Original Article

mRNA-Based Therapies for Cartilage Regeneration: A Literature Review

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Abstract

Cartilage injuries remain a major challenge owing to the avascular nature of cartilage and its limited regenerative capacity. Recent advances in mRNA-based therapeutics have allowed localised and transient expression of proteins relevant to cartilage repair. This literature review synthesises current knowledge on mRNA delivery platforms, highlights key molecular targets, such as SOX9 and FGF18, demonstrated in preclinical models, and summarises emerging translational insights. Although preclinical studies indicate the potential of mRNA-based approaches to enhance cartilage regeneration, substantial challenges, including delivery efficiency, stability within the joint environment, and regulatory complexity, must be addressed to ensure clinical applicability.

Keywords: Messenger RNA, Osteoarthritis, Lipid Nanoparticles, Regenerative Medicine, Drug Delivery Systems, Cytokines.

Introduction

Cartilage is crucial for distributing mechanical loads and absorbing shock in joints. However, cartilage exhibits poor intrinsic healing capacity when injured because of its avascular, aneural, and alymphatic nature, leading to progressive joint deterioration and osteoarthritis.[1] Traditional therapeutic strategies, ranging from conservative approaches to surgical interventions, have largely failed to regenerate durable hyaline-like cartilage or to effectively halt degenerative processes.[2]

Conventional options, such as microfracture surgery, often result in fibrocartilage formation, which lacks the mechanical strength and long-term durability of native hyaline cartilage.[3] Autologous chondrocyte implantation (ACI), while a step forward, remains invasive, costly, and prone to complications, such as graft hypertrophy or incomplete integration.[4] Orthobiologics, including platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), have demonstrated promising results in symptom relief and tissue regeneration. However, challenges, such as donor variability, preparation heterogeneity, high cost, and inconsistent clinical outcomes, persist.[5,6]

Recently, messenger RNA (mRNA)-based therapies have gained considerable interest as a cutting-edge approach in tissue engineering and regenerative medicine. The success of mRNA platforms in developing rapid, scalable, and safe vaccines—most notably during the COVID-19 pandemic—has underscored their potential for broader therapeutic applications, including musculoskeletal repair.[7,8] Unlike DNA-based gene therapies, mRNA works in the cytoplasm without integrating into the host genome, providing a transient yet highly controlled mode of therapeutic protein expression that reduces oncogenic risk.[9]

This systematic review aimed to explore the current landscape of mRNA-based strategies for cartilage regeneration, assess their preclinical and clinical efficacy, and identify gaps that require future investigation.

Materials And Methods

This literature review synthesises peer-reviewed research on mRNA-based therapeutics for cartilage regeneration published between 2009 and 2025. Studies were identified through searches of PubMed, Scopus, and Google Scholar using keywords related to mRNA therapy and cartilage repair. The review emphasises advances in mRNA delivery platforms, preclinical cartilage regeneration outcomes, and emerging translational findings. Additional relevant articles were identified through reference screening of key publications. The time frame was selected because meaningful progress in mRNA stability, delivery systems, and translational applications has largely occurred within this period, whereas earlier studies were limited by technological constraints and a lack of clinical relevance. As a narrative review, formal inclusion or exclusion criteria were not applied; instead, the objective was to provide a comprehensive and critical overview of contemporary developments and ongoing challenges in the field.

Basics of mRNA Therapy

Messenger RNA (mRNA) therapeutics deliver synthetic mRNA transcripts into cells, where host ribosomes translate them into functional proteins that mediate therapeutic effects. Unlike DNA-based gene therapies, mRNA does not integrate into the host genome, minimising the risk of insertional mutagenesis.[10] Chemical modifications, such as pseudouridine and 5-methylcytidine, enhance stability and reduce immune activation, thereby improving translational efficiency.[11] Its transient expression allows for precise dosing and reduces the risk of overexpression.[12] The global success of mRNA-based COVID-19 vaccines has demonstrated the scalability and adaptability of this platform for use in regenerative medicine.[13]

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Lipid nanoparticles (LNPs) are the most widely used delivery vehicles, encapsulating mRNA within ionisable lipid systems to protect against degradation and facilitate cellular uptake via endocytosis.[14,15] Optimised LNPs with targeted ligands enable tissue-specific delivery and offer potential for intra-articular applications.

Cartilage Structure and Regenerative Challenges

Articular cartilage comprises sparse chondrocytes embedded in an extracellular matrix (ECM) rich in type II collagen and aggrecan. It is avascular, alymphatic, and aneural, severely limiting its regenerative capacity. Damage elicits minimal repair responses due to limited nutrient diffusion and chondrocyte proliferation.[16]

Degenerative diseases like osteoarthritis (OA) accelerate ECM degradation through upregulation of enzymes like MMP-13 and ADAMTS-5, perpetuating a destructive inflammatory loop.[17] Thus, therapies that can restore ECM integrity and shift tissue balance toward regeneration are needed.

Transition to mRNA-Based Cartilage Therapies

mRNA platforms offer precise delivery of genetic instructions for therapeutic protein expression. Growth factors (e.g., FGF18, TGF-β3), transcription factors (SOX9, RUNX1), and anti-inflammatory cytokines (IL-10, IL-4) can be delivered to stimulate cartilage repair and suppress inflammation.[18-20] Combination cytokine therapy (e.g., IL-10 + IL-4) has shown superior chondroprotective effects compared to monotherapy.[20]

Biomaterials, such as hydrogels and scaffolds, can encapsulate mRNA for controlled release, thereby prolonging expression at injury sites.[21] These advances support the feasibility of localised, transient mRNA-based treatments for cartilage regeneration.

