



Immunomodulatory therapies for osteoarthritis: from bench to bedside

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Abstract: Osteoarthritis (OA) of the knee, particularly in the medial compartment, is driven by chronic synovial inflammation, immune dysregulation, and progressive cartilage degeneration. Increasing evidence indicates that modifying the complete inflammatory microenvironment of the joint, rather than focusing solely on cartilage, is essential for achieving true disease-modifying outcomes. This review provides an integrated bench-to-bedside overview of emerging immunomodulatory cell and cell-derived therapies for knee OA, summarizing mechanistic foundations, preclinical findings, and early clinical progress. We first outline the pathological features of the OA joint, emphasizing macrophage polarization, T-cell subsets, and cytokine-driven pathways that sustain synovitis and extracellular matrix breakdown. The review then highlights three major therapeutic strategies: (I) immunomodulatory cell therapies, including cartilage-activated T cells (CATs), which aim to restore immune homeostasis; (II) extracellular vesicle (EV) and miRNA-based therapies that modulate inflammation, enhance chondrocyte survival, and promote matrix synthesis; and (III) peripheral blood stem cell (PBSC)-assisted regenerative approaches used in combination with arthroscopic procedures. Preclinical studies consistently demonstrate reduced inflammation, improved chondrogenesis, and enhanced structural repair across these modalities. We further summarize recent phase I/II clinical trials, which report favorable safety profiles and early clinical benefits, particularly for MSC-derived EVs and PBSC-based interventions. Nonetheless, long-term efficacy, manufacturing scalability, product heterogeneity, and regulatory complexity remain significant obstacles to widespread clinical translation. In conclusion, immunomodulatory cell and cell-derived therapies represent promising disease-modifying strategies for knee OA. Future progress will rely on standardized potency assays, optimized GMP manufacturing, robust clinical trial designs, and precision medicine approaches for targeted patient selection.

Keywords: Osteoarthritis (OA); immunomodulation; extracellular vesicles (EVs); stem cell therapy; cartilage regeneration

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Introduction

Osteoarthritis (OA) is the most prevalent joint disease worldwide, significantly impacting quality of life (1). The medial compartment of the knee is particularly at risk due to its greater mechanical load, often leading to accelerated degeneration (2). Many existing treatments have demonstrated modest symptom relief; however, few are truly disease-modifying (3). The field of knee preservation has sought a disease-modifying regenerative medicine solution for osteochondral defects and early-stage OA for several generations. While a surefire solution continues to elude us, considerable progress has been made in understanding the mechanisms of cartilage regeneration and applying that knowledge to clinical treatments. Research into the proper preparation, application, proliferation, differentiation, and integration of pluripotent cells has been fraught with both hope and disappointment. Still, clinical and basic science studies continue to inch closer to an ideal solution. The following review highlights several emerging technologies that hold promise for regenerating a functional, durable hyaline cartilage-based osteochondral unit in the knee. It would be outside the scope of this review to include every published regenerative option, so the authors have chosen to focus on a select few with recent promise. These include immunomodulatory cell therapies, cell-derived vehicle therapies, and surgical interventions paired with peripheral blood stem cells (PBSCs).

Inflammatory microenvironment of the medial knee compartment

Medial compartment OA is driven by synovitis and infiltration of inflammatory macrophages and T cells. Key cytokines—including interleukin (IL)-1 β , tumor necrosis factor alpha (TNF- α), matrix metalloproteinases (MMPs), and NF- κ B-related mediators—accelerate cartilage degradation and disrupt cellular homeostasis (4,5). OA progression is characterized by reduced anabolic markers (COL2A1, aggrecan, COMP, HIF-1 α) and increased catabolic enzymes (MMPs, ADAMTSs, cathepsins) that promote ECM loss (6).

Synovial fluid becomes enriched with inflammatory and proteolytic mediators, impairing repair capacity. Bolander *et al.* showed that OA synovial fluid induces hypertrophy and dedifferentiation in healthy chondrocytes (4). Elevated synovial biomarkers—including MMP-3, VEGF, IL-6,

MIP-1 β , and MCP-1—are associated with increased progression to total knee arthroplasty (7). Together, these findings highlight the immune microenvironment as a key therapeutic target in OA.

Beyond cytokine dysregulation, immune cell dynamics further shape the inflammatory microenvironment. Macrophages are abundant in osteoarthritic synovium and shift toward a pro-inflammatory M1-like phenotype, producing IL-1 β , TNF- α , and MMPs that accelerate cartilage matrix degradation (8). In contrast, impaired M2-mediated resolution contributes to persistent, unresolved inflammation. T cells—particularly Th1 and Th17 subsets—accumulate within the synovium and release IFN- γ and IL-17A, amplifying macrophage activation and promoting chondrocyte catabolism (9). Meanwhile, regulatory T cells (Tregs), which normally suppress excessive immune responses, are reduced or functionally impaired in OA. These immune cell interactions reinforce the catabolic milieu and represent critical therapeutic targets for immunomodulatory and cell-based interventions discussed in subsequent sections.

In addition to immune cell dysregulation, several molecular mediators serve as key therapeutic targets in OA. Pro-inflammatory cytokines such as IL-1 β , TNF- α , IL-6, and IL-17A play central roles in driving synovitis, promoting chondrocyte catabolism, and accelerating extracellular matrix (ECM) degradation (10). These cytokines activate multiple downstream pathways, including NF- κ B and MAPK signaling, thereby amplifying inflammatory cascades and inhibiting chondrogenesis (11). Emerging evidence also highlights the involvement of mechanistic targets such as the NLRP3 inflammasome, oxidative stress regulators like NOX4, and mechanosensitive channels (Piezo1/2), all of which contribute to disease progression and represent promising points of therapeutic intervention.

Immunomodulatory therapies: basic and preclinical evidence

Many EV- and miRNA-based therapeutic strategies exert their effects by targeting specific cytokines, signaling pathways, and stress-related molecular regulators involved in OA progression. These include inhibition of IL-1 β - and TNF- α -mediated inflammation, suppression of NF- κ B and MAPK activation, activation of autophagy through modulation of mTOR, and regulation of mechanosensitive or oxidative pathways, such as Piezo1/2 and NOX4.

