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REVIEW

Future perspectives on mesenchymal stromal cell-derived secretomes in knee osteoarthritis

Anandanarayan Muruganandam, Naveen Jeyaraman, Ashika Mudilikulam Sukumaran, Swaminathan Ramasubramanian, Viji Devanand, Arulkumar Nallakumarasamy, Sathish Muthu, Madhan Jeyaraman

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Anandanarayan Muruganandam, Department of Orthopaedics, Faculty of Medicine - Sri Lalithambigai Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai 600095, Tamil Nadu, India

Naveen Jeyaraman, Madhan Jeyaraman, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai 600077, Tamil Nadu, India

Naveen Jeyaraman, Swaminathan Ramasubramanian, Arulkumar Nallakumarasamy, Sathish Muthu, Madhan Jeyaraman, Department of Regenerative Medicine, Agathisha Institute of Stemcell and Regenerative Medicine, Chennai 600030, Tamil Nadu, India

Naveen Jeyaraman, Sathish Muthu, Madhan Jeyaraman, Department of Orthopaedics, Orthopaedic Research Group, Chennai 641045, Tamil Nadu, India

Ashika Mudilikulam Sukumaran, Department of Biochemistry, Faculty of Medicine - Sri Lalithambigai Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai 600095, Tamil Nadu, India

Viji Devanand, Department of Physiology, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research, Chennai 600044, Tamil Nadu, India

Arulkumar Nallakumarasamy, Department of Orthopaedics, Jawaharlal Institute of Postgraduate Medical Education and Research, Karaikal 609602, Puducherry, India

Sathish Muthu, Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram 631552, Tamil Nadu, India

ORCID number: Naveen Jeyaraman 0000-0002-4362-3326; Swaminathan Ramasubramanian 0000-0001-8845-8427; Arulkumar Nallakumarasamy 0000-0002-2445-2883; Sathish Muthu 0000-0002-7143-4354; Madhan Jeyaraman 0000-0002-9045-9493.

Co-first authors: Anandanarayan Muruganandam and Naveen Jeyaraman.

Corresponding author: Madhan Jeyaraman, MD, PhD, Researcher, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Velappanchavadi, Chennai 600077, Tamil Nadu, India. madhanjeyaraman@gmail.com

Abstract

Knee osteoarthritis (OA) represents a progressive degenerative joint disorder characterized by articular cartilage degradation, chronic synovial inflammation, and pathological subchondral bone remodeling. Despite its prevalence and substantial socioeconomic impact, current therapeutic strategies remain predominantly symptomatic, failing to address the underlying disease mechanisms. Mesenchymal stromal cells (MSCs) have emerged as promising therapeutic agents, with accumulating evidence suggesting their efficacy stems primarily from paracrine signaling rather than direct cellular differentiation. The MSC-derived secretome, comprising extracellular vesicles (particularly exosomes), growth factors, cytokines, and immunomodulatory proteins, represents a sophisticated cell-free therapeutic platform capable of simultaneously targeting multiple pathological pathways in OA. This narrative review synthesizes current knowledge regarding the molecular mechanisms through which MSC-derived secretomes modulate the OA microenvironment, critically analyzes preclinical and emerging clinical evidence, and addresses the formidable challenges confronting clinical translation. We examine the secretome's role in chondroprotection, immunomodulation, and subchondral bone homeostasis, while identifying critical gaps in standardization, delivery optimization, and regulatory frameworks that must be addressed to realize the full therapeutic potential of this promising regenerative strategy.

Key Words: Bone marrow; Mesenchymal stromal cell; Secretomes; Osteoarthritis; Therapeutics

Core Tip: Mesenchymal stromal cell-derived secretomes, rich in exosomes, cytokines, and growth factors, offer a cell-free therapeutic strategy for knee osteoarthritis by modulating inflammation, promoting chondroprotection, and restoring subchondral bone homeostasis. Their paracrine-driven mechanisms target multiple pathological pathways simultaneously, surpassing symptomatic treatments. However, clinical translation demands rigorous standardization, optimized delivery systems, and clear regulatory frameworks to unlock their full regenerative potential in osteoarthritis management.

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INTRODUCTION

Knee osteoarthritis (OA) constitutes one of the most prevalent and debilitating musculoskeletal disorders worldwide, affecting approximately 365 million individuals globally and representing a leading cause of disability in aging populations[1,2]. The confluence of demographic aging, rising obesity rates, and increasing metabolic syndrome prevalence has amplified the disease burden substantially over recent decades[3,4]. OA imposes considerable socioeconomic costs through direct healthcare expenditures, lost productivity, and diminished quality of life, yet therapeutic options remain remarkably limited[5,6].

Current management strategies are largely confined to symptomatic palliation. Non-steroidal anti-inflammatory drugs, though widely prescribed, provide only temporary pain relief while carrying significant cardiovascular and gastrointestinal risks with chronic use[6,7]. Intra-articular corticosteroid injections offer short-term benefit but demonstrate diminishing efficacy with repeated administration and may paradoxically accelerate cartilage degradation[8,9]. Physical therapy and weight management, while beneficial, cannot reverse established structural damage[10]. Consequently, total knee arthroplasty remains the definitive intervention for end-stage disease, yet this surgical solution carries substantial morbidity, finite implant longevity, and considerable healthcare costs[11,12].

The fundamental limitation of existing therapies lies in their failure to address the core pathophysiological processes driving OA progression[13,14]. These include the inexorable degradation of articular cartilage through imbalanced matrix metalloproteinase activity, aberrant subchondral bone remodeling with increased sclerosis and osteophyte formation, and chronic low-grade synovial inflammation perpetuating a catabolic joint environment[15-17]. This pathophysiological cascade creates an urgent and unmet need for disease-modifying OA drugs capable of interrupting disease progression, promoting tissue regeneration, and preserving native joint architecture[18,19].

The emergence of regenerative medicine approaches, particularly mesenchymal stromal cell (MSC)-based therapies, initially generated considerable enthusiasm within the orthopedic community[20,21]. Early preclinical studies and pilot clinical trials demonstrated promising results through MSCs' potent anti-inflammatory capabilities and tissue repair potential[20,22]. However, the path toward widespread clinical adoption of whole-cell therapies encountered significant obstacles[23]. These challenges encompass inherent product variability arising from donor heterogeneity and culture conditions, limited cell viability and engraftment following transplantation, logistical complexities in manufacturing and distribution, regulatory hurdles, and theoretical concerns regarding immunogenicity and malignant transformation potential[23-26].

Building on the recognition of paracrine-mediated MSC effects described above[21,27], attention has shifted toward the MSC-derived secretome, a complex repertoire of bioactive components that includes extracellular vesicles (EVs), growth factors, cytokines, and immunomodulatory proteins[27,28]. The secretome represents a sophisticated, cell-free delivery system capable of simultaneously targeting multiple pathological pathways without the complications inherent to cellular transplantation[29,30]. The term 'secretome' encompasses both EVs (particularly exosomes) and soluble factors (growth factors, cytokines), though many therapeutic products consist of EV-enriched or small EV (sEV) fractions specifically isolated for clinical use.