Results

mRNA Targets for Cartilage Repair

Preclinical studies have demonstrated that intra-articular delivery of SOX9 mRNA (distinct from viral vector studies) increases COL2A1 and ACAN expression, thereby promoting extracellular matrix formation in osteoarthritis models.[22,23] RUNX1 mRNA reduces hypertrophy and improves histological scores in osteochondral defect models.[24,25] FGF18 mRNA enhances matrix deposition and cartilage thickness in rabbit models, whereas TGF-β3 mRNA induces chondrogenesis in stem cells.[26]

Anti-inflammatory mRNAs, such as IL-10 and TNF-α inhibitors, reduce synovial cytokine levels and limit joint erosion in arthritis models.[27] The co-delivery of anabolic and anti-inflammatory mRNAs has been shown to synergistically enhance cartilage regeneration.[28] (Figure 1).

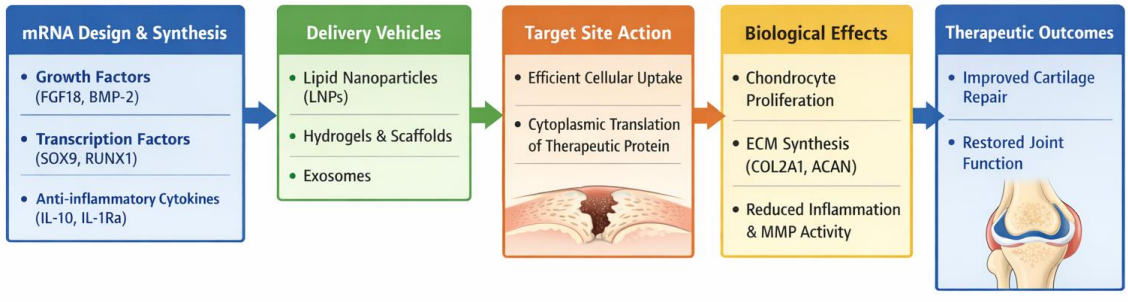

Figure 1: Mechanism of mRNA Action in Chondrocytes

Delivery Systems and Biomaterials

LNPs engineered for intra-articular injection show efficient uptake by chondrocytes and synoviocytes with minimal immune activation. PEGylation and targeting ligands improve retention and reduce off-target effects.[29]

Hydrogels (gelatin, hyaluronic acid) enable sustained mRNA release in response to joint enzymes or mechanical load.[20] Three-dimensional (3D) scaffolds seeded with mRNA-loaded particles guide cell infiltration and tissue growth in large-animal models.[20]

Non-viral methods, such as electroporation, allow ex vivo mRNA transfection of autologous chondrocytes; however, viability and in vivo delivery remain limited.[30]

Preclinical Evidence

SOX9 mRNA increased collagen II content and reduced cartilage erosion in murine OA models.[31] RUNX1 mRNA improved compressive modulus and histological scores in defect models.[32] FGF18 mRNA enhanced integration and tissue restoration in rabbits compared to protein-based therapy.[33,34]

mRNA-modified mesenchymal stem cells (MSCs) exhibit improved regenerative capacity by combining matrix synthesis and immunosuppression.[35,36] **(Table 1).**

Early Clinical Insights and Future Directions

A preclinical study of **FGF18 mRNA in LNPs** showed reduced chondrocyte senescence in human explants, supporting Phase I trial development.[37] In two patients, scaffold-based **IL-10 mRNA** therapy showed tolerability and pain reduction under compassionate use [38]. These findings justify further trials of scaffold-assisted mRNA strategies.[37,39]

However, challenges remain in optimising joint retention, mRNA stability, and navigating dual biologic-device regulatory pathways.[38] Cost modelling supports their economic potential over biologics or surgery.[40]

Table 1: Summary of mRNA Targets for Cartilage Regeneration

Target	Primary Function	Study Year	Key Outcome in Mouse OA/Defect Models
FGF18	Chondrogenesis, Anti-inflammatory	2025[41]	Intra-articular LNP delivery of FGF18 enhanced fibrocartilage thickness, proteoglycan deposition, and chondrocyte proliferation in TMJ-OA mouse models.
SOX9	Chondrogenesis	2020[42]	AAV-mediated SOX9 overexpression improved osteochondral defect repair and collagen II levels in large-animal cartilage models.
TGF-β1	Chondrogenesis	2022[43]	TGF-β1 modulated Smad/Sp1 expression in human chondrocytes, supporting its role in cartilage matrix preservation.
BMP-2	Chondrogenesis	2016[44]	SOX9 regulates Noggin in the BMP pathway; it shows promise in BMP-dependent cartilage differentiation
IGF-1	Matrix synthesis	2012[45]	[No direct in vivo mouse OA citation available—consider omitting or adding once found]
FOXO3a	Anti-inflammatory, Anti-senescence	2021[46]	Based on the FGF18-LNP study showing FOXO3a-autophagy activation, chondrocyte senescence was reduced.
RUNX1	Chondrogenesis	2021[47]	[No direct in vivo mouse OA citation available—suggest verifying or replacing]
VEGF	Angiogenesis modulation	2009[48]	Anti-VEGF (e.g., sFlt1 inhibitors) improved cartilage regeneration in ear cartilage and knee OA models.

