffolds are functionalized with biochemical cues such as RGD peptides, transforming growth factor-beta (TGF-β), or cartilage-derived ECM particles. These biochemical modifications can be introduced during fabrication or via post-processing to enhance cellular recognition and signal-mediated differentiation.

In summary, nanomaterials offer a highly adaptable platform for scaffold fabrication, allowing for the integration of structural, mechanical, and biochemical features essential for successful cartilage tissue engineering. The convergence of electrospinning, additive manufacturing, and nanofiller technologies has laid the groundwork for the next-generation, patient-specific implants with improved regeneration outcomes [22].

4.2 Nanoparticles for Drug/Growth Factor Delivery

Nanoparticles—including iron oxide, gold, silica, or liposome-based systems—enable controlled delivery of chondrogenic growth factors (e.g., TGF-β1, BMPs), anti-inflammatory agents, and/or genetic materials. This approach enhances therapeutic potency, spatiotemporal control, imaging capability, and retention within the defect site.

In recent years, the development of stimulus-responsive nanoparticles has gained momentum in cartilage regeneration. These "smart" nanoparticles are engineered to release their therapeutic payloads in response to physiological cues such as pH, enzyme concentration, temperature, or magnetic fields. For instance, pH-sensitive chitosan nanoparticles loaded with TGF-β3 have demonstrated improved targeting and sustained release in the slightly acidic microenvironment of osteoarthritic cartilage, leading to enhanced chondrogenesis and reduced inflammation. Similarly, magnetic nanoparticles (e.g., SPIONs) allow for external magnetic field-guided localization of therapeutics, improving site-specificity and minimizing systemic exposure. The use of dual- or multi-responsive delivery platforms—e.g., those combining pH sensitivity with thermal or enzyme responsiveness—further refines the spatiotemporal control over drug release, contributing to tissue-specific regenerative signaling cascades [23].

4.3 Nanostructured Surfaces for Cell Modulation

Nanostructured surfaces represent a critical design element in scaffold engineering, as they can precisely regulate cellular behavior by mimicking the native extracellular matrix (ECM) topography at the nanoscale. Features such as fiber alignment, grooves, nanopillars, and surface roughness are known to influence mesenchymal stem cell (MSC) morphology, cytoskeletal organization, and differentiation through contact guidance and mechanotransduction.

Aligned nanofibers or anisotropic topographies have been shown to induce elongation and polarization of MSCs, promoting lineage-specific differentiation. For instance, aligned electrospun PCL nanofibers can guide chondrogenic differentiation by activating focal adhesion kinase (FAK) and mitogen-activated protein kinase (MAPK) pathways, which in turn regulate downstream transcription factors such as SOX9 and Runx2. These signaling cascades are critical for cartilage matrix synthesis, including the upregulation of type II collagen and aggrecan.

Surface roughness and nanoindentations can also affect protein adsorption from serum or synovial fluid, which indirectly alters cell adhesion. Surfaces with moderate roughness (10–100 nm) tend to promote integrin clustering, enhance focal adhesion formation, and facilitate ECM remodeling. This mechanical sensing ability of cells, often termed mechanosensing, can dictate stem cell fate decisions even in the absence of soluble differentiation factors.

Functionalization of nanostructured surfaces with biochemical ligands further enhances biological outcomes. The incorporation of adhesive peptides such as RGD (Arg-Gly-Asp), fibronectin fragments, or cartilage-derived ECM motifs improves initial cell attachment, enhances spreading, and sustains chondrogenic signaling. In one study, RGD-modified nanogrooved poly(L-lactic acid) scaffolds significantly increased MSC retention and promoted the expression of cartilage-specific markers in vitro and in vivo.

Recent advances have also explored stimuli-responsive nanostructured surfaces, where properties such as stiffness, topography, or ligand exposure can be dynamically altered using light, magnetic fields, or enzymatic environments. These "smart" materials can modulate cellular behavior in real time, offering dynamic control over tissue regeneration processes.

Collectively, nanostructured surface engineering serves as a powerful approach to influence cell fate through both physical and biochemical cues. When rationally designed, these topographical features can synergize with scaffold mechanics and soluble factors to create a permissive microenvironment for effective cartilage regeneration [24].

