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Review Article

Advancing Regenerative Therapies for Companion Animal Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is a leading cause of chronic pain, disability, and diminished quality of life in companion animals, imposing substantial economic and emotional burdens on caregivers and veterinary systems. Despite widespread use of nonsteroidal anti-inflammatory drugs, corticosteroids, rehabilitation, and surgery, current standards of care primarily palliate symptoms and do not reestablish joint homeostasis or halt structural degeneration.

Unmet Need: Mesenchymal stromal/stem cell (MSC) based interventions have entered clinical practice, yet outcomes remain variable and often transient, reflecting heterogeneity in cell source, manufacturing, dosing, and delivery. Adipose-derived MSCs (AD-MSCs), the most commonly utilized to date, are constrained by donor-to-donor variability (age, metabolic status), potential pro-inflammatory secretory profiles associated with senescence, and the procedural burden of surgical harvest and ex vivo expansion.

Focus: This review critically evaluates the biological and translational limitations of AD-MSCs and synthesizes emerging evidence supporting umbilical-derived MSCs (U-MSCs) as a next-generation alternative. U-MSCs exhibit a younger, immune-favorable phenotype with higher proliferative capacity, lower baseline immunogenicity, and secretomes enriched for anti-inflammatory and trophic factors. Banked, donor-screened, allogeneic U-MSC products enable consistent lot release, scalable manufacturing, and point-of-care availability. Preclinical canine and equine OA studies, and early randomized clinical data, suggest superior synovial immunomodulation, chondroprotection, and functional improvement relative to historical AD-MSC benchmarks. One-Health aims to sustainably balance and optimize the health of humans, animals and ecosystems with implementations heavily focused on collaboration between human and animal sectors.

Conclusion: AD-MSCs have paved the way for regenerative OA therapy but face intrinsic barriers to consistency, potency, and durability. By contrast, U-MSCs offer a promising, scalable, and potentially more effective platform for disease-modifying treatment of veterinary OA. Realization of this potential requires multicenter, head-to-head randomized trials; standardized GMP/CQAs with mechanism-linked potency assays (e.g., IDO1, PGE_2, macrophage polarization); harmonized outcome measures (force-plate kinetics, imaging, synovial biomarkers, caregiver-reported pain); and One-Health aligned regulatory pathways to accelerate translation to both veterinary and human OA care.

Keywords: Stem Cell, Pet, Osteoarthritis

Introduction

Osteoarthritis (OA) is one of the most prevalent and debilitating chronic musculoskeletal disorders in companion animals, with far-reaching clinical, welfare, and economic implications across species. It represents the primary cause of chronic pain and mobility loss in aging dogs, cats, and horses and serves as a critical translational model for human degenerative joint disease. Epidemiological studies estimate that approximately 20 % of dogs over one year of age exhibit clinical or radiographic evidence of OA, and prevalence rises sharply with age, body weight, and breed-specific predisposition [1-3]. Large and giant breeds (e.g., Labrador Retrievers, German Shepherds, Golden Retrievers, Rottweilers) demonstrate lifetime OA risk exceeding 70 %, often associated with developmental orthopedic disorders such as hip and elbow dysplasia or cranial cruciate ligament rupture [1,4,5].