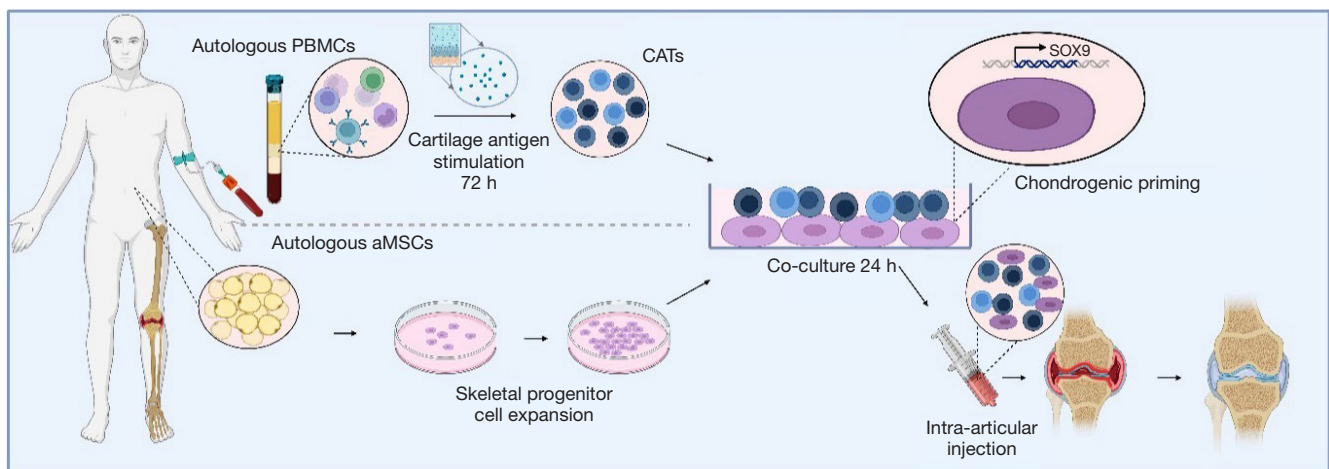


Figure 1 Schematic overview of the immunomodulatory concept to restore synovial joint homeostasis in OA patients via autologous IA injection therapy. Mechanistic studies using synovial fluid-derived cells from OA patients revealed impaired regenerative potential in the presence of autologous SF. Insights from these findings guided the design of an immunomodulatory cell therapy based on peripheral blood-derived mononuclear cells that was activated to become CATs, which, upon 24 h co-culture with autologous aMSCs, drove the chondrogenic programming of the aMSCs. Upon IA injection, the dual cell therapy was shown to restore a pro-regenerative joint environment and ultimately joint homeostasis. Intra-articular injection in a compassionate use study demonstrated restoration of cartilage and joint homeostasis, highlighting the therapeutic relevance of immune-progenitor cell interactions in OA. aMSCs, adipose-derived mesenchymal stem cells; CATs, cartilage-activated T cells; IA, intra-articular; OA, osteoarthritis; PBMC, peripheral blood mononuclear cell; SF, synovial fluid.

Immunomodulatory cell therapies

Immunomodulatory cell therapies were recently addressed in a study by Bolander *et al.* (12), which has advanced our understanding of the synovial microenvironment in OA, demonstrating its dual role as both a contributor to cartilage degeneration and a barrier to endogenous repair (Figure 1). Specifically, the authors reveal that the synovial fluid of OA patients contains molecular cues that actively suppress the regenerative potential of local progenitor cells, thereby perpetuating joint deterioration. Using *in vitro* assays with human patient-derived cells and *in vivo* animal models, the study shows that although synovial-resident progenitor cells retain the intrinsic capacity to migrate, proliferate, and differentiate into cartilage-forming cells under standard culture conditions, exposure to synovial fluid from OA joints significantly impairs these functions. The synovial fluid was found to inhibit cell migration into cartilage defects, limit clonal expansion, and suppress the expression of chondrogenic markers such as SOX9 and PRG4. In contrast, it promoted expression of pro-fibrotic genes, suggestive of a pathological shift toward fibrosis rather than cartilage regeneration. Further, proteomic and cytokine profiling revealed a pro-inflammatory milieu

within OA synovial fluid, characterized by elevated levels of IL-6, IL-17A, and TNF- α , alongside a relative deficiency in immunoregulatory and regenerative mediators such as IL-2, IL-4, and IL-10. This unbalanced immune environment was shown to reprogram the fate of progenitor cells, undermining their reparative capabilities.

To overcome this hostile microenvironment, the authors developed a novel immunomodulatory cell therapy based on autologous peripheral blood-derived mononuclear cells, which were activated with cartilage antigen for 72 h to become cartilage-activated T cells (CATs) that secrete anti-inflammatory cytokines and cartilage-related proteins. Upon 24 h co-culture with autologous adipose-derived mesenchymal stem cells (aMSCs), the CATs initiated the chondrogenic differentiation program in the aMSCs. This combinatorial approach aimed to restore immune homeostasis and reestablish conditions that enable cartilage repair. In a rat model of OA, intra-articular (IA) injection of the combined cell therapy led to superior outcomes compared to either cell type alone, including restoration of cartilage thickness and structure, reduction of synovitis, and preservation of subchondral bone integrity. Next, the authors tested therapeutic efficacy in a compassionate-use trial in a small cohort of 9 patients with advanced

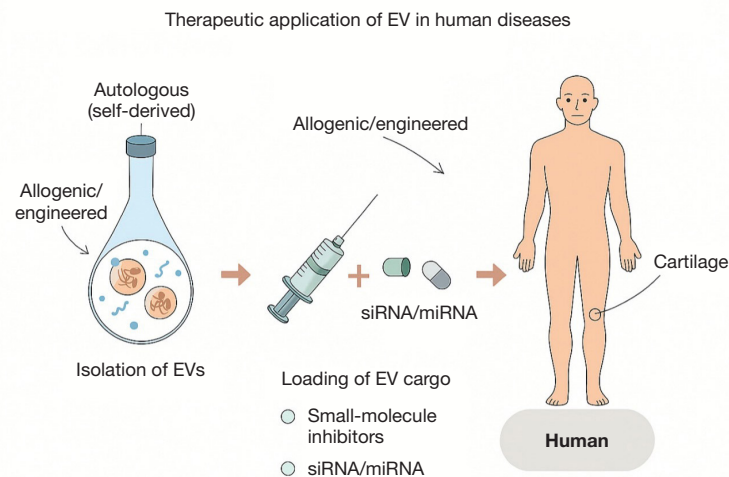


Figure 2 The basic therapeutic workflow of EV-based treatment. An illustrative overview of the basic therapeutic workflow of EV-based treatments, including EV isolation, cargo loading, and targeted delivery to affected cartilage tissues. A growing body of preclinical evidence has confirmed that both native and engineered EVs can delay OA progression and promote cartilage repair. The following sections summarize representative preclinical studies, categorized by EV source, animal models, and mechanisms of action. EV, extracellular vesicle; OA, osteoarthritis.