The utilization of MSC-derived secretomes as therapeutic agents offers substantial practical advantages[29]. These include enhanced product stability, simplified standardization protocols, streamlined storage and distribution logistics, elimination of cell viability concerns, and potentially reduced immunogenic risk[30,31]. While numerous isolated studies have confirmed chondroprotective and immunomodulatory properties in various OA models, a comprehensive synthesis bridging fundamental molecular mechanisms with clinical translation potential remains necessary[21,32]. The comparative injectable regenerative therapies for knee OA are summarized in Table 1.

This narrative review aims to consolidate the expanding literature on MSC-derived secretomes in knee OA[33]. We systematically examine the secretome's molecular composition, elucidate detailed mechanisms through which it modifies the OA microenvironment, critically analyze existing preclinical and clinical evidence, address formidable challenges related to product standardization and delivery optimization, and delineate future perspectives necessary to translate this promising cell-free strategy into robust clinical therapy[21,33,34]. Beyond summarizing existing evidence, this review advances the field by integrating mechanistic insights into EV-associated and soluble MSC secretome components with a critical evaluation of the manufacturing-to-clinic continuum, encompassing good manufacturing practice (GMP)-compliant production, potency assay development, and regulatory considerations. By situating these analyses within the broader regenerative therapy landscape and outlining a pragmatic translational roadmap with defined milestones, the manuscript directly links biological understanding to the practical requirements of clinical implementation in OA.

LITERATURE REVIEW

This narrative review synthesizes the expanding literature through a comprehensive search of PubMed, Scopus, and Web of Science databases (January 2015 to November 2024) using key terms including 'mesenchymal stromal cells', 'secretome', 'extracellular vesicles', 'exosomes', and 'osteoarthritis'. While we acknowledge that a systematic review with PRISMA methodology would provide additional rigor in evidence grading, our narrative approach allows broader conceptual integration of mechanistic, preclinical, and translational data across this rapidly evolving field. This narrative review emphasizes conceptual connections and practical relevance, rather than formal evidence grading used in systematic reviews or meta-analyses.

Molecular composition of MSC-derived secretomes

Terminology in this field requires clarification: 'secretome' refers to the complete collection of factors secreted by MSCs, encompassing both membrane-bound EVs (including exosomes, microvesicles, and apoptotic bodies) and soluble proteins, growth factors, and cytokines. Many therapeutic products are EV-enriched or sEV fractions obtained through differential centrifugation or filtration. Throughout this review, we use 'secretome' when discussing the complete mixture, 'EVs' or 'exosomes' when referring to vesicular components specifically, and note the product composition when describing individual studies. Most mechanistic and clinical data discussed derive from EV-enriched preparations, though soluble factors contribute importantly to therapeutic effects, particularly in whole-conditioned medium applications. MSC-derived secretome comprises a heterogeneous mixture of bioactive components that collectively orchestrate therapeutic effects in OA[35]. Its complexity underlies the multifaceted mechanisms through which secretomes modulate joint pathology, spanning EVs, soluble growth factors, and immunomodulatory molecules[36].

EVs and exosomes

EVs are arguably the most critical component of the MSC secretome, serving as nature's evolved system for intercellular communication[37]. EVs include exosomes (30-150 nm, endosomal origin), microvesicles (100-1000 nm, plasma membrane budding), and apoptotic bodies (> 1000 nm). Among these, exosomes warrant particular attention due to their abundance, stability, and cargo specificity[38].

Exosomes originate from multivesicular bodies and are enriched with molecular cargo. Their membranes contain characteristic proteins (CD9, CD63, CD81, tumor susceptibility gene 101) that facilitate targeting and uptake[39]. Encapsulated biomolecules - microRNAs (miRNAs), messenger RNAs, proteins, lipids, and metabolites - are protected from degradation and delivered to recipient cells such as chondrocytes, synoviocytes, and macrophages[39]. This transfer alters cellular function *via* post-transcriptional regulation, protein delivery, and metabolic modulation. Xu *et al*[40] highlighted exosome-mediated communication as a sophisticated system coordinating multicellular responses to pathological stimuli.

Exosomal miRNAs are particularly relevant in OA. These approximately 22 nucleotide regulators bind target mRNAs to repress translation or induce degradation. MSC-derived exosomes deliver miRNAs with chondroprotective effects such as miR-140-5p promotes chondrocyte proliferation and matrix synthesis while suppressing catabolism[41]; miR-146a attenuates nuclear factor kappa B (NF-κB)-driven inflammation[42]; and miR-21 enhances survival and reduces apoptosis in stressed chondrocytes[43]. Exosomal proteins also contribute significantly. Cheng *et al*[44] identified over 1000 proteins involved in extracellular matrix organization, immune regulation, and metabolism. This molecular diversity enables

Table 1 Comparative analysis of regenerative approaches for knee osteoarthritis

Parameter	MSC secretomes	Whole-cell MSCs	PRP	Hyaluronic acid
Mechanism	Paracrine signaling *via* EVs, growth factors, cytokines	Paracrine + potential differentiation	Growth factor delivery, platelet-derived factors	Viscosupplementation, mild anti-inflammatory
Standardization	Moderate challenge; biochemical characterization possible	High challenge; cellular variability	High variability; preparation method dependent	Well-established; pharmaceutical-grade products
Storage/stability	Freeze/Lyophilize possible; moderate stability	Requires cryopreservation; viability concerns	Fresh preparation typically required	Excellent; room temperature stable
Regulatory pathway	Evolving; biological therapeutic	Complex; cellular product regulations	Variable; may be considered device or biologic	Established; device or drug depending on claims
Manufacturing scalability	Good potential with optimization	Limited; donor and passage constraints	Limited; autologous preparation	Excellent; large-scale synthesis feasible
Immunogenicity risk	Minimal; cell-free	Low to moderate depending on allogeneic *vs* autologous	Minimal; typically autologous	Minimal; well-tolerated
Chondroprotective mechanism	Direct: Matrix synthesis, MMP inhibition	Direct and indirect through secretome	Indirect: Growth factor stimulation	Minimal direct chondroprotection
Anti-inflammatory potency	High; multiple mechanisms	High; primarily *via* secretome	Moderate; transient	Mild
Subchondral bone effects	Demonstrated in preclinical models	Demonstrated in preclinical models	Limited evidence	Minimal
Clinical evidence level	Phase I/II; early data	Phase II/III; mixed results	Multiple RCTs; modest benefit	Extensive RCTs; modest, transient benefit
Cost considerations	Moderate; dependent on manufacturing scale	High; labor-intensive production	Low to moderate	Low; established manufacturing
Practical advantages	Off-the-shelf potential, consistent dosing	Potentially more potent for severe disease	Point-of-care preparation, familiar to clinicians	Established reimbursement, physician familiarity
Practical limitations	Novel product; limited clinical data	Viability concerns, regulatory complexity	High preparation variability	Limited efficacy; short duration

MSC: Mesenchymal stromal cell; PRP: Platelet-rich plasma; EVs: Extracellular vesicles; MMP: Matrix metalloproteinase; RCTs: Randomised controlled trial.

simultaneous engagement of multiple therapeutic targets, a capability unmatched by single-molecule drugs.