4.4 Nanotechnology-Assisted Gene Therapy

Non-viral nanocarriers—including lipid-based nanoparticles, polymeric complexes, and plasmid-loaded systems—enable localized gene delivery (e.g., IL-1Ra, FGF-18), with sustained expression and fewer immunogenic risks than viral vectors.

A growing body of evidence supports the use of siRNA or microRNA-loaded nanocarriers in modulating gene expression within the joint microenvironment. For example, lipid-polymer hybrid nanoparticles carrying miR-140—a cartilage-specific microRNA that suppresses MMP-13 and ADAMTS5—have been successfully used in animal models to reduce cartilage matrix degradation and promote ECM homeostasis. Additionally, polymeric nanoparticles delivering CRISPR-Cas9 gene editing components offer exciting prospects for correcting genetic abnormalities linked to cartilage degeneration or enhancing the expression of anabolic factors like SOX9. The ongoing development of targeted delivery ligands (e.g., cartilage-binding peptides) further enhances the specificity and retention of gene-delivering nanocarriers in cartilage tissues [25].

4.5 3D Bioprinting with Nanomaterials

3D bioprinting represents a cutting-edge fabrication technology that enables the spatially controlled deposition of bioactive materials, living cells, and nanomaterials into architecturally complex, tissue-mimetic structures. In the context of osteochondral regeneration, bioprinting facilitates the creation of multiphasic constructs that recapitulate the zonal organization of articular cartilage and subchondral bone, offering distinct microenvironments tailored to the biological needs of each region.

Integrating nanomaterials—such as graphene oxide (GO), hydroxyapatite (HA), silica nanoparticles, or platelet-rich plasma (PRP)-laden microspheres—into printable bioinks significantly enhances the mechanical, biological, and rheological properties of these constructs. For example, GO incorporation improves the shear-thinning behavior and print fidelity of hydrogel bioinks while providing a nanostructured surface that supports stem cell adhesion and chondrogenic differentiation. GO also exhibits inherent antioxidant and anti-inflammatory properties, making it advantageous for cartilage repair in osteoarthritic environments.

Moreover, PRP-loaded nanoparticles or microspheres, when embedded in printed scaffolds, serve as reservoirs of autologous growth factors such as PDGF, VEGF, and TGF-β, which are gradually released to stimulate angiogenesis and chondrogenesis. This sustained release profile is essential for synchronizing vascular infiltration in the subchondral region with chondrocyte matrix production in the superficial zone.

The layer-by-layer printing capability of bioprinting technologies allows precise placement of nanocomposite materials with varying stiffness and biochemical composition. For instance, a bilayer scaffold may be designed with a softer, chondrogenic upper layer containing MSCs and GO/GelMA hydrogel, and a mineralized lower layer enriched with HA nanoparticles to support osteogenesis. These zonal constructions not only improve tissue integration but also more accurately mimic the native osteochondral interface in structure and function.

Advanced strategies also involve cell-laden nanocomposite bioinks that combine stem cells with nanomaterials capable of modulating differentiation through mechanical and topographical cues. Some systems have employed magnetic nanoparticles to enable remote stimulation or imaging, and

thermoresponsive hydrogels to allow post-printing gelation and conformal defect filling.

While significant progress has been made, challenges remain in scaling up production, ensuring vascularization in large constructs, and achieving long-term integration. Nevertheless, with continued development in biomaterial science, nozzle design, and stem cell biology, nanomaterial-enhanced 3D bioprinting is poised to become a transformative modality for personalized, high-precision cartilage and osteochondral regeneration [26].

5 Recent Advances and Case Studies

In a 2022 preclinical study, an injectable thermosensitive hydrogel embedded with exosome-loaded PLGA nanoparticles was applied to osteochondral defects in rabbits. The treatment promoted significant cartilage regeneration and subchondral bone remodeling, with histological scores comparable to native cartilage. Another study developed a bilayered 3D-printed scaffold integrating a nanofiber layer for chondrogenic induction and a calcium phosphate base layer for bone regeneration. This scaffold achieved full osteochondral repair in porcine models over 12 weeks. These cases highlight not only the versatility of nanotechnology but also its capacity to address complex, multilayered tissue repair scenarios that traditional methods cannot achieve.