OA, further supporting the translational potential of this approach. Patients receiving the dual cell therapy exhibited sustained reductions in joint pain, improved mobility, and signs of cartilage repair on MRI and radiography up to 1 year post-treatment. Notably, these benefits were observed in individuals who had previously failed conventional treatments such as corticosteroid injections, arthroscopy, or physiotherapy. The implications of this work are significant: it reframes OA not merely as a disease of cartilage wear and tear, but as a condition driven by a chronically dysregulated immune environment that must be therapeutically addressed to enable regeneration. Furthermore, the reported findings suggest that immunomodulation—specifically targeting the synovial niche—may be a necessary adjunct to any regenerative strategy aimed at restoring joint integrity.

The immunoregulatory activity of CAT therapy aligns with these therapeutic targets by suppressing IL-1 β and TNF- α , downregulating NF- κ B signaling, and promoting a shift toward anti-inflammatory and regenerative cytokine profiles, such as IL-10.

Taken together, this study provides compelling evidence for the active role of synovial fluid in steering joint pathology and repair, and it introduces a promising therapeutic avenue that leverages immune-engineered cell therapy to tip the balance from degeneration to regeneration.

Extracellular vesicle (EV) and miRNA-based therapies: preclinical evidence

In recent years, EVs, particularly those derived from mesenchymal stem cells (MSCs), have emerged as a promising cell-free therapeutic strategy for OA (Figure 2). Due to their ability to carry bioactive molecules such as miRNAs, lncRNAs, and proteins, EVs can regulate cartilage metabolism, immune-inflammatory responses, and tissue regeneration, making them a research hotspot in OA therapy. According to recent studies, EVs can be isolated from autologous or allogeneic sources. They can be further engineered to load specific nucleic acids or small-molecule drugs, thereby enhancing their therapeutic efficacy. Representative preclinical studies investigating EV- and miRNA-based therapies for OA are summarized in Table 1.

Targeting inflammation and pyroptosis: EVs as immunomodulators

Chronic inflammation plays a crucial role in the progression of OA. Several studies explored how EVs enriched with anti-inflammatory miRNAs can attenuate local joint inflammation: MiR-223 in engineered MSC-EVs suppressed NLRP3 inflammasome activation, reduced IL-1 β , and inhibited pyroptosis, showing precision control over inflammatory cell death mechanisms (13). MiR-21

Table 1 Pre-clinical studies on immunomodulatory therapies

EV source	Model type	Main findings	Mechanism/miRNA	Reference
Umbilical-MSC EVs (miR-223)	Rat + <i>in vitro</i> chondrocytes	miR-223 EVs target NLRP3, reduce joint inflammation and cartilage degeneration	miR-223 → ↓ NLRP3 inflammasome → ↓ inflammation	Liu, Liu (13)
BM-MSC-Exos (miR-21)	Rat OA + <i>in vitro</i>	EVs-miR-21 downregulated miR-21 and TLR7, reduced IL-1 β and TNF- α levels, increased IL-4 and IL-10 expression, and alleviated cartilage inflammation and oxidative stress	miR-21 ↓ → inhibits TLR7 → anti-inflammatory	El-Din, Aboulhoda (14)
hBMSC-Exos (miR-361-5p)	Rat ACLT-induced OA model combined + IL-1 β -stimulated chondrocytes	Exosomes derived from hBMSCs enriched with miR-361-5p downregulate DDX20, inhibit the NF- κ B signaling pathway, significantly reduce MMPs (such as MMP-13) and inflammatory factors (IL-6, TNF- α , iNOS), thereby alleviating cartilage degeneration	miR-361-5p → ↓ DDX20 → ↓ NF- κ B	Tao, Zhou (15)
Synovial fluid EVs (miR-182-5p)	Human plasma samples + OA mouse model	The level of miR-182-5p is elevated in synovial fluid EVs, which promotes chondrocyte autophagy (via LC3 signaling) and targets TNFAIP8 to alleviate cartilage degeneration	miR-182-5p → inhibits TNFAIP8 → ↑ Mitophagy	Ji, Xiong (16)
Synovial fibroblast-EVs (miR-126-3p)	Rat ACLT OA + human chondrocytes	EVs-miR-126-3p downregulates IL-1 β , TNF- α , and MMP-13; promotes chondrocyte proliferation and migration; enhances COL2A1 expression; and inhibits osteophyte formation	miR-126-3p → anti-inflammatory → ↑ COL2A1	Zhou, Ming (17)
BM-MSC-Exos (miR-9-5p)	Rat ACLT OA	Bone marrow MSC-derived exosomes enriched with miR-9-5p, when injected into OA joints, significantly reduce inflammatory cytokines (IL-1, IL-6, TNF- α), oxidative stress markers (NO, MDA, iNOS, COX2), and cartilage degradation indicators (MMP-13, COMP, and AKP), thereby alleviating cartilage degeneration	miR-9-5p → ↓ Syndecan-1 → anti-inflammatory	Jin, Ren (18)
Synovial MSC-EVs (miR-155-5p)	Rat OA + IL-1 β treated cells	miR-155-5p EVs promote proliferation/migration, reduce apoptosis, enhance ECM secretion	miR-155-5p → anti-apoptosis → ↑ proliferation & ECM	Wang, Yan (19)
BMMSC-EVs (miR-92a-3p)	<i>In vitro</i> + mouse cartilage injury model	miR-92a-3p EVs downregulate WNT5A, promote COL2A1/SOX9/COMP expression, slow OA progression	miR-92a-3p ↓ WNT5A → inhibits ECM degradation	Mao, Zhang (20)
BMMSC-EVs (miR-136-5p)	<i>In vitro</i> + traumatic OA mouse model	miR-136-5p targets ELF3, promotes COL2A1/aggrecan/SOX9, inhibits MMP-13, delays cartilage degeneration	miR-136-5p → inhibits ELF3 → ↑ COL2A1/aggrecan/SOX9, ↓ MMP-13 → slows down cartilage degeneration	Chen, Shi (21)
BM-MSC-Exos (miR-127-3p)	IL-1 β chondrocytes (rat)	Exosomes derived from BM-MSCs enriched with miR-127-3p can target and inhibit CDH11 expression, block activation of the Wnt/ β -catenin signaling pathway, significantly enhance chondrocyte viability and proliferation, and reduce IL-1 β -induced MMP-13 expression and cell apoptosis	miR-127-3p → ↓ CDH11 → Wnt/ β -catenin block → ECM ↑	Dong, Li (22)
miR-140-5p SMSC-Exos	Mouse OA + <i>in vitro</i>	miR-140-5p-enriched exosomes enhance chondrocyte proliferation and migration, prevent ECM loss, and alleviate OA via the RalA-Wnt-YAP signaling pathway	miR-140-5p → ↓ RalA → activates YAP	Tao, Yuan (23)
miR-140-5p DPSC-Exos	Rat IL-1 β OA model (<i>in vitro</i> + <i>in vivo</i>)	Exosomes derived from DPSC enriched with miR-140-5p significantly reduce chondrocyte apoptosis, enhance the expression of COL2A1, aggrecan, and SOX9, and improve OA histological scores	miR-140-5p → anti-apoptosis, ECM stabilization	Lin, Wu (24)