Soluble growth factors and anabolic mediators

Beyond vesicles, MSC-derived secretome contains soluble factors that directly regulate tissue homeostasis and repair. These act through receptor-mediated signaling to promote anabolic processes and suppress catabolism.

Transforming growth factor-beta: A key chondroprotective factor. Through SMAD2/3 signaling, transforming growth factor-beta (TGF-β) induces cartilage-specific genes [SRY-related HMG-box gene 9, collagen type II alpha 1 chain (COL2A1), aggrecan]. Ying *et al*[45] showed MSC-derived TGF-β1 enhances chondrocyte differentiation while preventing hypertrophy, maintaining stable cartilage phenotype.

Insulin-like growth factor-1: Potent anabolic mediator stimulating proliferation, proteoglycan synthesis, and survival *via* phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinases/extracellular regulated protein kinases pathways. Montaseri *et al*[46] demonstrated insulin-like growth factor-1 (IGF-1) counteracts interleukin (IL)-1β-induced catabolism, preserving matrix synthesis and preventing apoptosis.

Bone morphogenetic proteins: Particularly bone morphogenetic protein (BMP)-2 and BMP-7, which stimulate chondrocyte differentiation, matrix synthesis, and subchondral bone remodeling. Kang *et al*[47] emphasized BMPs' dual role, as aberrant activity may drive osteophyte formation, necessitating precise regulation.

Vascular endothelial growth factor: Plays a nuanced role. While angiogenesis supports subchondral bone integrity and synovial perfusion, excessive vascular endothelial growth factor (VEGF) promotes pathological vascular invasion into cartilage. Palamà *et al*[48] and Műzes and Sipos[31] highlighted MSC-derived secretome modulation of VEGF as a mechanism to normalize aberrant angiogenesis in OA.

Anti-inflammatory and immunomodulatory molecules

The immunomodulatory capacity of MSC-derived secretomes is central to their therapeutic potential. Chronic low-grade

inflammation drives OA progression, and secretome-derived molecules actively resolve this state[21].

IL-10: A potent anti-inflammatory cytokine. Through signal transducer and activator of transcription 3 activation, IL-10 suppresses NF-κB-driven pro-inflammatory gene expression. Hutchins *et al*[49] showed MSC-derived IL-10 reduces synovial inflammation, shifting the cytokine milieu toward anti-inflammatory dominance.

Prostaglandin E2: Exerts immunosuppressive effects *via* EP2/EP4 receptor signaling, reducing pro-inflammatory cytokines and promoting regulatory T cell differentiation. Jin *et al*[50] noted dose-dependent effects, with physiological levels suppressing inflammation but excessive concentrations potentially enhancing certain pathways.

Tumor necrosis factor-stimulated gene-6: A multifunctional glycoprotein with strong anti-inflammatory properties. Tumor necrosis factor (TNF)-stimulated gene-6 (TSG-6) inhibits neutrophil infiltration, reduces cytokine production, and stabilizes extracellular matrix *via* hyaluronan interactions. Choi *et al*[51] demonstrated that TSG-6 knockdown diminishes MSC-derived secretome efficacy in arthritis models. Exosomes also contribute to immunomodulation. miRNAs such as miR-146a and miR-223 suppress inflammatory signaling in immune cells, while exosomal proteins including TGF-β and hepatocyte growth factor directly engage macrophages and T cells to promote immunosuppression[52].

Mechanisms of action in knee OA pathophysiology

The therapeutic potential of MSC-derived secretomes stems from their capacity to simultaneously target multiple interconnected pathological processes driving OA progression (Figure 1). This section examines in detail the mechanisms through which secretomes modulate chondrocyte function, inflammatory pathways, and subchondral bone homeostasis [53].

Chondroprotection and cartilage matrix homeostasis

Articular cartilage degradation is the hallmark of knee OA, driven by imbalance between anabolic synthesis and catabolic breakdown. The MSC secretome restores this equilibrium through complementary mechanisms[52].

Stimulation of chondrocyte anabolism: Secretome-derived growth factors promote chondrocyte proliferation and extracellular matrix synthesis. Dalle Carbonare *et al*[54] showed upregulation of SRY-related HMG-box gene 9, the master regulator of chondrogenesis, which drives COL2A1 and aggrecan expression. Guo *et al*[55] confirmed enhanced COL2A1 transcription and translation, increasing type II collagen deposition. Wen *et al*[56] demonstrated increased aggrecan synthesis with reduced ADAMTS-5-mediated degradation, preserving cartilage's compressive resilience. Mechanistically, TGF-β activates SMAD2/3 signaling, while IGF-1 engages phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinases/extracellular regulated protein kinases cascades. Hui *et al*[57] highlighted synergistic effects of combined TGF-β and IGF-1, yielding superior chondroprotection.

Suppression of catabolic enzyme activity: MSC-derived secretomes directly suppress matrix-degrading enzymes. Matrix metalloproteinase 13 (MMP-13), the principal collagenase in OA, is reduced *via* NF-κB and AP-1 inhibition, mediated by exosomal miRNAs and soluble anti-inflammatory factors[58]. ADAMTS-5 downregulation occurs through transcriptional repression and miRNA targeting, preserving aggrecan[59]. Lu *et al*[60] identified broad suppression of catabolic enzymes (MMP-1, MMP-3, cathepsins), indicating global reprogramming of chondrocyte gene expression toward anabolism.

miRNA-mediated gene regulation: Exosomal miRNAs fine-tune chondrocyte gene expression. Li *et al*[61] identified dysregulated miRNAs in OA cartilage, with MSC exosomes delivering corrective signals. miR-140-5p promotes proliferation and matrix synthesis while suppressing ADAMTS-5 and inflammatory genes[62]. miR-146a reduces IL-1β-induced inflammation by targeting TNF receptor-associated factor 6 and IL-1 receptor-associated kinase 1[63]. miR-21 protects against apoptosis *via* phosphatase and tensin homolog/protein kinase B modulation, though its effects can be context-dependent[64]. Collectively, these miRNAs reprogram chondrocytes toward anabolic and anti-inflammatory states.

Anti-inflammatory and immunomodulatory effects

Chronic synovial inflammation drives OA progression and pain. The MSC secretome exerts potent anti-inflammatory actions.

Cytokine modulation and NF-κB suppression: Secretome treatment reduces TNF-α, IL-1β, and pathological IL-6[65]. Mechanisms include receptor antagonism, enhanced IL-1Ra production, and direct signaling suppression. NF-κB inhibition is central: TSG-6 and exosomal miRNAs block nuclear translocation and DNA binding dampening inflammatory gene expression[51,66].