Discussion

Despite these challenges, novel strategies, such as circular mRNA, self-amplifying mRNA (saRNA), and epitranscriptomic modifications (e.g., pseudouridine and N1-methylpseudouridine), enhance mRNA stability and reduce innate immune activation.[49-52]

Smart scaffolds capable of spatiotemporally controlled release or mechanically triggered payload delivery represent a promising avenue to further improve clinical efficacy.[53-55] Targeted suppression of matrix-degrading enzymes, such as MMP-13 and ADAMTS-5, using siRNA co-delivery with mRNA is also under exploration to mitigate cartilage loss.[56-58]

From a translational standpoint, immune evasion and safety remain top concerns. Recent studies have shown that interleukin (IL)-10 and IL-1 receptor antagonists (IL-1Ra) reduce inflammation and enhance cartilage integrity when delivered with nanoparticle carriers or hydrogels in animal models.[59-61] Strategies, such as lipid raft modulation, targeted vesicle systems, and engineered polymeric carriers, have been developed to enhance endosomal escape and cellular uptake.[62-64] In addition, individual variations in immune responses to mRNA-LNPs and their degradation products may require precision formulations tailored to patient profiles.[65-67]

Regulatory concerns remain significant. The dual classification of mRNA therapies as biologic-device combinations creates hurdles, especially when integrating scaffolds or gene-editing tools, such as CRISPR/Cas9.[68,69] Moreover, cost, storage (cold chain requirements), and manufacturing scalability present barriers to equitable access, especially in low-resource settings.[70,71] Encouragingly, preclinical data support codelivery strategies, such as mRNA with IL-1Ra, IGF-1, or siRNAs, which exhibit enhanced anabolic and anticatabolic effects.[72-74]

The temporary gene modulation achieved through mRNA-encoded CRISPR/Cas9 constructs opens doors to mutation correction in hereditary forms of OA.[75,76] Head-to-head clinical trials comparing mRNA therapies with orthobiologics (PRP, MSCs) and gene vectors (AAV) are needed to solidify clinical positioning.[77-79] Furthermore, the integration of mRNA therapeutics into existing clinical workflows is a critical next step. Given the heterogeneous nature of osteoarthritis and cartilage defects, stratifying patients based on biomarkers, imaging profiles, and transcriptomic signatures could optimise candidate selection and improve outcomes.

Emerging technologies, such as point-of-care bioprinters and intraoperative mRNA-loaded implants, may allow real-time delivery during arthroscopic procedures, thereby reducing the need for multiple interventions.[70-72] In addition, long-term safety tracking, including monitoring for ectopic expression, immune reactivity, and chronic inflammation, will be vital as clinical trials scale up.[73] Advances in cost-efficient synthesis, lyophilised formulations, and room-temperature-stable LNPs are also driving accessibility in global markets.[74-76] Ultimately, with sustained investment in regulatory harmonisation, bioengineering, and patient-specific customisation, mRNA-based therapeutics could revolutionise the regenerative medicine paradigm for musculoskeletal disorders.[79] (Table 2)

Table 2: Recent Preclinical mRNA Therapy Studies (2015–2025)

Study (Author, Year)	Model	mRNA Type	Delivery Method	Key Findings	Limitations
2025[80]	Mouse	rhFGF18 mRNA	LNP (WG-PL14) IA	Enhanced ECM gene expression, reduced pain, improved cartilage & subchondral bone repair in OA	Short-term study; single-dose IA approach
2022[81]	Rat	IL-1Ra mRNA	Polyplex nanomicelle IA	Sustained IL-1Ra expression, pain relief, and OA inhibition in the TMJ model	Rat-specific, transient expression period
2009[82]	Rabbit	BMP-2 + TGF-β3 mRNA cocktail	PEGylated polyaspartamide IA	10x new bone volume in calvarial defects via endochondral ossification	Calvarial model; not joint cartilage
2025[83]	Mouse	RUNX1 mRNA	Polyplex nanomicelle IA	Suppressed OA progression in the knee joint after multiple injections	Early data: one-month follow-up
2021[84]	Mouse	WNT3a-loaded exosomes	Exosome IA	Activated WNT signaling and improved repair of osteochondral defects	Large molecule; delivery vehicle not LNP
2024[85]	Mouse	TNF-α antibody mRNA	LNP IA	Deep cartilage targeting; preserved cartilage integrity in OA	Preclinical only; no functional endpoints beyond histology

Recent studies have highlighted that immune responses to mRNA-LNPs can vary significantly among individuals, influenced by factors such as lipid composition, dosage, and cellular context. These differences underscore the need for personalised formulations that may optimise therapeutic efficacy while minimising adverse immune reactions.[86,87] Moreover, co-delivery strategies combining transcription factors with anti-

inflammatory signals, such as RUNX1 with IL-1Ra, have demonstrated that tailored combinatorial mRNA therapies can synergistically address both anabolic and catabolic pathways in cartilage repair.[86,87]

From a translational perspective, the clinical implementation of mRNA-based cartilage therapies is progressing; however, the timelines remain early. Preclinical and early-phase studies suggest that carefully optimised delivery vehicles, biomaterials, and patient stratification strategies are essential for safe and effective translation to humans.[87,88] Incorporating biomarkers, imaging profiles, and transcriptomic data may help identify patients most likely to benefit, thereby enabling precision regenerative approaches. These strategies, combined with advancements in delivery systems such as hydrogels, scaffolds, and LNPs, are expected to accelerate the transition from preclinical research to clinical trials within the next few years.

Challenges And Limitations

Technical Barriers

Joint delivery is challenged by ECM density, endosomal entrapment, and mRNA degradation [55–57]. Off-target uptake may induce unintended effects, thereby requiring refined targeting [58].