Table 1 (continued)

Table 1 (continued)

EV source	Model type	Main findings	Mechanism/miRNA	Reference
Hypoxia-preconditioned MSC-EVs	Rat model + <i>in vitro</i> chondrocytes	EVs rich in miR-122-5p promote autophagy/proliferation, reduce cartilage damage and OARSI score	miR-122-5p → DUSP2 → ERK1/2 & p38 → ↑ Mitophagy	Zhang, Yang (25)
IPFP-MSC-EVs (miR-100-5p)	Mouse DMM OA + human chondrocytes	miR-100-5p EVs inhibit mTOR-Mitophagy, slow OA progression, improve cartilage structure and gait	miR-100-5p → inhibits mTOR → activates mitophagy	Wu, Kuang (26)
BMSC-Exos (lncRNA MEG3)	Mouse OA + IL-1 β	EVs enriched with lncRNA MEG3 can inhibit IL-1 β -induced inflammation and apoptosis in chondrocytes, significantly enhance the expression of COL2A1 and aggrecan, reduce ECM degradation, and improve OA	MEG3 → anti-inflammatory/apoptotic → ↑ ECM	Wang, Hu (27)
hUCMSC-Exos (miR-100-5p)	Human chondrocytes <i>in vitro</i>	hUCMSC-derived exosomes enriched with miR-100-5p inhibit NOX4 expression, reduce ROS production and apoptosis, improve ECM stability, protect cartilage structure, and alleviate osteoarthritic lesions	miR-100-5p → ↓ NOX4 → ↓ ROS → Protect ECM	Li, Wang (28)
KGN-BMSC-Exos	Mouse OA + <i>in vitro</i>	KGN pretreatment ↑ SOX9/COL2A1 in EVs, enhances cartilage repair	KGN → ↑ ECM expression	Liu, Li (29)
BMMSC-EVs	Mouse DMM OA	Homologous MSC-EVs slow OA progression and improve cartilage structure	No specific miRNA reported; EV efficacy related to age	Wakale, Chen (30)
BMSC-Exos (miR-206)	Rat ACLT OA model + osteoblasts (<i>in vitro</i>)	EVs derived from bone marrow MSCs enriched with miR-206 can promote osteoblast proliferation and differentiation by downregulating E1f3 expression, enhancing bone formation potential, and thereby improving the pathological condition of OA	miR-206 → ↓ E1f3 → ↑ osteogenesis genes (Runx2, COL1A1)	Zhang, Wang (31)
hUCMSC-Exos miR-140-3p	Rat RA model	Although based on a RA model, the study also demonstrated that miR-140-3p-enriched exosomes effectively inhibited joint inflammation and cartilage destruction, providing valuable insights for OA treatment	miR-140-3p → ↓ SGK1 → anti-inflammatory	Huang, Chen (32)
Synovial fibroblast-EVs (miR-214-3p)	Human OA synovial fluid + rat ACLT/MMx	In OA patients, miR-214-3p is significantly downregulated in synovial fluid-derived EVs; supplementation of miR-214-3p can reduce inflammation and enhance chondrocyte survival	miR-214-3p ↓ → ↑ inflammation; supplementation → reverses	Lai, Liao (33)
ESC-MSC-Exos	Mouse ACLT OA	ESC-MSC-Exos activate AKT/ERK/AMPK, ↓ MMP-13, ↑ COL2A1/S-GAG, improve ECM	AKT/ERK/AMPK ↑ → ECM protection	Jeyaraman, Muthu (34)
UC-MSC-sEVs (GMP)	OA mouse + IA	sEVs induce M2 polarization, cartilage regeneration, no adverse events in 12 months	M2 polarization → regeneration	Figueroa-Valdés, Luz-Crawford (35)
hUCMSC-Exos (review)	OA animal review	MSC-derived exosomes demonstrate therapeutic potential by modulating inflammation, immunity, ECM, and bone metabolism, but further engineering is needed to optimize their delivery efficiency	General miRNA cargo	Wu, Li (36)
SMMSC-Exos	Mouse OA	EVs improved ICRS scores, reduced OARSI scores and cartilage fissures, and enhanced COL2A1 expression	No miRNA focus; unengineered EVs	Ni, Zhou (37)

↓, decrease; ↑, increase. ACLT, anterior cruciate ligament transection; BM-MSCs, bone marrow mesenchymal stem cells; DMM, destabilization of the medial meniscus; ECM, extracellular matrix; GMP, Good Manufacturing Practice; hUCMSC, human umbilical cord mesenchymal stem cells; IA, intra-articular; ICRS, International Cartilage Repair Society; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; mTOR, mechanistic target of rapamycin; NLRP3, NOD-like receptor family pyrin domain containing 3; NOX4, NADPH oxidase 4; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; RA, rheumatoid arthritis; sEV, small extracellular vesicle; SMMSC, synovial membrane mesenchymal stem cells.

and miR-361-5p, delivered via BMSC-EVs, respectively modulated TLR7 and NF- κ B signaling, leading to decreased pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and oxidative stress (14,15). MiR-126-3p (from synovial fibroblast-EVs) and miR-182-5p (from synovial fluid EVs) also showed strong anti-inflammatory effects, downregulating MMP-13 and enhancing autophagy via LC3 signaling (16,17). MiR-9-5p-enriched BMMSC-EVs significantly decreased inflammatory markers and cartilage degradation enzymes (e.g., MMP-13, COMP) in rat ACLT models (18). Additionally, EVs derived from synovial MSCs enriched with miR-155-5p have demonstrated significant anti-inflammatory and tissue-reparative effects in both *in vitro* and *in vivo* studies. Through promoting chondrocyte proliferation and migration, inhibiting apoptosis, and enhancing ECM secretion, these EVs effectively delay the progression of OA (19). These studies underline the role of EVs as targeted immunomodulators, shifting the joint microenvironment from a pro-inflammatory to a reparative state.