Macrophage polarization and immune modulation: MSC-derived secretomes reprogram macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. Cho *et al*[67] showed reduced M1 markers (inducible nitric oxide synthase, TNF-α, IL-1β) and increased M2 markers (arginase-1, CD206, IL-10). Mechanisms include prostaglandin E2-mediated EP2/EP4 signaling, exosomal miR-146a/miR-223 transfer, and soluble IL-10/TGF-β signaling[68,69]. M2 macrophages not only suppress inflammation but also promote repair *via* debris clearance and growth factor secretion [69].

Resolution of synovial inflammation: Khatab *et al*[70] demonstrated reduced synovial thickening, immune infiltration, and normalized fluid composition after secretome treatment, correlating with pain reduction. Mancuso *et al*[21]

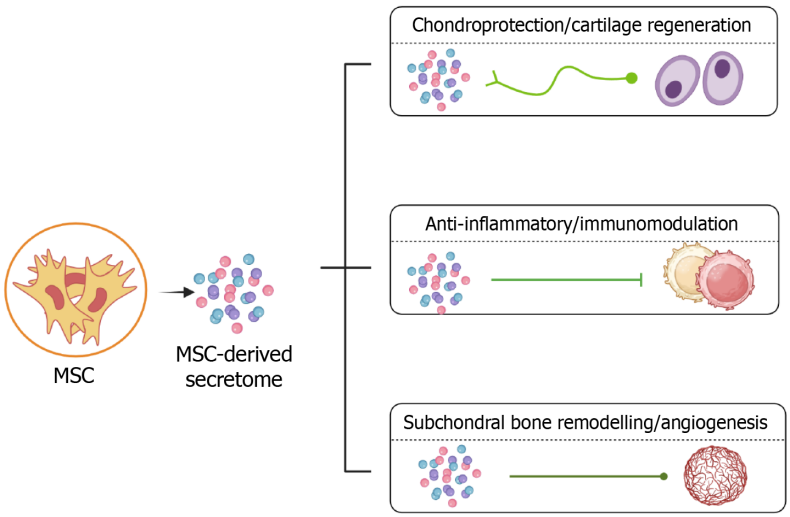


Figure 1 Key therapeutic effects of mesenchymal stromal cell-derived secretomes in knee osteoarthritis. MSC: Mesenchymal stromal cell.

documented cytokine profile shifts and increased anti-inflammatory mediators, indicating transformation of the joint microenvironment into a repair-permissive state.

Subchondral bone remodeling and osteochondral unit homeostasis

OA involves the entire osteochondral unit, including pathological subchondral bone remodeling with sclerosis and osteophyte formation.

Regulation of bone cell activity: Secretome components normalize osteoblast and osteoclast activity. Zhang *et al*[71] showed enhanced osteoblast differentiation and mineralization *via* BMP/Wnt signaling, balanced by osteoclast regulation. Cho *et al*[72] demonstrated reduced osteoclastogenesis through altered receptor activator of NF-κB ligand/osteoprotegerin ratios.

Modulation of pathological angiogenesis: Aberrant vascularization contributes to remodeling and pain. Li *et al*[73] described hypervascularization and impaired perfusion in OA bone. MSC-derived secretome VEGF supports balanced angiogenesis, improving perfusion without cartilage invasion[28]. Sears and Ghosh[74] emphasized the secretome's ability to normalize angiogenesis through combined pro-angiogenic and regulatory factors.

Inhibition of osteophyte formation: Osteophytes, driven by aberrant BMP signaling, impair mobility and cause pain. Giannasi *et al*[75] showed secretome treatment reduced osteophyte size and BMP-2 expression. Chou *et al*[76] identified TSG-6 as a key mediator inhibiting inflammatory signals that initiate osteophyte development. Together, these effects highlight the secretome's ability to address structural joint changes beyond cartilage preservation.

Critical analysis of preclinical evidence

Preclinical studies of MSC-derived secretome therapy in knee OA span *in vitro* systems, small animal models, and large animal experiments. Collectively, they support therapeutic potential, but critical appraisal highlights both strengths and limitations that shape clinical translation.

In vitro evidence and mechanistic studies

Cell culture systems remain the main entry point for dissecting MSC-derived secretome mechanisms in OA. Across multiple studies, MSC-derived EVs and broader secretome fractions consistently enhance anabolic markers such as COL2A1 and aggrecan, while suppressing catabolic mediators including MMP-13, ADAMTS-5, IL-1β, and TNF-α in primary human OA chondrocytes and synoviocytes[33,77-79]. These effects are particularly clear in experiments that use patient-derived cartilage or synovium rather than immortalised lines, which better preserve OA-specific transcriptional and epigenetic changes[33,79]. Three-dimensional pellet or hydrogel systems help maintain chondrocyte phenotype and allow evaluation of matrix deposition, but introduce variability in diffusion, nutrient gradients, and EV penetration, complicating dose standardisation and between-laboratory comparability[77,80].

Mechanistically, EV cargo appears central rather than soluble proteins alone. Exosomes enriched in specific miRNAs reproducibly modulate canonical OA pathways: MiR-140-5p-overexpressing synovial MSC-EVs enhance cartilage matrix synthesis and reduce MMP-13 and ADAMTS-5 in IL-1β-challenged chondrocytes and prevent OA development in rat models; miR-92a-3p-rich EVs promote chondrogenesis and inhibit WNT5A-driven catabolic signaling; hypoxia-enhanced miR-216a-5p or miR-122-5p in MSC-EVs improves chondrocyte proliferation, survival, and autophagy through JAK2/signal transducer and activator of transcription 3 and DUSP2-regulated pathways[81-86]. These data support a model in which specific miRNA-target pairs, rather than bulk trophic factors, drive much of the observed chondroprotection.

Co-culture and organoid approaches partially address the oversimplification of single-cell-type monolayers. Tri- or multi-cell co-cultures including chondrocytes, synovial fibroblasts, and macrophage-lineage cells show that MSC-EVs simultaneously dampen inflammatory cytokine release, shift macrophage phenotype toward an M2-like profile, and preserve cartilage matrix, effects that are substantially weaker in isolated chondrocyte cultures[33,78,87]. However, even sophisticated *in vitro* models cannot recapitulate joint biomechanics, subchondral bone crosstalk, or adaptive immune contributions. Dose-response curves are another limitation: Secretome concentrations needed to normalise catabolic marker expression often exceed by one to two orders of magnitude the joint levels that are realistically achievable *in vivo* with a single intra-articular injection, even if one assumes slow clearance[33,77,87,88].