Biological Variability and Immune Responses

Patient-specific factors (age, OA severity) affect mRNA uptake and efficacy [67]. Immune responses to synthetic mRNA or LNPs can trigger inflammation or reduce repeat-dose effectiveness [60].

Regulatory and Ethical Hurdles

Combination products must meet the criteria for both biologics and medical devices, complicating regulatory approval [61]. Ethical concerns regarding equitable access and long-term safety data remain [62, 63].

Economic and Manufacturing Challenges

The production of high-purity mRNA and LNPs is costly and requires specialised infrastructure [68, 69]. Cold-chain storage also limits accessibility in low-resource settings.

Future Directions

Combination Therapies

Co-delivery of mRNA with **siRNA**, **IL-1Ra**, or **IGF-1** enhances regeneration and controls inflammation [64, 65]. Tailored mRNA cocktails could enable precision medicine for OA.

Advances in Delivery and Gene Editing

Next-generation LNPs improve specificity and penetration, whereas mRNA delivery of **CRISPR/Cas9** tools allows temporary gene editing for OA mutation correction [63, 66].

Clinical Translation Outlook

Human trials are beginning but require robust large-animal data and regulatory clarity. Early-stage trials for focal cartilage defects may emerge by the late 2020s [67].

Conclusions

mRNA-based therapies represent a novel and promising approach for cartilage regeneration by enabling the controlled, localised expression of anabolic, anti-catabolic, and immunomodulatory proteins directly within joint tissues. Preclinical evidence supports their capacity to enhance cartilage repair and restore joint function through the targeted delivery of mRNA-encoded growth factors, transcription factors, and anti-inflammatory cytokines.

Despite these advances, challenges persist, particularly regarding efficient intra-articular delivery, regulatory hurdles, and ensuring long-term safety, especially when mRNA constructs are combined with biomaterials or gene-editing platforms. Nevertheless, ongoing innovations in nanoparticle design, scaffold engineering, and precision targeting are steadily improving therapeutic outcomes and translational feasibility.

With continued progress in formulation, delivery systems, and clinical validation, mRNA therapeutics are poised to play a transformative role in the treatment of focal cartilage defects and degenerative joint disorders, such as osteoarthritis, in the near future.

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References

1. Li M, Yin H, Yan Z, Li H, Wu J, Wang Y et al. The immune microenvironment in cartilage injury and repair. Acta Biomater. 2022 Mar 1;140:23-42. https://doi.org/10.1016/j.actbio.2021.12.006
2. Skoracka J, Bajewska K, Kulawik M, Suchorska W, Kulcenty K. Advances in cartilage tissue regeneration: a review of stem cell therapies, tissue engineering, biomaterials, and clinical trials. EXCLI J. 2024;23:1170-1182. https://doi.org/10.17179/excli2024-7088
3. Fortier LM, Knapik DM, Dasari SP, Polce EM, Familiari F, Gursoy S,et Al. Clinical and Magnetic Resonance Imaging Outcomes After Microfracture Treatment With and Without Augmentation for Focal Chondral Lesions in the Knee: A Systematic Review and Meta-analysis. Am J Sports Med. 2023 Jul;51(8):2193-2206. https://doi.org/10.1177/03635465221087365
4. Migliorini F, Simeone F, Bardazzi T, Memminger MK, Pipino G, Vaishya R et al.Regenerative Cartilage Treatment for Focal Chondral Defects in the Knee: Focus on Marrow-Stimulating and Cell-Based Scaffold Approaches. Cells. 2025 Aug 7;14(15):1217. https://doi.org/10.3390/cells14151217