Promoting ECM synthesis and cartilage regeneration: direct matrix modulation

Another primary strategy involves enhancing the production and stability of cartilage ECM: EVs carrying miR-92a-3p, miR-136-5p, or miR-127-3p promoted the expression of chondrogenic markers such as COL2A1, aggrecan, and SOX9 while inhibiting catabolic genes such as MMP-13 and WNT5A (20-22). miR-140-5p, one of the most frequently studied miRNAs in OA, enhanced chondrocyte proliferation, inhibited ECM loss, and activated RalA-Wnt-YAP signaling (in SMSC-derived exosomes) or suppressed apoptosis (in DPSC-derived exosomes) (23,24). miR-95-5p, derived from primary chondrocyte EVs, targeted HDAC2/8 and induced hMSC chondrogenic differentiation, contributing to both cartilage repair and EV source specificity (24).

Collectively, these approaches demonstrate that EV-based miRNA delivery can directly regulate ECM turnover and shift the balance toward cartilage regeneration.

Activating autophagy and mitophagy: a metabolic reprogramming approach

Recent insights have highlighted the role of cellular metabolism and mitochondrial quality control in OA. Several EVs demonstrated therapeutic effects through activation of autophagy and mitophagy: MiR-122-5p enriched EVs (from hypoxia-preconditioned MSCs)

promoted mitophagy via the DUSP2-ERK1/2-p38 axis, reducing OARSI scores in rats (25). miR-100-5p, delivered via both IPFP-MSC-EVs and hUCMSC-EVs, consistently activated mitophagy and suppressed mTOR or NOX4 signaling, thereby reducing ROS accumulation and preventing cartilage apoptosis (26-28). miR-182-5p, found elevated in human OA synovial fluid EVs, further supported the role of LC3-dependent autophagy in cartilage preservation (16).

This theme illustrates how EVs can be employed not only to inhibit inflammation or ECM degradation but also to correct energy imbalance and mitochondrial dysfunction in OA chondrocytes.

Cell-specific engineering and functional enhancement of EVs

To enhance therapeutic specificity and potency, multiple studies modified the EV source cells or preconditioned them: Kartogenin (KGN) treatment of BMSCs resulted in EVs enriched in SOX9 and COL2A1, effectively enhancing ECM production in OA cartilage (29). Hypoxia conditioning and dual-targeted EVs (e.g., miR-223 with cartilage-targeting peptide) further demonstrated that functional optimization strategies could significantly amplify regenerative outcomes (13,25). Comparative studies, such as that by Wakale *et al.*, also found that young-donor MSC-EVs were more effective than aged counterparts in protecting cartilage, indicating donor factors influence EV efficacy (30). Notably, miR-206 has also been identified as a promising molecule enriched in BMMSC-derived EVs. It enhances osteogenesis and improves OA-related osteochondral interface changes by downregulating ELF3 and activating osteogenic genes, such as Runx2 and COL1A1 (31).

These studies represent a shift from generic EV therapy to tailored, engineered vesicle-based delivery platforms, setting the stage for clinical-grade precision therapeutics.

The role of miR-140 family: a conserved cartilage-protective axis

Among the various miRNAs explored in OA-related EV therapy, the miR-140 family (miR-140-5p and miR-140-3p) stands out as one of the most consistently cartilage-protective and mechanistically versatile.

In one study, synovial mesenchymal stem cell (SMSC)-derived EVs were engineered to overexpress miR-140-5p, which suppressed RalA and activated downstream YAP signalling. These changes enhanced chondrocyte

proliferation and migration, and preserved ECM integrity in both *in vitro* and *in vivo* models (23). Similarly, dental pulp stem cell (DPSC)-derived exosomes enriched with miR-140-5p reduced IL-1 β -induced chondrocyte apoptosis, increased COL2A1, aggrecan, and SOX9 expression, and improved histological OA scores in rat models (24). Beyond OA-specific models, miR-140-3p derived from hUCMSC-EVs was shown to silence SGK1 in a rheumatoid arthritis (RA) model. This pathway led to suppressed joint inflammation and cartilage destruction. Although the study was RA-focused, the mechanism holds translational promise for OA, especially given the role of SGK1 in inflammation and cell survival (32).

Collectively, these findings position miR-140 as a “core” miRNA in cartilage homeostasis, acting via multiple axes—including anti-apoptotic, ECM-stabilizing, and signalling modulation effects. Its repeated validation across different stem cell sources and disease models suggests high translational value and encourages further exploration as a standardized EV cargo in OA therapy.

Beyond MSCs: alternative EV sources and translational steps

While most EVs were derived from MSCs, several studies explored alternative sources or clinical translation strategies: synovial fibroblast-derived EVs (e.g., with miR-214-3p) and primary chondrocyte-derived EVs (e.g., with miR-95-5p) offer tissue-specific advantages and target disease-relevant pathways (24,33). ESC-MSC-EVs, activating AKT/ERK/AMPK signaling, provided broad-spectrum ECM protection in OA joints (34). GMP-compliant UC-MSC-sEVs, tested in long-term mouse studies, demonstrated excellent safety and regenerative effects without adverse outcomes, signaling readiness for clinical translation (35). Furthermore, the review study further highlights the multifunctionality of EVs in the treatment of OA, including their critical roles in suppressing oxidative stress, modulating immune responses, and reconstructing the joint microenvironment, thereby providing a theoretical basis for the standardized development of EV-based therapies (36,37).