Small animal models

Rodent OA models, whether surgically induced (*e.g.*, destabilization of medial meniscus, anterior cruciate ligament transection) or chemically induced (*e.g.*, monoiodoacetate), consistently show that MSC-EVs or broader secretomes reduce cartilage degeneration scores, preserve proteoglycan content, and attenuate synovial inflammation[33,77,78,84,86,87]. These outcomes are supported by meta-analyses indicating significant improvements in histological OA scores and pain-related behaviours compared with vehicle controls[86,89,90]. Reduction of CGRP-positive nerve fibres in subchondral bone and normalisation of spinal microglial activation in some studies suggest that EVs modulate pain circuits in addition to local cartilage biology[33,78].

These models are well suited to mechanistic dissection. Genetic manipulation of donor MSCs or recipient mice has linked specific EV components to functional outcomes, for example miR-140-5p or miR-92a-3p in exosomes, and has clarified that macrophage reprogramming is a major contributor to reduced synovitis and pain[81,82,87,90,91]. Yet several features limit translational relevance. Disease in rodents progresses rapidly over weeks, which magnifies the apparent benefit of early intervention and does not capture the decades-long, multifactorial course of human OA[78,87,88]. Many protocols use preventive or very early treatment immediately after joint insult, whereas patients typically present with established cartilage loss and chronic synovitis. Follow-up rarely exceeds 8-12 weeks, so durability of structural and symptomatic benefit remains largely unknown[33,77,84,86]. Histological scoring at a single endpoint remains the dominant outcome, with relatively few studies combining serial imaging, behavioural measures, and molecular readouts in the same animals.

Large animal models

Large animals such as rabbits, dogs, sheep, and minipigs offer joint size, cartilage thickness, and loading patterns that more closely approximate the human knee. Secretome and EV studies in these species have demonstrated improved cartilage integrity, reduced osteophyte formation, and better biomechanical properties after intra-articular administration, sometimes in combination with hyaluronic acid (HA) or hydrogels[77,78,88,91,92]. For example, in rabbit and minipig models of post-traumatic OA, exosome-enriched preparations from bone marrow or umbilical cord MSCs have led to thicker, more organised cartilage repair tissue with higher Safranin O staining intensity and improved indentation modulus compared with vehicle or HA alone[33,77,92].

Despite this anatomical relevance, the evidence base in large animals is thin and heterogeneous. Sample sizes are often underpowered, blinding of histological and biomechanical assessment is inconsistently reported, and outcome measures vary widely between laboratories. Most models rely on surgical injury rather than spontaneous age-related OA, and follow-up rarely extends beyond 3-6 months[77,78,88,91,92]. These constraints mean that large-animal data are more useful for optimisation of delivery strategies and surgical techniques than for definitive efficacy estimates. They do, however, provide a realistic testbed for clinically relevant injection volumes, imaging protocols, and repeated-dose schedules.

Comparative efficacy studies

Head-to-head comparisons of MSC-derived secretomes with standard intra-articular therapies are comparatively scarce. In rodent and rabbit models, EV-based preparations have generally outperformed HA, platelet-rich plasma, or corticosteroids in terms of histological cartilage preservation and pain-related behaviours[33,77,78,86,87,89]. However, many of these experiments use aggressive induction of OA, high doses of regenerative products, and relatively short follow-up, which tend to accentuate differences in favour of more potent anabolic or anti-inflammatory agents.

Comparisons between whole-cell MSC therapy and acellular secretomes are particularly informative. Several preclinical studies using paired designs have found broadly similar structural and functional outcomes when total EV dose is scaled to the secretory output of the corresponding cell number, with secretomes showing reduced risk of ectopic tissue formation and greater batch-to-batch uniformity[33,87,88,92,93]. Yet true dosing equivalence is difficult to define. EV preparations are quantified using protein mass, particle number, or specific marker content, while cell therapies are dosed by viable cell counts. The relationship between these metrics and intra-articular exposure at the tissue level is not linear, so apparent "equivalence" probably masks meaningful differences in pharmacokinetics and tissue targeting.

Clinical translation: Current evidence and challenges

The translation of MSC-derived secretomes from preclinical promise to clinical reality requires addressing multiple interconnected challenges spanning manufacturing, regulatory approval, and clinical validation. The following sections examine the current state of clinical evidence and the principal barriers to widespread therapeutic adoption.

Early clinical experience

The clinical data set for MSC-derived secretomes in knee OA remains small but is growing. Phase I/II trials have

primarily evaluated safety of intra-articular EV or secretome injections derived from placental, umbilical cord, or bone-marrow MSCs[93-95]. A recent triple-blind, randomised, placebo-controlled trial of placental MSC-derived EVs in bilateral knee OA (grade 2-3) used a within-patient design, with one knee receiving EVs and the contralateral knee saline. A single 5-mL injection containing a clinically standardised EV dose was safe over 12 months, with no serious adverse events and only transient local reactions, but did not significantly improve Western Ontario and McMaster Universities Arthritis Index pain or function *vs* placebo[94]. These neutral efficacy findings are important, because they temper expectations derived from aggressive rodent models.

In parallel, first-in-human work with clinical-grade umbilical cord MSC sEVs has shown that large-scale, GMP-compliant manufacturing with reproducible miRNA and protein profiles is feasible and that intra-articular administration appears well tolerated in early cohorts of OA patients[95]. Although these early studies are underpowered for efficacy, modest improvements in pain scores and function have been reported in some open-label series, but the absence of rigorous controls and the known magnitude of placebo responses after intra-arterial injection make these signals difficult to interpret.

Clinical trial design challenges

Several aspects of trial design remain unresolved. Dose optimisation is particularly complex. EV products can be quantified by total protein, particle number, or copy number of specific bioactive miRNAs, and the clinically relevant parameter is likely a composite of these features[93,96-98]. Translation from preclinical dosing is hindered by scale differences between rodent and human joints and by differences in clearance kinetics. Most planned or ongoing trials use one or two injections separated by weeks to months, whereas preclinical protocols often use multiple closely spaced doses.

Outcome measures present further difficulties. Structural endpoints such as magnetic resonance imaging cartilage thickness or T2 mapping change slowly and require large sample sizes and long follow-up to detect disease-modifying effects. Patient-reported outcomes such as Western Ontario and McMaster Universities Arthritis Index or visual analog scale scores are sensitive but prone to large placebo responses that can exceed the expected incremental benefit of a single biologic injection[94]. Biomarkers including serum or synovial cartilage oligomeric matrix protein, C-telopeptide of type II collagen, or neoepitope fragments of collagen may offer earlier signals, yet none is validated as a surrogate endpoint for regulatory decisions in OA. Heterogeneity of patient populations, with diverse disease phenotypes under the umbrella of "knee OA", further dilutes treatment effects.

Regulatory pathway considerations

For regulators, MSC-derived secretomes occupy a grey zone between biologics and advanced therapy medicinal products. In most jurisdictions, EVs isolated from MSCs with more than minimal manipulation are regulated as biologic drugs, while whole MSCs are classified as cell-based advanced therapy medicinal products; classification can shift depending on processing steps and intended mechanism of action[95-97,99]. This ambiguity affects requirements for preclinical safety, potency assays, and lot-release criteria. On the positive side, the acellular, non-replicative nature of EV preparations simplifies viral safety testing, sterility assurance, and stability studies compared with living cell products, which may ultimately make large-scale, standardised manufacturing more tractable once regulatory expectations are fully defined.