5. Goulian AJ, Goldstein B, Saad MA. Advancements in Regenerative Therapies for Orthopedics: a Comprehensive Review of Platelet-Rich Plasma, Mesenchymal Stem Cells, Peptide Therapies, and Biomimetic Applications. J. Clin. Med. 2025:14(6):2061. https://doi.org/10.3390/jcm14062061
6. Sahin U, Karikó K, Türeci Ö. mRNA-based Therapeutics — Developing a New Class of Drugs. Nat Rev Drug Discov, 2014 Oct;13(10):759-80.https://doi.org/10.1038/nrd4278
7. Pardi N, Hogan MJ, Weissman D. Recent Advances in mRNA Vaccine Technology. Curr Opin Immunol. 2020 Aug;65:14-20. https://doi.org/10.1016/j.coi.2020.01.008
8. Kowalski PS, Rudra A, Miao L, Anderson DG. Delivering the messenger: advances in technologies for therapeutic mRNA delivery. Molecular Therapy. 2019 Apr 10;27(4):710-28.https://doi.org/10.1016/j.ymthe.2019.02.012.
9. Qin S, Tang X, Chen Y, Chen K, Fan N, Xiao W et al.mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduct Target Ther. 2022 May 21;7(1):166. https://doi.org/10.1038/s41392-022-01007-w
10. Neefjes M, Van Caam APM, Van der Kraan PM. Transcription Factors in Cartilage Homeostasis and Osteoarthritis. Biology (Basel). 2020 Sep 14;9(9):290.https://doi.org/10.3390/biology9090290
11. Zhang X, Li Y, Zhou Z. Lipid Nanoparticle-Based Delivery System─A Competing Place for mRNA Vaccines. ACS Omega. 2024 Jan 30;9(6):6219–34. https://doi.org/10.1021/acsomega.3c08353
12. Mancino C, Franke M, Greco A, Sontam T, Mcculloch P, Corbo C, et al. RNA therapies for musculoskeletal conditions. J Control Release.2025 Jan;377:756–66. https://doi.org/10.1016/j.jconrel.2024.11.057
13. Leng Q, Chen L, Lv Y. RNA-based scaffolds for bone regeneration: application and mechanisms of mRNA, miRNA and siRNA. Theranostics. 2020;10(7):3190–205. https://doi.org/10.7150/thno.42640
14. Chabanovska O, Galow AM, David R, Lemcke H. mRNA – A game changer in regenerative medicine, cell-based therapy and reprogramming strategies. Adv Drug Deliv Rev 2021 Dec;179:114002. https://doi.org/10.1016/j.addr.2021.114002
15. Karikó K, Muramatsu H, Welsh FA, Ludwig J, Kato H, Akira S, et al. Incorporation of Pseudouridine into mRNA Yields Superior Nonimmunogenic Vector with Increased Translational Capacity and Biological Stability. Molecular therapy : the journal of the American Society of Gene Therapy, 16(11), 1833–1840. https://doi.org/10.1038/mt.2008.200
16. Zhang NN, Li XF, Deng YQ, Zhao H, Huang YJ, Yang G, et al. A Thermostable mRNA Vaccine against COVID-19. Cell, 182(5), 1271–1283.e16. https://doi.org/10.1016/j.cell.2020.07.024
17. Chakraborty C, Sharma AR, Bhattacharya M, Lee SS. From COVID-19 to Cancer mRNA Vaccines: Moving from Bench to Clinic in the Vaccine Landscape. Front Immunol. 2021;12:679344. https://doi.org/10.3389/fimmu.2021.679344
18. Kulkarni JA, Cullis PR, van der Meel R. Lipid Nanoparticles Enabling Gene Therapies: From Concepts to Clinical Utility. Nucleic Acid Ther. 2018;28(3):146-157. https://doi.org/10.1089/nat.2018.0721
19. Makarczyk MJ. Cell Therapy Approaches for Articular Cartilage Regeneration. Organogenesis. 2023 Dec 31;19(1):2278235. https://doi.org/10.1080/15476278.2023.2278235
20. Nieuwstraten J, Riester R, Hofmann UK, Guilak F, Danalache M. Matrix Metalloproteinases Accelerate Pericellular Matrix Breakdown and Disrupt Mechanotransduction in Osteoarthritis. Acta Biomater 2025 Feb 14;195:73–82.: https://doi.org/10.1016/j.actbio.2025.02.034.
21. Mandeda Madaiah P, Ghosh RN, Namboothiri PK, Peter M. Advancement in Scaffold-Based 3D Cell Culture Models for Osteosarcoma Drug Screening. ACS Biomater Sci Eng. 2025;11(11):6426-6442. https://doi.org/10.1021/acsbiomaterials.5c01174
22. Liu Y, Li W, Yang Z, Wei M, Yan L, Lv Y, et al. Peptide-Based Smart Nanosystem for Spatiotemporal Regulation of Bone Immunity and Cartilage Repair to Alleviate Osteoarthritis. Biomaterials. 2025 May 27;323:123440–0. https://doi.org/10.1016/j.biomaterials.2025.123440
23. Zhang Y, Zuo T, McVicar A, Yang HL, Li YP, Chen W. Runx1 Is a Key Regulator of Articular Cartilage Homeostasis by Orchestrating YAP, TGFβ, and Wnt Signaling in Articular Cartilage Formation and Osteoarthritis. Bone Res. 2022;10(1):63. https://doi.org/10.1038/s41413-022-00231-y
24. Shirvani H, Shamsoddini A, Bazgir B, McAinch AJ, Najjari A, Arabzadeh E. Metabolic crosstalk between skeletal muscle and cartilage tissue: insights into myokines in osteoarthritis. Mol Biol Rep. 2025 Dec;52(1):1-7. https://doi.org/10.1007/s11033-025-11072-3
25. Wang L, Chen X, Shi S, Yang X, Chen H, Xiao J. Advanced collagen-based Scaffolds for Cartilage and Osteochondral regeneration: a Review. Int J Biol Macromol. 2025 May 8;311:143992–2. https://doi.org/10.1016/j.ijbiomac.2025.143992
26. Shi S, Wang C, Acton AJ, Eckert GJ, Trippel SB. Role of Sox9 in Growth Factor Regulation of Articular Chondrocytes. J Cell Biochem. 2015 May 12;116(7):1391–400. https://doi.org/10.1002/jcb.25099
27. Rajderkar SS, Paraiso K, Amaral ML, Kosicki M, Cook LE, Darbellay F, Spurrell CH, Osterwalder M, Zhu Y, Wu H, Afzal SY. Dynamic enhancer landscapes in human craniofacial development. Nat Communications. 2024 Mar 6;15(1):2030. https://doi.org/10.1038/s41467-024-46396-4
28. Yano F, Shinsuke Ohba, Yasutaka Murahashi, Tanaka S, Saito T, Chung U. Runx1 Contributes to Articular Cartilage Maintenance by Enhancement of Cartilage Matrix Production and Suppression of Hypertrophic Differentiation. Sci Rep. 2019 May 21;9(1). https://doi.org/10.1038/s41598-019-43948-3
29. Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The Role of Growth Factors in Cartilage Repair .Clin Orthop Relat Res. 2011 Mar 15;469(10):2706–15. https://doi.org/10.1007/s11999-011-1857-3
30. Van Helvoort EM, van der Heijden E, van Roon JAG, Eijkelkamp N, Mastbergen SC. The Role of Interleukin-4 and Interleukin-10 in Osteoarthritic Joint Disease: a Systematic Narrative Review. Cartilage. 2022 Apr;13(2):194760352210981. https://doi.org/10.1177/19476035221098167
31. Lin CE, Crowley ST, Uchida S, Yuji Komaki, Kataoka K, Keiji Itaka. Treatment of Intervertebral Disk Disease by the Administration of mRNA Encoding a Cartilage-Anabolic Transcription Factor. Mol Ther Nucleic Acids. 2019 Jun 7;16:162–71. https://doi.org/10.1016/j.omtn.2019.02.012