These findings highlight that the field is expanding beyond the traditional MSC-EV paradigm and moving toward source optimization and clinical feasibility.

PBSCs: biological rationale

Mesenchymal stromal cells have shown promise in pre-clinical OA models, reducing synovial inflammation and

preserving cartilage integrity by secreting anti-inflammatory mediators such as IL-10 and TGF- β . Early-phase clinical trials demonstrate safety and symptomatic improvement, but structural outcomes remain variable. Other cell therapies, including regulatory T cells and macrophage reprogramming approaches, are in early exploratory phases.

PBSC-assisted regeneration may also exert therapeutic effects by modulating inflammatory cytokines and activating signaling pathways that support cartilage repair, including suppression of NF- κ B signaling and enhancement of anabolic pathways involved in matrix synthesis.

A study conducted by Saw *et al.* aimed to evaluate the safety and efficacy of IA injections of autologous PBSCs plus hyaluronic acid (HA) after arthroscopic subchondral drilling to treat massive chondral defects in the knee joint (38) (*Figure 3*). The randomized controlled trial included 69 patients aged 18 to 55 with grade 3 and 4 chondral lesions. Patients were divided into two groups: a control group receiving HA plus physiotherapy and an intervention group receiving arthroscopic subchondral drilling followed by PBSCs plus HA injections. Starting on the fourth postoperative day, patients received subcutaneous filgrastim injections for 3 consecutive days. On the seventh postoperative day, PBSCs are collected from the patient's blood through apheresis. This involves drawing blood from the patient, separating the stem cells, and returning the remaining blood components to the patient. The collected PBSCs are then cryopreserved (frozen) for future use. All patients received 14 IA injections in total over 18 months. For the intervention group, on postoperative day 7, an 8 mL fresh PBPC aliquot was mixed with 2 mL HA and injected into the operated knee joint under aseptic conditions in the outpatient clinic immediately after the apheresis process. This was performed supine via a superolateral approach without ultrasound guidance. Postoperative hemarthrosis was aspirated before each injection. At four subsequent weekly intervals, an 8-mL aliquot of the frozen PBSCs was thawed to room temperature, mixed with 2 mL of HA, and injected into the operated knee joint. At 6-, 12-, and 18-month following surgery, three additional weekly IA injections comprising 4 mL thawed cryopreserved PBSCs and 2 mL HA were given. The control group received 2 mL HA for each IA injection at the same time points as the intervention group, as seen in *Figure 3*. Any knee effusion was first aspirated before the injections. The primary endpoints were the International Knee Documentation Committee (IKDC) and Knee Injury and OA Outcome Score (KOOS) pain subdomain at 24 months. Secondary

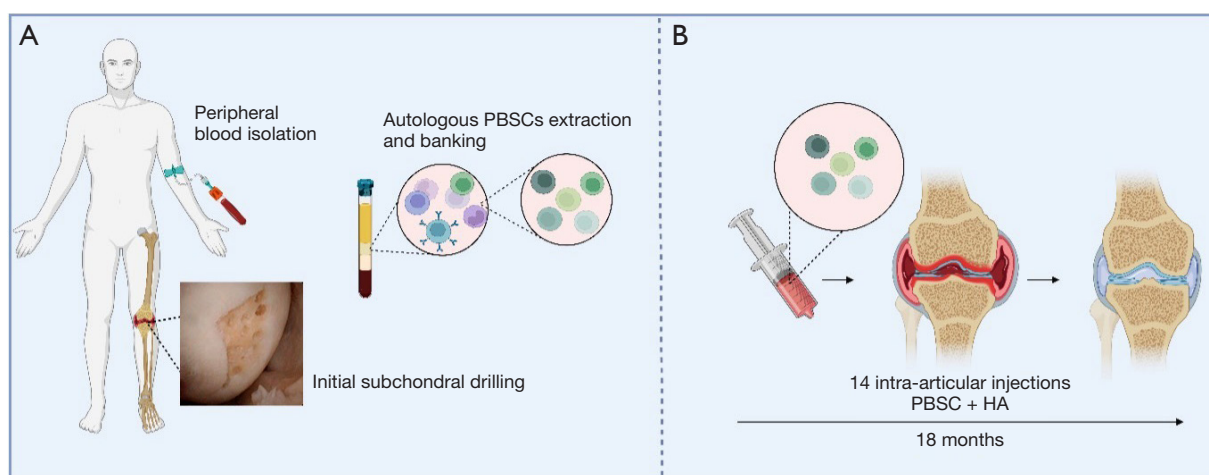


Figure 3 Schematic overview of autologous PBSC injection therapy by Saw *et al.* (38). (A) Overview of the randomized controlled trial evaluating IA injections of autologous PBSCs combined with HA following arthroscopic subchondral drilling for the treatment of massive chondral defects in the knee. A total of 69 patients (aged 18–55 years) with grade 3–4 chondral lesions were enrolled. (B) Results demonstrated significant clinical and radiological improvements in the intervention group compared with controls. At 24 months, the PBSC + HA group showed higher mean IKDC and KOOS-pain scores, with all KOOS subdomains, NRS, and MOCART scores significantly improved. The treatment was safe, with no unexpected adverse events, and outperformed HA plus physiotherapy; however, full restoration of the osteochondral unit was not achieved, remaining a limitation for younger patients. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and OA Outcome Score; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; NRS, Numeric Rating Scale; PBSC, peripheral blood stem cell.

endpoints included other KOOS subdomains, the Numeric Rating Scale (NRS) for pain, and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores. Results showed significant improvements in the intervention group compared to the control group. At 24 months, the intervention group had higher mean IKDC and KOOS-pain scores, and all other KOOS subdomains, NRS, and MOCART scores were statistically significant. The study concluded that the PBSCs plus HA treatment is safe and more effective than HA plus physiotherapy in improving clinical and radiologic outcomes for massive knee chondral defects. No unexpected adverse events were reported. However, complete restoration of the osteochondral unit was not observed and would remain an issue for younger patients.

Clinical translation of immunomodulatory and cell-derived therapies

In recent years, EV-based therapies have steadily progressed from bench to bedside. An increasing number of clinical trials are exploring the potential of EVs in treating OA. Most current studies focus on MSC-derived EVs,

particularly those from umbilical cord, placenta, and bone marrow. These EVs are typically administered via IA injection and have shown promising effects in cartilage repair, inflammation suppression, and immune modulation. An overview of representative clinical trials evaluating EV-based and cell-derived therapies for knee OA is provided in Table 2.