MANUFACTURING AND STANDARDISATION CHALLENGES

Source MSC variability

Secretome composition is highly sensitive to the characteristics of the parental MSC population. Tissue origin, donor age, comorbidities, and passage number all influence EV cargo and soluble factor profiles[33,88,93,96,98-100]. Bone marrow MSCs tend to generate EVs enriched in chondrogenic and osteogenic factors, whereas adipose-derived MSCs show stronger immunomodulatory signatures; umbilical cord MSCs, sourced from young donors, often display greater proliferative capacity and produce EVs with distinct miRNA spectra that may favour anti-inflammatory and anti-senescent effects[33,78,80,84,92]. MSCs from older or comorbid donors generally show reduced secretory potency, which constrains autologous approaches and favours allogeneic master cell banks[33,93,98-100]. Passage number is equally important: Late-passage MSCs display senescence-associated transcriptomic and secretory changes, with EVs that may lose chondroprotective capacity or become pro-fibrotic, which argues for tight control of expansion protocols[96,98,100].

Secretome collection and processing

Collection conditions profoundly shape the final product. Serum-free or xeno-free media avoid contaminating bovine EVs but can stress MSCs and alter secretome composition; supplementation with human platelet lysate introduces competing vesicles and growth factors that complicate downstream characterisation[33,87,98]. Duration of conditioning, typically 24-72 hours, trades off yield against accumulation of cell debris, apoptotic bodies, and metabolic waste. Isolation methods including ultracentrifugation, size-exclusion chromatography, tangential-flow filtration, polymer precipitation, and immunoaffinity capture differ in scalability, purity, and preservation of vesicle integrity[95-98]. Ultracentrifugation remains widely used in academic studies but is poorly suited to GMP scale; precipitation methods yield abundant but impure products, while chromatography and filtration approaches offer better scalability at the cost of more complex validation. Minimal Information for Studies of Extracellular Vesicles 2018 and the more recent Minimal Information for

Studies of Extracellular Vesicles 2023 update define minimal requirements for EV characterisation, including particle and protein quantification, marker profiling, and basic functional assays[95,96]. However, these guidelines were not written specifically for therapeutic manufacturing, so they need adaptation for lot-release testing and regulatory submissions.

Quality control and potency assessment

Secretomes contain thousands of proteins, lipids, and nucleic acids, which challenges conventional single-analyte quality control (Figure 2). Basic batch-release criteria generally include sterility, endotoxin, total protein, and EV particle size and concentration, but these metrics do not adequately capture biological potency[93,96-98]. Functional potency assays are increasingly advocated. Examples include *in vitro* readouts of chondrocyte proliferation and matrix synthesis under inflammatory stress, suppression of macrophage TNF-α or IL-6 secretion and promotion of M2 markers, or reduction of catabolic gene expression in OA synoviocytes[33,87,97,98]. Gimona *et al*[97] emphasise the need for assays that reflect the proposed mechanism of action and that correlate with *in vivo* outcomes, while remaining robust enough for routine GMP use. At present, no universally accepted potency assay exists for MSC-EV products in OA, which complicates cross-trial comparison and may explain some variability in clinical responses.

Stability and storage

Stability is a practical constraint for multi-centre trials and eventual commercialisation. Fresh or short-term refrigerated preparations show the highest activity, but cold-chain distribution at 4 °C is logistically demanding. Storage at -80 °C or in vapour phase nitrogen maintains EV integrity for months, yet repeated freeze-thaw cycles can cause aggregation and loss of function[93,96-98]. Lyophilisation with appropriate excipients has emerged as a promising strategy to enable room-temperature storage, but formulations must be carefully optimised to prevent damage to lipid membranes and labile miRNAs[93,96]. Different components of the secretome exhibit distinct stability profiles; proteins are generally more resilient than small RNAs, which suggests that degradation may selectively erode some mechanistic pathways over time.

DELIVERY OPTIMISATION AND PHARMACOKINETICS

Intra-articular retention and clearance

Intra-articular injection is the logical route for knee OA, but pharmacokinetics within the joint are unfavourable. Classical tracer studies show that albumin-sized molecules clear from the joint within 1-13 hours, and native HA clears within roughly a day, although stabilised or crosslinked HA formulations can achieve half-lives of several days to weeks[101,102]. EVs are larger than most soluble cytokines and may persist somewhat longer, yet the synovial capillary bed and lymphatics still clear particles in the 50-200 nm range relatively quickly[101,103,104]. This rapid turnover aligns with clinical observations that many intra-articular biologics produce only transient symptom relief after a single injection.

Nanoparticle studies provide a useful analogy. Cationic nanoparticles can increase residence time from hours to around one week in animal knees, showing that electrostatic interactions and size can be exploited to retard clearance, but even these systems eventually drain *via* lymphatic pathways[103,104]. Secretome-based therapies that are delivered as a simple bolus injection probably suffer from similar rapid washout, particularly for the soluble fraction.

Cellular uptake and target engagement

Therapeutic benefit requires not only residence in the joint but also effective uptake by relevant cell types. EV internalisation by chondrocytes is limited by the dense, negatively charged cartilage matrix and by reduced diffusion in late-stage OA where fibrillation and calcification alter tissue architecture[77,78,87]. *In vitro*, chondrocytes take up EVs through clathrin- and caveolin-mediated endocytosis, macropinocytosis, and possibly direct membrane fusion, whereas *in vivo*, a substantial proportion of intra-articular EVs are captured by synovial macrophages and lining cells, which can be beneficial for immunomodulation but reduces the amount reaching deep cartilage[78,87]. Engineering EV surfaces with cartilage-binding peptides or antibodies has improved chondrocyte targeting and cartilage penetration in preclinical studies, but these approaches add manufacturing complexity and may introduce new immunogenic epitopes[105,106].

Advanced delivery systems

To counteract rapid clearance and limited penetration, multiple groups have combined secretomes or EVs with advanced delivery systems. Hydrogels based on HA, chitosan, PEG, or composite materials can entrap EVs and provide sustained release while physically filling cartilage defects and supporting tissue repair[107-111]. Thermosensitive or injectable adhesive hydrogels loaded with EVs have improved cartilage regeneration and reduced OA progression in small-animal models, with better retention of fluorescently labelled EVs in the joint space over weeks compared with free EV injections [112-114]. Scaffold-based systems are being explored for focal cartilage defects, where local high-density delivery of EVs or secretomes can be maintained within engineered matrices[113-115].

Nanoparticle platforms, including PLGA and lipid-based carriers, offer another route to provide controlled release and protect EV cargo from enzymatic degradation, though scaling, regulatory scrutiny, and long-term safety remain considerable hurdles[103,104,113]. Secretome-HA co-formulations and other combinations with established viscosupplements may provide incremental benefit by combining mechanical lubrication, extended residence time, and biological activity, but robust comparative data are lacking.