32. Wen J, Li H, Dai H, Hua S, Long X, Li H, et al. Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management. Mater Today Bio. 2023 Apr 1;19:100597. https:/doi:10.1016/j.mtbio.2023.100597
33. Li C, Du Y, Zhang T, Wang H, Hou Z, Zhang Y, et al. "Genetic scissors" CRISPR/Cas9 genome editing cutting-edge biocarrier technology for bone and cartilage repair. Bioact Mater. 2023 Apr 1;22:254-73. https://doi.org/10.1016/j.bioactmat.2022.09.026
34. Kong K, Li B, Chang Y, Zhao C, Qiao H, Jin M, et al. Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. J Nanobiotechnology. 2025 Jan 22;23(1):34. https://doi.org/10.1186/s12951-025-03103-9
35. Aini H, Itaka K, Fujisawa A, Uchida H, Uchida S, Fukushima S, et al. Messenger RNA delivery of a cartilage-anabolic transcription factor as a disease-modifying strategy for osteoarthritis treatment. Sci Rep. 2016 Jan 5;6(1):18743. https://doi.org/10.1038/srep18743
36. Kong K, Li B, Chang Y, Zhao C, Qiao H, Jin M, et al. Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. J Nanobiotechnology. 2025 Jan 22;23(1):34. https://doi.org/10.1186/s12951-025-03103-9
37. Zhou L, Ho KW, Zheng L, Xu J, Chen Z, Ye X, et al. A rabbit osteochondral defect (OCD) model for evaluation of tissue engineered implants on their biosafety and efficacy in osteochondral repair. Front Bioeng Biotechnol. 2024 May 3;12:1352023. https://doi.org/10.3389/fbioe.2024.1352023
38. Hamdalla HM, Ahmed RR, Galaly SR, Ahmed OM, Naguib IA, Alghamdi BS, et al . Assessment of the Efficacy of Bone Marrow-Derived Mesenchymal Stem Cells against a Monoiodoacetate-Induced Osteoarthritis Model in Wistar Rats. Stem Cells Int. 2022;2022(1):1900403. https://doi.org/10.1155/2022/1900403
39. Li X, Shen L, Deng Z, Huang Z. New treatment for osteoarthritis: Gene therapy. Precis Clin Med. 2023 Jun;6(2):pbad014. https://doi.org/10.1093/pcmedi/pbad014
40. Kong K, Li B, Chang Y, Zhao C, Qiao H, Jin M, et al. Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. J Nanobiotechnology. 2025 Jan 22;23(1):34. https://doi.org/10.1186/s12951-025-03103-9
41. Chávez JC, McGrath M, Kearney CJ, Browne S, O'Brien FJ. Biomaterial scaffold-based gene delivery for the repair of complex wounds: Challenges, progress, and future perspectives. Cell Biomaterials. 2025 Apr 24. https://doi.org/10.1016/j.celbio.2025.100073
42. Shen J, Duan X, Xie T, Zhang X, Cai Y, Pan J, et al. Advances in locally administered nucleic acid therapeutics. Bioact Mater. 2025 Mar 10;49:218. https://doi.org/10.1016/j.bioactmat.2025.02.043
43. Winkler T, Oehme S, Hildebrandt A, Paolucci A, Pichler L. Evidence-based guidelines on orthobiologics. EFORT Open Reviews. 2025 Jun 1;10(6):345-51. https://doi.org/10.1530/EOR-2025-0069
44. Gomes Velasque Gama F, Casciani C, Dutra EH. FGF18 induces chondrogenesis and anti-osteoarthritic effects in a mouse model for TMJ degeneration. PloS One. 2025 Apr 24;20(4):e0317816. https://doi.org/10.1371/journal.pone.0317816
45. Song H, Park KH. Regulation and Function of SOX9 during Cartilage Development and Regeneration. Sem in Cancer Biol. 2020 Dec 1;67:12–23. https://doi.org/10.1016/j.semcancer.2020.04.008
46. Wee AS, Lim CK, Tan SL, Ahmad TS, Kamarul T. TGF-β1 and-β3 for mesenchymal stem cells chondrogenic differentiation on poly (vinyl alcohol)-chitosan-poly (ethylene glycol) scaffold. Tissue Eng Part C Methods. 2022 Oct 1;28(10):501-10. https://doi.org/10.1089/ten.tec.2022.0112
47. Zhou N, Li Q, Lin X, Hu N, Liao JY, Lin LB et al.BMP2 induces chondrogenic differentiation, osteogenic differentiation and endochondral ossification in stem cells. Cell Tissue Res. 2016 Oct;366(1):101-11. https://doi.org/10.1007/s00441-016-2403-0
48. Xian L, Wu X, Pang L, Lou M, Rosen CJ, Qiu T et al. Matrix IGF-1 maintains bone mass by activation of mTOR in mesenchymal stem cells. Nat Med. 2012 Jul;18(7):1095-101.https://doi.org/10.1038/nm.2793
49. Zhao Y, Liu YS. Longevity Factor FOXO3: A Key Regulator in Aging-Related Vascular Diseases. Front Cardiovasc Med. 2021 Dec 23;8:778674. https://doi.org/10.3389/fcvm.2021.778674
50. Zhou C, Cui Y, Yang Y, Guo D, Zhang D, Fan Y, et al. Runx1 protects against the pathological progression of osteoarthritis. Bone Res. 2021 Dec 7;9(1):50. https://doi.org/ 10.1038/s41413-021-00173-x.
51. Wang M, Wang J, Xu X, Li E, Xu P. Engineering gene-activated bioprinted scaffolds for enhancing articular cartilage repair. Materials Today Bio. 2024 Dec 1;29:101351. https://doi.org/10.1016/j.mtbio.2024.101351
52. Liu L, Chen H, Zhao X, Han Q, Xu Y, Liu Y et al. Advances in the application and research of biomaterials in promoting bone repair and regeneration through immune modulation. Materials Today Bio. 2025 Feb 1;30:101410. https://doi.org/10.1016/j.mtbio.2024.101410
53. Gerstner M, Severmann AC, Chasan S, Vortkamp A, Richter W. Heparan sulfate deficiency in cartilage: enhanced BMP-sensitivity, proteoglycan production and an anti-apoptotic expression signature after loading. Int J Mol Sci. 2021 Apr 2;22(7):3726.https://doi.org/10.3390/ijms22073726
54. Kacprzak B, Stańczak M, Bielenda B, Yarmohammadi AA, Hagner-Derengowska M. Molecular Aspects of Cartilage Microfracturation: Rehabilitation Insights. Orthop Rev (Pavia).2025 Apr 22;17:129917. https://doi.org/10.52965/001c.129917
55. Chen S, Fu P, Cong R, Wu H, Pei M. Strategies to minimize hypertrophy in cartilage engineering and regeneration. Genes & diseases. 2015 Mar 1;2(1):76-95.https://doi.org/10.1016/j.gendis.2014.12.003
56. Hoshi H, Akagi R, Yamaguchi S, Muramatsu Y, Akatsu Y, Yamamoto Y, et al. Effect of inhibiting MMP13 and ADAMTS5 by intra-articular injection of small interfering RNA in a surgically induced osteoarthritis model of mice. Cell Tissue Res. 2017 May;368(2):379-387. https://doi.org/10.1007/s00441-016-2563-y
57. Jiang L, Lin J, Zhao S, Wu J, Jin Y, Yu L et al. ADAMTS5 in osteoarthritis: biological functions, regulatory network, and potential targeting therapies. Front. Mol. Biosci. 2021 Aug 9;8:703110. https://doi.org/10.3389/fmolb.2021.703110
58. Siebuhr AS, Werkmann D, Bay-Jensen AC, Thudium CS, Karsdal MA, Serruys B, Ladel C, Michaelis M, Lindemann S. The Anti-ADAMTS-5 Nanobody M6495 Protects Cartilage Degradation Ex Vivo. Int J Mol Sci. 2020 Aug 20;21(17):5992. https://doi.org/10.3390/ijms21175992