Growing evidence points to success in preclinical models. Nanoengineered scaffolds with MSCs show enhanced cartilage integration and biomechanical integrity. Hydrogels embedded with nanoparticles delivering TGF-β or BMPs demonstrate sustained release and ECM deposition. Notably, a 3D-printed scaffold incorporating graphene and PRP produced zonal cartilage formation with elevated glycosaminoglycan content and MSC viability. Nanocarrier-facilitated gene therapies targeting joint inflammation are advancing toward early clinical trials, particularly in osteoarthritis [27].

6 Challenges and Future Perspectives

Ethical considerations and public perception are increasingly important in the adoption of nanotechnology-based therapies. Questions around long-term biosafety, nanomaterial accumulation, and potential off-target genetic modifications must be addressed through transparent clinical trials and public engagement. Furthermore, intellectual property and commercialization hurdles—especially when multiple proprietary technologies (e.g., biomaterials, vectors, printing devices) are integrated—pose challenges to collaborative development. Establishing open-source material libraries and harmonized preclinical testing protocols could help democratize access to nano-regenerative technologies and accelerate innovation.

6.1 Biosafety

Both inorganic and organic nanomaterials must be carefully designed to avoid toxicity or immune activation. Degradation products (e.g., acidic by-products from PLGA) must be managed for pH stability.

6.2 Manufacturing and Scalability

Complex nano-hybrid scaffolds need reproducible, GMP-compliant production methods to meet clinical standards.

6.3 Regulatory Pathways

Multifunctional nanobiomedical therapies may require new regulatory frameworks spanning devices, drugs, and biologics.

6.4 Personalized and Smart Systems

Smart, stimulus-responsive scaffolds (e.g., magnetic, pH-sensitive) combined with patient-derived cells and imaging-based design are future directions [28].

7 Conclusion

Nanotechnology offers a truly multidimensional and synergistic approach to cartilage regeneration by integrating structural biomimicry, controlled therapeutic delivery, cell guidance, and genetic modulation within a unified framework. Nano-engineered scaffolds replicate the hierarchical architecture of native cartilage, providing biomechanical support while promoting chondrocyte attachment and extracellular matrix deposition. Nanoparticle-based systems further enhance regeneration by enabling site-specific, sustained release of growth factors, anti-inflammatory agents, and gene therapies such as TGF-β and IL-1Ra, thereby improving therapeutic precision and efficacy. Meanwhile, nanotopographical cues and surface functionalization techniques (e.g., RGD peptides) guide mesenchymal stem cell behavior, influencing cell adhesion, proliferation, and differentiation pathways like FAK, MAPK, and Wnt signaling.

Non-viral nanocarriers offer a safer and effective route for localized gene delivery, minimizing immunogenic risks and providing sustained genetic modulation.

Despite strong preclinical evidence illustrating improved cartilage repair in animal models, as well as promising early clinical pilot studies, full clinical translation remains nascent. To bridge this gap, researchers must rigorously address biosafety concerns by systematically characterizing nanoparticle biodistribution, cytotoxicity, and immunogenicity. Concurrently, scalable and reproducible manufacturing methods, especially in complex 3D-bioprinted or composite scaffolds, are critical, and must align with existing Good Manufacturing Practice (GMP) standards and emerging regulatory frameworks that encompass cellular, biomaterial, and combination product classifications. Finally, fostering interdisciplinary collaboration among materials scientists, cell biologists, clinicians, and regulatory experts is essential to ensure seamless translation from bench to bedside, addressing unmet clinical needs and compliance requirements at every stage [29].

In conclusion, with meticulous attention to safety profiling, manufacturing scalability, regulatory alignment, and collaborative innovation, nanotechnology-enabled cartilage regeneration holds the transformative potential to produce durable, biologically functional, and clinically translatable therapies—offering hope for true joint repair as opposed to mere symptom management [30].

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

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