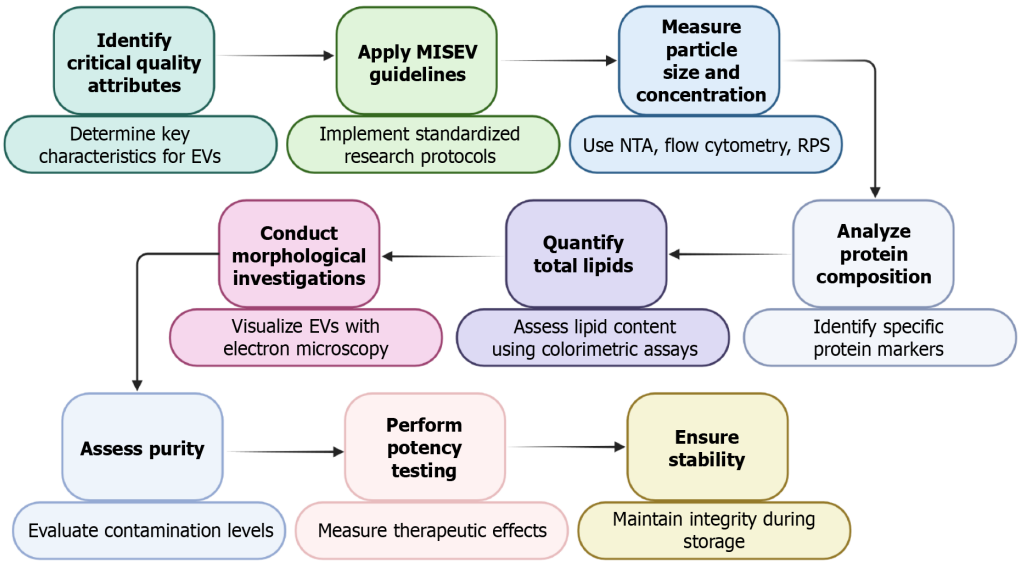


Figure 2 Steps involved in the quality control of secretomes containing extracellular vesicles. MISEV: Minimal Information for Studies of Extracellular Vesicles; NTA: Nanoparticle tracking analysis; RPS: Resistive pulse sensing; EVs: Extracellular vesicles.

FUTURE DIRECTIONS

MSC preconditioning strategies

Preconditioning MSCs before secretome collection is one of the most active areas of optimisation. Hypoxic culture (typically 1%-5% O_2) increases EV yield and enriches pro-regenerative miRNAs such as miR-216a-5p and miR-122-5p, leading to improved chondrocyte proliferation, migration, matrix synthesis, and autophagy *in vitro* and enhanced cartilage repair in OA models[83,85,88,92,93]. Inflammatory priming with IL-1β, TNF-α, or interferon gamma can upregulate anti-inflammatory mediators such as TSG-6, prostaglandin E2, indoleamine 2,3-dioxygenase, and specific miRNAs, strengthening immunomodulatory effects but sometimes reducing chondrogenic potential[87,93,99,100]. Three-dimensional spheroid culture reshapes MSC phenotype and enhances secretion of angiogenic and chondrogenic factors, often producing EVs with stronger cartilage-regenerative effects than those from two-dimensional cultures[87,88,99]. The challenge will be to balance enhanced potency with manufacturing complexity. Each preconditioning strategy effectively defines a new product from a regulatory standpoint, and combining multiple stimuli (*e.g.*, hypoxia plus inflammatory priming plus three-dimensional culture) may yield synergistic effects at the cost of substantially more demanding process validation.

Genetic engineering approaches

Genetic modification of MSCs enables targeted enrichment of secretome cargo (Figure 3). Overexpression of specific growth factors (such as TGF-β3, BMP-7, or IGF-1), anti-inflammatory cytokines, or therapeutic miRNAs (miR-140-5p, miR-92a-3p, miR-155-5p, among others) in MSCs leads to EVs with amplified chondroprotective properties and more robust disease modification in animal OA models[81,82,87,97]. Viral vectors remain the most efficient tool for stable engineering but raise concerns about insertional mutagenesis in donor cells and theoretical risks of genomic alterations in recipient tissues, even though EVs themselves do not replicate. CRISPR-based editing offers more precise modulation of MSC transcriptional programmes and EV cargo, but applications to clinical-grade MSCs and their secretomes are still largely preclinical.

Actionable strategies for translational gap resolution

Hydrogel-based sustained delivery systems: Injectable thermosensitive hydrogels (*e.g.*, chitosan-glycerophosphate or pluronic F-127 formulations) loaded with EVs can provide 2-4 weeks sustained release profiles while maintaining EV integrity. Optimization requires balancing gel degradation kinetics with EV release rates and demonstrating preserved bioactivity post-encapsulation through standardized chondroprotection assays.

Artificial intelligence-guided secretome optimization: Machine learning algorithms trained on multi-omics secretome datasets (proteomics, lipidomics, miRNA profiles) paired with functional outcomes can identify minimal effective cargo signatures. This approach could streamline manufacturing by focusing on defined critical quality attributes rather than whole-secretome complexity, enabling rational design of next-generation products.

Bioengineering cargo enrichment: Beyond genetic modification, biophysical preconditioning protocols combining specific oxygen tension (2%-5% O_2), mechanical stimulation mimicking joint loading, and inflammatory priming with defined cytokine cocktails can systematically tune EV cargo. Standardized preconditioning platforms with real-time monitoring would enable reproducible potency enhancement while maintaining GMP compliance.

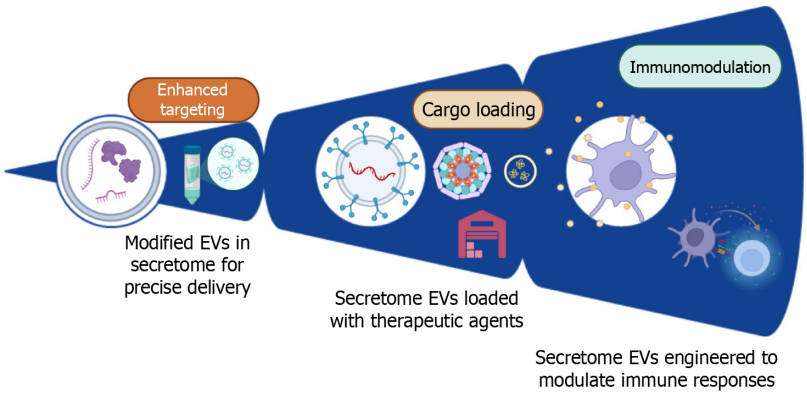


Figure 3 Mechanisms of engineering extracellular vesicle containing secretomes for targeted action. EVs: Extracellular vesicles.