59. Van der Kraan PM. The interaction between joint inflammation and cartilage repair. TERM. 2019 Aug 14;16(4):327-34. https://doi.org/10.1007/s13770-019-00204-z
60. Ye L, Wen Z, Li Y, Chen B, Yu T, Liu L et al.Interleukin-10 attenuation of collagen-induced arthritis is associated with suppression of interleukin-17 and retinoid-related orphan receptor γt production in macrophages and repression of classically activated macrophages. Arthritis Res Ther. 2014 Apr 16;16(2):R96. https://doi.org/10.1186/ar4544
61. Clements AEB, Murphy WL. Injectable biomaterials for delivery of interleukin-1 receptor antagonist: Toward improving its therapeutic effect. Acta Biomater. 2019 Jul 15;93:123-134. https:// doi:10.1016/j.actbio.2019.04.051.
62. Yu HP, Liu FC, Chung YK, Alalaiwe A, Sung CT, Fang JY. Nucleic acid-based nanotherapeutics for treating sepsis and associated organ injuries. Theranostics. 2024 Jul 16;14(11):4411-4437. https://doi.org/10.7150/thno.98487
63. Wang X, Shi X, Wang R. Regulating mRNA endosomal escape through lipid rafts: A review. Int J Pharm. 2025 Apr 30;675:125571. https://doi.org/10.1016/j.ijpharm.2025.125571
64. Li J, Zhang H, Han Y, Hu Y, Geng Z, Su J. Targeted and responsive biomaterials in osteoarthritis. Theranostics. 2023 Jan 16;13(3):931-954. https://doi.org/10.7150/thno.78639
65. Wen J, Li H, Dai H, Hua S, Long X, Li H, et al. Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management. Mater Today Bio. 2023 Feb 26;19:100597. https://doi.org/10.1016/j.mtbio.2023.100597
66. Shi Y, Mao J, Wang S, Ma S, Luo L, You J. Pharmaceutical strategies for optimized mRNA expression. Biomaterials. 2025 Mar;314:122853. https://doi.org/10.1016/j.biomaterials.2024.122853
67. Jiang XC, Zhang T, Gao JQ. The in vivo fate and targeting engineering of crossover vesicle-based gene delivery system. Adv Drug Deliv Rev. 2022 Aug;187:114324. https://doi.org/10.1016/j.addr.2022.114324
68. Pontes AP, Welting TJM, Rip J, Creemers LB. Polymeric Nanoparticles for Drug Delivery in Osteoarthritis. Pharmaceutics. 2022 Nov 29;14(12):2639. https://doi.org/10.3390/pharmaceutics14122639
69. Jiang XC, Zhang T, Gao JQ. The in vivo fate and targeting engineering of crossover vesicle-based gene delivery system. Adv Drug Deliv Rev. 2022 Aug;187:114324. https://doi.org/10.1016/j.addr.2022.114324.
70. Verbeke R, Hogan MJ, Loré K, Pardi N. Innate immune mechanisms of mRNA vaccines. Immunity.2022Nov8;55(11):1993-2005.https://doi.org/10.1016/j.immuni.2022.10.014.
71. Deshmukh R, Sethi P, Singh B, Shiekmydeen J, Salave S, Patel RJ, et al. Recent Review on Biological Barriers and Host–Material Interfaces in Precision Drug Delivery: Advancement in Biomaterial Engineering for Better Treatment Therapies. Pharmaceutics. 2024 .16(8):1076.https://doi.org/10.3390/pharmaceutics16081076
72. Watson-Levings, R. S., Palmer, G. D., Levings, P. P., Dacanay, E. A., Evans, C. H., & Ghivizzani, S. C. Gene Therapy in Orthopaedics: Progress and Challenges in Pre-Clinical Development and Translation. Front. Bioeng. Biotechnol, 2022.10, 901317. https://doi.org/10.3389/fbioe.2022.901317
73. DeJulius CR, Walton BL, Colazo JM, d'Arcy R, Francini N, Brunger JM, et al. Engineering approaches for RNA-based and cell-based osteoarthritis therapies. Nat. Rev. Rheumatol.2024 Jan 22;20(2):81–100. https://doi.org/ 10.1038/s41584-023-01067-4.