As of 2025, more than ten clinical trials involving EV-based therapies for OA have been registered on ClinicalTrials.gov. Some phase I/II trials have already published results, consistently reporting favorable safety profiles with no serious adverse events (SAEs) and improvements in pain relief, physical function, and imaging outcomes. In a first-in-human trial of umbilical cord MSC-derived EVs for knee OA, patients demonstrated sustained improvements in pain and function over a 12-month follow-up period, and MRI findings indicated partial preservation of cartilage (39). A separate randomized controlled trial using placenta-derived MSC-EVs also showed significant improvement in WOMAC scores with no serious adverse effects (40). In another study, ExoFlo—a placenta MSC-derived EV formulation—effectively reduced pain and levels of inflammatory cytokines such as IL-1 β and CRP in a phase

Table 2 Clinical studies on immunomodulatory cell therapies

Source of EVs	Study type/phase	Primary outcome	Mechanism/research focus	Reference/ registration number
Allogeneic MSC-sEVs	Phase I—preclinical safety assessment (mouse model) + safety of IA injection in humans	MSC-derived sEVs induced M2 macrophage polarization in synovial tissue in the ACLT mouse model of OA. In the first human OA patient receiving IA injection, no SAEs were observed during 12-month follow-up, indicating good tolerability	STAT1-mediated synovial M2 macrophage polarization → modulation of joint microenvironment and promotion of regeneration	Figuerola-Valdés, Luz-Crawford (35)
Allogeneic UC-MSC sEVs	Phase II exploratory dose-escalation IA injection	To evaluate safety and tolerability of different doses, used a three-arm design (low/medium/high dose), with 4 patients in each group (12 patients total). Safety outcomes (SAE rate) and preliminary efficacy were assessed (WOMAC score)	Anti-inflammatory effect + modulation of joint microenvironment to promote cartilage regeneration	NCT06431152 (35)
UC-MSC-sEV (clinicalgrade-)	Phase I, open-label-dose-escalation	Single intra-articular injection; 12 patients planned for enrollment, with 12-month follow-up. Currently, no published data; safety monitoring is ongoing		NCT06431152 (35)
Placental MSC-EVs (ExoFlo)	Phase I/II triple-arm randomized controlled trial (placebo-controlled)	WOMAC total score decreased by 25% ($P<0.01$), with pain improvement of 30% and functional improvement of 20%. VAS score decreased by an average of 3.5 points. No serious adverse events occurred within 4 months; only mild local discomfort was reported. Levels of IL-1 β and CRP decreased significantly	Anti-inflammatory effects ($\downarrow$ IL-1 β , $\downarrow$ TNF- α), cartilage protection, and improved joint microenvironment	Wang, Kong (39)
UC-MSC-Exos	First-in-human clinical validation study	This study evaluated the safety and preliminary efficacy of intra-articular injection of UC-MSC-derived exosomes in patients with moderate-to-severe knee OA. No serious adverse events were observed within 12 months. MRI in some patients indicated a trend toward cartilage edge regeneration, with a 15–25% reduction in WOMAC scores and significant improvement in VAS pain scores	EVs exert anti-inflammatory effects, induce M2 macrophage polarization in the synovium, modulate the immune microenvironment, and promote cartilage regeneration	Wang, Kong (39)
Placental MSC-EVs	Randomized, double-blind, placebo-controlled phase III clinical trial	OA patients receiving IA injection showed significant improvement in WOMAC pain and function scores (approximately 20–30%). No SAEs, local infections, or immune reactions were observed during the 4-month follow-up	EVs exert anti-inflammatory and chondroprotective effects by modulating the synovial microenvironment through downregulation of inflammatory cytokines such as IL-1 β and TNF- α	Carneiro, Araújo (40)
Cellstem-OA (umbilical cord-derived MSC extracellular vesicles)	Randomized, double-blind Phase I/II clinical trial (human)	Single IA injection; no SAEs within 12 months. Significant improvement in WOMAC, NRS, and SF-36 scores ($P<0.05$); MRI WOMS scores showed no signs of degeneration	Anti-inflammatory effects and regenerative potential	Pico, Espinoza (41)

Table 2 (continued)

Table 2 (continued)

Source of EVs	Study type/phase	Primary outcome	Mechanism/research focus	Reference/ registration number
EV/KneeUJCTC (MSCEVs-)	Phase I IA injection trial	Planned enrollment of 50 patients with KL grade III–IV knee OA; received two doses of EV IA injection; evaluated safety, MRI structural changes, and clinical outcome scores	Anti-inflammatory effect + ECM remodeling	NCT06937528 (42)
Porcine MSC-Exos	Preclinical (porcine model)	In a cartilage defect model, MSC-Exos significantly promoted cartilage repair and tissue regeneration, improved structural integrity, and showed positive results in clinical scoring and MRI assessments	Enhanced extracellular matrix synthesis, inhibited apoptosis, and promoted cell migration	Zhang, Wong (43)
hESC-MSC Exos	Preclinical (rat model)	Stem cell-derived exosomes (Exos) significantly promoted cartilage/bone defect repair at 6–12 weeks, with tissue architecture approaching normal. M2 macrophages increased, while M1 macrophages decreased	Mediated through the AKT/ERK/AMPK signaling pathway, contributing to ECM remodeling	Zhang, Chuah (44)
Autologous MSCs (non-EV)	Phase I–II clinical trial	Intra-articular injection of <i>ex vivo</i> expanded autologous MSCs was safe and associated with pain reduction and MRI-based evidence of cartilage regeneration in knee OA patients	Cartilage repair and regeneration; clinical safety and feasibility	Soler <i>et al.</i> , 2016 (45)
Mesenchymal stem cell exosomes	Systematic review and meta-analysis (preclinical animal studies)	A total of 13 animal studies involving 434 animals were included. MSC-Exos significantly improved cartilage damage and tissue structure. The average OARSJ score decreased by approximately 3.54 ($P < 0.00001$). Inflammatory and pain-related symptoms in the animal models were generally alleviated	Promoted cartilage cell proliferation, enhanced ECM deposition, and reduced inflammatory factors (IL-1 β , MMP-13)	Tan, Tjio (46)
Autologous BM-MSCs (XCEL-M-ALPHA)	Open-label prospective cohort study, Phase I/II	After IA injection, patients were followed for 12 months: VAS pain scores improved significantly (from day 8, lasting for 12 months); SF-36 quality-of-life scores increased; WOMAC and Lequesne functional scores decreased; MRI T2-mapping showed cartilage regeneration trends	Enhanced cartilage matrix content + long-term pain relief	NCT01183728 (47)
BM-MSC ExoFlo	Phase I/II – completed	Participants: 33 patients (58 knees); results (after 6 months): BPI $\downarrow$ 77%, LEFS/ODI $\uparrow$ 76–80% ($P < 0.001$); 95% of improvement occurred within the first 6 weeks; only mild local side effects (4 with joint pain, 1 with back pain, 1 with dry eyes); no SAEs		Dordevic and East (48)