Recent global insurance-claims and electronic health-record (EHR) analyses confirm a steady increase in OA incidence, attributed to enhanced diagnostic imaging, improved longevity, and the rising prevalence of obesity [6-8]. Data from the VetCompass UK consortium (2023) revealed a 32 % decade-long increase in canine OA diagnoses, with obesity (body-condition score ≥ 7/9) conferring a 2.8-fold greater risk [9,10]. Comparable U.S. datasets (e.g., Nationwide, Trupanion) show OA-related veterinary claims escalating by 66 % between 2013 and 2022, now ranking as the second most common chronic condition among insured dogs [11,12]. Feline OA, historically underdiagnosed due to subtle behavioral expression and low owner recognition, is now understood to be highly prevalent and clinically impactful [13]. Force-plate and computed-tomography (CT) studies demonstrate that over 50 % of cats older than ten years exhibit measurable mobility impairment, and up to 90 % of cats older than twelve display radiographic joint degeneration [14,15]. Unlike canine OA, feline disease tends to be non-weight-bearing, multifocal, and insidious, making it challenging to detect before advanced joint remodeling occurs [13]. Equine OA carries similarly grave implications. OA is responsible for more than 60% of lameness and early retirement cases in performance horses [16,17]. Pathogenesis commonly involves repetitive microtrauma, synovitis, and post-traumatic remodeling, providing a robust large-animal model for evaluating regenerative interventions relevant to both veterinary and human medicine [18]. Beyond its biological burden, OA imposes significant emotional and financial strain on owners and society. The average annual cost of OA management in large-breed dogs ($700 1200 USD) approaches that of chronic human arthritis, encompassing diagnostics, long-term pharmacotherapy, surgery, and rehabilitation.[118] These expenditures, coupled with progressive pain and reduced mobility, diminish animal welfare, impair the human animal bond, and contribute to caregiver stress and compassion fatigue.[119] Early retirement in horses related to OA has been associated with annual global economic losses exceeding $1 billion USD [19]. Consequently, OA in companion animals has emerged as a major One-Health (OH) issue, linking animal, human, and environmental health through shared risk factors (e.g., age, obesity, sedentary lifestyle, chronic inflammation) [20]. Collectively, these findings underscore osteoarthritis as a pervasive, multifactorial disease with profound welfare and economic implications across species, reinforcing the urgency for improved preventive, diagnostic, and regenerative strategies.

Current OA management paradigms remain largely palliative, aiming to control pain and preserve mobility rather than restore joint integrity [21]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids constitute first-line pharmacologic therapy and can provide temporary relief, yet they do not alter underlying disease progression and are associated with gastrointestinal ulceration, nephrotoxicity, and hepatotoxicity during chronic administration [22]. Adjunctive modalities, including (but not limited to) physiotherapy, weight management, nutraceutical supplementation (e.g., omega-3 fatty acids, glucosamine/chondroitin sulfate) and surgical interventions (i.e., arthroscopy, joint replacement, arthrodesis), offer incremental benefit but are costly, invasive, or variably effective depending on disease stage [23]. Surgical correction or replacement may improve biomechanics but rarely halts biochemical and inflammatory deterioration within the synovium and cartilage matrix. As a result, OA progression is often inevitable, leading to chronic pain, fibrosis, and irreversible functional decline despite multimodal care.

In response to these limitations, regenerative medicine has transformed the conceptual approach to OA management, shifting emphasis from symptom control toward disease modification and restoration of joint homeostasis. Among emerging strategies, mesenchymal stromal/stem cell (MSC) based therapies have gained substantial traction in veterinary practice due to their anti-inflammatory, trophic, and immunomodulatory capabilities [24,25]. Experimental and clinical studies demonstrate that MSCs can suppress pro-inflammatory cytokines (IL-1β, TNF-α), up-regulate anabolic growth factors (TGF-β, IGF-1, VEGF), enhance cartilage matrix synthesis, and promote macrophage polarization toward a reparative phenotype [26,27]. Consequently, MSC-based interventions are increasingly positioned as putative disease-modifying OA therapies across canine, feline, and equine species, representing a paradigm shift toward biologically guided veterinary orthopedics. Despite this promise, critical questions remain unanswered. Considerable heterogeneity exists in the sourcing of MSCs, with source ranging from autologous and allogeneic bone marrow, adipose tissue, and umbilical cord blood. Each source has variable manufacturing, dosing, and administration protocols [28]. The absence of standardized, comparative assessments of MSC sources hampers consensus regarding optimal therapeutic strategies and complicates regulatory oversight. Rigorous, head-to-head studies evaluating the safety, efficacy, and mechanistic

differences between MSC preparations are urgently required to inform evidence-based clinical adoption and guide future therapeutic development [27].