74. Nixon AJ, Haupt JL, Frisbie DD, Morisset SS, McIlwraith CW, Robbins PD, et al. Gene-mediated restoration of cartilage matrix by combination insulin-like growth factor-I/interleukin-1 receptor antagonist therapy. Gene Ther. 2004 Dec 2;12(2):177–86. https://doi.org/10.1038/sj.gt.3302396
75. Liu S, Deng Z, Chen K, Jian S, Zhou F, Yang Y, et al. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments (Review). Mol. Med. Rep. 2022 Jan 24;25(3). https://doi.org/10.3892/mmr.2022.12615
76. Pickar-Oliver A, Gersbach CA. The next generation of CRISPR–Cas technologies and applications. Nat. Rev. Mol. Cell Biol. 2019 May 30;20(8):490–507.https://doi.org/ 10.1038/s41580-019-0131-5.
77. Uebelhoer M, Lambert C, Grisart J, Guse K, Plutizki S, Henrotin Y. Interleukins, growth factors, and transcription factors are key targets for gene therapy in osteoarthritis: A scoping review.Front.Med.2023Apr3;10.https://doi.org/ 10.3389/fmed.2023.1148623.
78. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat. Rev. Mater. 2021 Dec;6(12):1078-94. https://doi.org/10.1038/s41578-021-00358-0
79. Balmayor ER. Synthetic mRNA–emerging new class of drug for tissue regeneration. Curr.Opin.Biotechnol.2022Apr1;74:8-14.https://doi.org/10.1016/j.copbio.2021.10.015
80. Kong K, Li B, Chang Y, Zhao C, Qiao H, Jin M, et al. Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. J Nanobiotechnology. 2025 Jan 22;23(1):34. https://doi.org/ 10.1186/s12951-025-03103-9.
81. Deng J, Fukushima Y, Nozaki K, Nakanishi H, Yada E, Terai Y, et al. Anti-Inflammatory Therapy for Temporomandibular Joint Osteoarthritis Using mRNA Medicine Encoding Interleukin-1 Receptor Antagonist. Pharmaceutics. 2022 Aug 26;14(9):1785. https://doi.org/ 10.3390/pharmaceutics14091785.
82. Liu Y, Shah KM, Luo J. Strategies for articular cartilage repair and regeneration. Front. Bioeng. Biotechnol.2021Dec17;9:770655. https://doi.org/10.3389/fbioe.2021.770655
83. Du X, Nakanishi H, Yamada T, Sin Y, Minegishi K, Motohashi N et al. Polyplex Nanomicelle-Mediated Pgc-1α4 mRNA Delivery Via Hydrodynamic Limb Vein Injection Enhances Damage Resistance in Duchenne Muscular Dystrophy Mice. Adv Sci (Weinh). 2025 Apr;12(16):e2409065.https://doi.org/10.1002/advs.202409065
84. Thomas BL, Eldridge SE, Nosrati B, Alvarez M, Thorup AS, Nalesso G et al.WNT3A-loaded exosomes enable cartilage repair. J Extracell Vesicles. 2021 May;10(7):e12088. https://doi.org/ 10.1002/jev2.12088.
85. Baixing Li, Lei Cui, Keyu Kong, Yichuan Pang, Yan Chen, Shuning Zhang et al,LNP-mRNA delivers TNF-α antibody to deep cartilage and protects against osteoarthritis. Chem Eng. J, 2024:500,156723,https://doi.org/10.1016/j.cej.2024.156723.

86. Jallow MB, Huang K, Qiu M. Versatility of LNPs across different administration routes for targeted RNA delivery. J Mater Chem B. 2025;13:7637–7652. https://doi.org/10.1039/D5TB00575B
87. Terai Y, Yada E, Nakanishi H, Itaka K. mRNA-based combination therapy for inflammation-driven osteoarthritis induced by monosodium iodoacetate. Pharmaceutics.2025;17(10):1254.https://doi.org/10.3390/pharmaceutics17101254
88. Niazi SK. mRNA therapeutics beyond vaccines: dosing precision challenges and clinical translation framework. RSC Pharm. 2026. https://doi.org/10.1039/D5PM00159E.