↓, decrease; ↑, increase. ACLT, anterior cruciate ligament transection; BM-MSCs, bone marrow mesenchymal stem cells; CRP, C-reactive protein; ECM, extracellular matrix; EV, extracellular vesicle; IA, intra-articular; IL, interleukin; KL, Kellgren-Lawrence; LEFS, lower extremity functional scale; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; MSC-Exos, MSC-derived exosomes; NRS, Numeric Rating Scale; OA, osteoarthritis; OARSJ, Osteoarthritis Research Society International; ODI, Oswestry Disability Index; SAEs, serious adverse events; sEV, small extracellular vesicle; TNF- α , tumor necrosis factor alpha; UC-MSCs, umbilical cord mesenchymal stem cells; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities OA Index.

I/II trial (39). Other approaches include cryopreserved umbilical cord MSC-EVs (Cellistem-OA), which in early trials significantly improved WOMAC, SF-36, and MRI WOMS scores (41). Additionally, small extracellular vesicles (sEVs) have shown immunomodulatory activity by inducing M2 macrophage polarization via STAT1 signaling in both animal and early human studies (35).

Several phase II/III trials are currently underway (e.g., NCT06431152, NCT06937528) to further define optimal dosage, delivery strategies, and structural cartilage endpoints. Despite encouraging progress, challenges remain in GMP-grade manufacturing, large-scale production, and regulatory approval. Beyond published data, multiple trials are in the registration or implementation phase, such as EXO-OA01 and EV-for-Knee-Osteoarthritis, which aim further to assess EV safety, dosing, and structural improvement (35,42). These efforts reflect growing global interest in EV-based OA therapies. Some preclinical findings have also been extended to large animal models. For example, Zhang *et al.* demonstrated that MSC-derived EVs promoted functional osteochondral repair in a porcine OA model, supporting their translational potential (43). Earlier studies by the same group also showed that EVs facilitate cartilage regeneration by enhancing chondrocyte proliferation, reducing apoptosis, and modulating immune responses (44).

Although not EV-based, a well-known clinical study by Soler *et al.* used autologous MSC injections to promote cartilage regeneration successfully and demonstrated good safety outcomes in OA patients (45), serving as a valuable clinical comparator for EV therapies. In addition, an IRB-approved pilot safety study in the U.S. applied EV therapy to patients with post-traumatic OA, offering early support for the use of EVs in OA subtypes beyond idiopathic knee OA.

Finally, a systematic review by Tan *et al.* summarized key preclinical and early clinical trials of EV-based interventions for OA, providing a strong rationale for ongoing development in this field (46).

Challenges and limitations

Despite promising preclinical and early clinical data, several challenges and limitations must be addressed before immunomodulatory cell and cell-derived therapies can be widely implemented in clinical practice. Safety: for cell-based therapies, potential risks include immunogenicity, ectopic tissue formation, and malignant transformation, particularly when using highly proliferative cells or iPSC-

derived products. Long-term follow-up data are still limited, and most clinical trials have relatively small sample sizes and short observation periods. For EV-based products, the complex cargo composition and the possibility of transferring oncogenic or pro-inflammatory molecules also raise safety concerns. Standardized protocols for donor screening, viral testing, and long-term pharmacovigilance are needed to ensure patient safety. Efficacy and durability: although many studies report improvements in pain and function, robust evidence for sustained structural modification of OA is still scarce. The heterogeneity of patient populations (age, BMI, disease stage, comorbidities) and of outcome measures (clinical scores, imaging, biomarkers) makes it difficult to compare results across trials. Furthermore, the durability of clinical benefit beyond 1–2 years remains uncertain, and repeated injections may be required, which could increase cost and procedural risk. Manufacturing and regulatory challenges: both cell-based and EV-based products require GMP-compliant manufacturing environments, stringent quality control, and reproducible potency standards. However, standardized critical quality attributes (CQAs) and validated potency assays for MSCs, EVs, and iPSC-derived products are still lacking. Donor variability, batch-to-batch inconsistency, and difficulties in scaling up production remain major obstacles. For EV-based therapies in particular, issues related to purity, yield, isolation methods, and storage stability require further optimization and harmonization. Additionally, these advanced therapy medicinal products (ATMPs) face evolving, heterogeneous regulatory frameworks across countries, complicating multicenter and multinational clinical trials. Challenges also persist in product characterization, traceability, labeling, and long-term registries. Moreover, the high cost of personalized or autologous products may limit accessibility and create reimbursement barriers within healthcare systems.

These safety, efficacy, manufacturing, and regulatory challenges highlight the need for carefully designed, adequately powered clinical trials and for international consensus on quality standards for next-generation regenerative therapies.

Conclusions

Immunomodulatory cell and cell-derived therapies represent promising disease-modifying approaches for knee OA by targeting the dysregulated inflammatory microenvironment. Further, MSC-derived EVs provide an

off-the-shelf, cell-free platform that modulates immune responses and supports cartilage matrix repair. iPSC-derived products further expand regenerative options by providing a renewable source of chondrocytes, progenitors, and immune-regulatory cells. However, it should be clear that there is no one therapy fits all, thus there is a critical need to characterize the patient, and tailor the therapy accordingly.

Further, for these therapies to reach routine clinical application, several advances are needed, including standardized potency assays, improved manufacturing consistency, long-term safety data, and clearer regulatory pathways. Future progress will likely depend on combining biological interventions with patient stratification, mechanical alignment strategies, and multimodal treatment approaches.

If these challenges can be addressed, next-generation immunomodulatory and cell-derived therapies have the potential to provide durable and genuinely disease-modifying treatments for patients with knee OA.

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