Pathophysiology of OA: Targets for Regeneration

OA pathogenesis in companion animals mirrors that in humans, characterized by progressive deterioration of the joint microenvironment, leading to chronic pain and loss of mobility. The articular cartilage, normally composed of highly organized type II collagen and proteoglycan-rich extracellular matrix (ECM), undergoes enzymatic degradation and structural breakdown under OA conditions [27]. Chondrocytes exhibit a phenotypic shift from matrix synthesis to catabolism, with impaired capacity for repair. Concurrently, the synovium develops chronic low-grade inflammation marked by hyperplasia of the synovial lining, infiltration of macrophages, and increased vascularity [29]. Subchondral bone undergoes pathological remodeling, including sclerosis, microfractures, and osteophyte formation, which exacerbate biomechanical instability and further accelerate cartilage degeneration [30] This triad of cartilage degradation, synovitis, and subchondral bone remodeling forms a self-perpetuating cycle of joint pathology that underpins the clinical manifestations of OA.

Inflammatory mediators play a central role in driving OA progression. Pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) are upregulated in synovial fluid and cartilage tissue of OA-affected joints, where they activate nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways in chondrocytes30. These cascades enhance expression of matrix-degrading enzymes including matrix metalloproteinases (MMP-1, MMP-3, MMP-13) and aggrecanases (ADAMTS-4, ADAMTS-5), leading to accelerated breakdown of collagen and aggrecan [31]. Additionally, pro-inflammatory cytokines suppress anabolic signals such as transforming growth factor-beta (TGF-β) and insulin-like growth factor-1 (IGF-1), shifting the balance toward net catabolism [32].

Beyond cartilage destruction, cytokine-driven synovial inflammation promotes angiogenesis, nociceptor sensitization, and effusion, contributing to chronic pain and functional decline [33]. This highlights the importance of immunomodulation as a therapeutic strategy. Modulating the inflammatory milieu, either through inhibition of catabolic mediators or induction of anti-inflammatory cytokines such as interleukin-10 (IL-10), represents a critical step toward restoring anabolic-catabolic equilibrium and preserving joint integrity [34]. Given the multifactorial pathogenesis of OA, regenerative strategies must extend beyond analgesia to target the fundamental disease mechanisms. The primary therapeutic goals include: (1) pain reduction through modulation of inflammatory pathways and nociceptor sensitization, (2) restoration of joint homeostasis by rebalancing anabolic and catabolic processes within cartilage and synovium, and (3) structural repair/regeneration of cartilage, subchondral bone, and other joint tissues [35]. Achieving these outcomes requires therapies capable of modifying the disease trajectory, not merely alleviating symptoms. Emerging regenerative approaches, particularly MSC-based therapies, aim to meet these objectives through paracrine signaling, immunomodulation, and stimulation of resident progenitor cells [36]. By secreting trophic factors such as prostaglandin E2, TGF-β, and vascular endothelial growth factor (VEGF), MSCs exert anti-inflammatory and pro-regenerative effects, positioning them as promising candidates for disease-modifying OA therapy [37].

Adipose-Derived MSCs (AD-MSCs): Current Use and Limitations

Adipose-derived MSCs (AD-MSCs) have emerged as one of the most widely utilized cell sources in veterinary regenerative medicine due to their relative abundance and accessibility. Adipose tissue yields higher concentrations of MSCs compared to bone marrow aspirates, with estimates suggesting a 500-fold greater frequency of stem/progenitor cells per unit volume [38]. The minimally invasive harvest procedures, often through subcutaneous fat excision or liposuction, make AD-MSCs attractive for autologous applications in canine, feline, and equine patients [39].