Direct secretome modification

Post-collection engineering bypasses modification of the parental cells. EVs can be loaded with small molecules, siRNAs, or proteins *via* electroporation, sonication, or membrane permeabilisation, creating hybrid therapeutics that combine endogenous targeting properties of EVs with defined pharmacologic agents[115,116]. Surface modification with cartilage-homing peptides, antibodies, or aptamers can enhance retention within cartilage and uptake by chondrocytes while reducing non-specific clearance by synovial macrophages[115,116]. These engineered EVs blur the line between biological and nanomedicine products and will likely face some of the most demanding regulatory scrutiny, but they may also offer the most substantial gains in efficacy per dose.

Combination therapies

Given the multifactorial nature of OA, it is unlikely that MSC-derived secretome monotherapy will deliver durable disease modification in advanced disease. Rational combinations are therefore an attractive direction. These include pairing EVs with biomaterial scaffolds for focal cartilage repair, combining intra-articular secretomes with HA or other viscosupplements to extend residence time, and integrating biologic injections with structured physiotherapy and weight-management programmes to optimise joint mechanics[112-115]. An important question for future trials will be whether secretomes are best positioned as stand-alone injectables, as adjuncts to arthroscopic or osteotomy procedures, or as part of staged regimens in early OA to delay the need for joint replacement.

Future perspectives and research priorities

The advancement of MSC-derived secretome therapy in knee OA requires coordinated efforts across manufacturing, clinical validation, and translational science. The critical challenges in MSC-derived secretome translation for clinical usage is tabulated in Table 2.

Immediate research priorities (1-3 years): Consensus protocols for MSC culture, secretome collection, and EV isolation are urgently needed, with collaboration among International Society for Extracellular Vesicles, International Society for Cell and Gene Therapy, and regulators. Parallel efforts must validate candidate potency assays against clinical outcomes, enabling their adoption as quality control tools. Early clinical trials should integrate bioanalytical assessments to link *in vitro* assays with therapeutic efficacy. Preclinical studies in large animal models with longitudinal follow-up are essential to optimize delivery formulations, comparing hydrogels, nanoparticles, and HA combinations.

Medium-term goals (3-5 years): Definitive phase III trials must be adequately powered, placebo-controlled, and of sufficient duration (12-24 months) to assess durability. Standardized outcome measures and patient stratification will be critical. Identification of predictive biomarkers - imaging features, synovial fluid cytokines, or genetic variants - will enable precision medicine and improve trial efficiency. Concurrently, engineering next-generation secretomes with enhanced potency, improved targeting, or integration with complementary therapeutics should progress alongside validation of first-generation products.

Long-term vision (5-10 years): The ultimate goal is personalized secretome medicine, tailoring products to disease stage, phenotype, or patient-specific autologous sources. Proven efficacy in established OA could extend applications to prevention in high-risk groups, such as post-traumatic or obesity-related OA, shifting therapy toward prophylaxis. Finally, secretomes will likely integrate into multimodal treatment algorithms, complementing physical therapy, weight management, and biomechanical optimization to achieve comprehensive disease modification.

CONCLUSION

MSC-derived secretomes represent a paradigm shift in regenerative medicine for knee OA, offering cell-free therapies

Table 2 Critical challenges in mesenchymal stromal cell-derived secretome translation and proposed solutions

Challenge category	Specific issues	Current status	Proposed solutions	Timeline to resolution
Product standardization				
Source MSC variability	Donor age, tissue source, comorbidities affect secretome	Widely recognized; limited consensus	Establish standardized donor selection criteria; focus on allogeneic young, healthy donors; develop potency-based lot selection	2-3 years
Isolation method heterogeneity	Multiple protocols yield different products	MISEV guidelines provide research framework	Develop GMP-compliant isolation protocols; comparative studies of methods *vs* clinical outcomes	3-5 years
Batch-to-batch consistency	Manufacturing variability affects reproducibility	Early-stage optimization in progress	Implement process analytical technology; establish critical quality attributes	3-5 years
Quality control				
Potency assay development	Lack of validated functional assays	Multiple candidate assays under evaluation	Validate multi-parameter potency testing; correlate with clinical outcomes	4-6 years
Characterization complexity	Thousands of components; incomplete understanding of active elements	Improving with advanced analytics	Employ systems biology approaches; identify critical therapeutic components	5-7 years
Stability testing	Degradation kinetics poorly defined	Limited systematic data	Conduct comprehensive stability studies across formulations; develop real-time potency monitoring	2-4 years
Delivery optimization				
Rapid intra-articular clearance	Limits sustained therapeutic effect	Well-documented in preclinical models	Develop sustained-release formulations; explore biomaterial carriers; optimize injection timing	3-5 years
Limited cartilage penetration	Chondrocyte targeting inefficient	Recognized challenge; solutions in early development	Engineer targeting moieties; optimize EV size for matrix penetration	4-6 years
Dosing regimen uncertainty	Single *vs* multiple injections; optimal intervals unknown	Clinical trials using variable regimens	Conduct systematic dose-finding and dose-timing studies	5-7 years
Clinical validation				
Lack of phase III data	Efficacy *vs* placebo unproven	Phase I/II ongoing; phase III planning	Execute large, adequately powered RCTs with appropriate controls	5-8 years
Patient selection optimization	Ideal disease stage and phenotype undefined	Exploratory analyses in early trials	Develop predictive biomarkers; conduct stratified analyses	4-6 years
Outcome measure sensitivity	Traditional outcomes require large N and long duration	Alternative outcomes under evaluation	Validate imaging and biochemical biomarkers; incorporate patient-reported outcomes	3-5 years
Regulatory challenges				
Classification ambiguity	Unclear regulatory pathway	Ongoing agency discussions	Establish precedent through lead product approvals; develop guidance documents	3-5 years
Manufacturing requirements	GMP standards incompletely defined for secretomes	Evolving with agency feedback	Develop industry consensus standards; leverage existing biologic manufacturing frameworks	3-5 years
Economic challenges				
Reimbursement pathway	Unclear payer coverage for novel biologic	No established codes or reimbursement	Demonstrate cost-effectiveness *vs* current care; establish value-based pricing	5-10 years
Manufacturing economics	Production costs potentially prohibitive	Economies of scale not yet achieved	Optimize yields; develop scalable processes; explore biosimilar pathways post-approval	5-7 years

MSC: Mesenchymal stromal cell; GMP: Good manufacturing practice; MISEV: Minimal Information for Studies of Extracellular Vesicles; EV: Extracellular vesicle.

that address multiple pathological processes simultaneously. Through exosomal miRNAs, growth factor signaling, and immunomodulation, secretomes provide chondroprotective, anti-inflammatory, and bone-modulating effects, enabling comprehensive disease modification. Translating this promise requires standardized manufacturing, validated potency assays, and optimized delivery systems. Rigorous phase III trials are essential to confirm efficacy and safety. If phase III trials demonstrate efficacy, MSC-derived secretomes may potentially achieve clinical adoption within 5-10 years, offering promise for disease modification beyond symptomatic relief.

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