Mechanistically, AD-MSCs display hallmark MSC properties including adherence to plastic, multipotent differentiation capacity (osteogenic, chondrogenic, adipogenic lineages), and immunomodulatory activity [40], through prostaglandin E_2 (PGE_2), tumor necrosis factor-stimulated gene-6 (TSG-6), and interleukin-10 release [41], along with trophic factors that support angiogenesis and extracellular matrix synthesis [42]. Intra-articular AD-MSC administration in canine OA reduces synovial IL-1β and TNF-α concentrations within two weeks, correlating with improved kinetic gait metrics. These attributes suggest potential for both symptomatic relief and disease modification in OA. Clinical use of AD-MSCs in companion animals has expanded rapidly, though the evidence base remains heterogeneous and largely limited to small, uncontrolled studies. In dogs with OA, intra-articular injections of autologous AD-MSCs have been associated with short-term improvements in lameness scores, pain reduction, and enhanced mobility [43,44]. Similar findings have been reported in equine studies, where intra-articular AD-MSCs produced transient functional improvements [45]. However, robust evidence for cartilage regeneration or durable disease modification remains limited. Radiographic and MRI evaluations rarely demonstrate structural repair, and histological confirmation of cartilage regeneration is scarce. Moreover, the magnitude of clinical benefit varies widely between studies, with some reporting minimal or no long-term efficacy beyond 6-12 months post-treatment [46].

Concerns and Challenges

Despite their therapeutic potential, AD-MSCs carry risks associated with donor tissue biology. Most notably, adipose tissue

harvested from older or obese animals may contain senescent MSCs with diminished proliferative and differentiation capacity [47,48]. Furthermore, adipose depots can harbor pro-inflammatory cytokines (e.g., TNF-α, IL-6), raising concerns that transplanted cells may exacerbate local inflammation under certain conditions [49]. MSC quality is influenced by donor age, metabolic status, and comorbidities, factors that directly impact their immunomodulatory and regenerative function [50]. Autologous approaches may therefore be suboptimal in geriatric or metabolically compromised patients, the very populations most affected by OA. Harvesting adipose tissue requires surgical intervention under anesthesia, with attendant risks and costs. Ex vivo expansion to achieve therapeutic cell numbers introduces additional delays and expense, while repeat dosing, frequently necessary for sustained benefit, further compounds logistical challenges [51]. A major obstacle in AD-MSC therapy is variability in manufacturing standards across veterinary clinics. Differences in tissue processing, expansion protocols, and cell characterization can yield heterogeneous products with inconsistent potency [52]. The absence of uniform regulatory oversight in veterinary regenerative medicine compounds this variability, creating barriers to reproducibility and cross-study comparisons [53].

Umbilical-Derived MSCs (U-MSCs): A Next-Generation Solution

Umbilical-derived MSCs (U-MSCs) have garnered attention as a superior alternative to traditional adipose- and bone marrow derived MSCs. Biologically, U-MSCs possess an immune-privileged phenotype, characterized by low expression of major histocompatibility complex (MHC) class II molecules and costimulatory factors, reducing the risk of host immune recognition [54]. U-MSCs exhibit higher proliferative and differentiation capacity compared to adult tissue derived MSCs, attributable to their fetal origin and relatively "younger" biological status [55]. Importantly, U-MSCs secrete lower levels of pro-inflammatory cytokines such as TNF-α and IL-6 while maintaining robust secretion of trophic and anti-inflammatory mediators (IL-10, TGF-β, prostaglandin E2) [56]. This profile promotes a more regenerative intra-articular environment. Unlike autologous adult MSCs, U-MSCs are derived from standardized, donor-screened allogeneic sources, enabling greater consistency in product quality and potency [57].

One of the most compelling advantages of U-MSCs is their scalability. A single umbilical cord can yield millions of MSCs, which may be cryopreserved and expanded into large, bankable cell stocks [58]. This allows for the creation of off-the-shelf, allogeneic products that can be administered at the point of care without the need for invasive tissue harvest or ex vivo culture for each individual patient [59]. Compared to adipose- or bone marrow derived MSCs, U-MSCs thus provide a more cost-effective, logistically efficient solution for widespread clinical use.

Preclinical studies in companion animals support the therapeutic potential of U-MSCs in OA. In canine models, intra-articular administration of U-MSCs has been shown to reduce synovial inflammation, improve gait function, and preserve cartilage architecture compared to untreated controls or animals receiving AD-MSCs [60]. Equine studies similarly demonstrate that U-MSCs enhance cartilage integrity, modulate the synovial immune milieu, and result in superior lameness scores [61]. Mechanistically, MSC benefits appear to arise from paracrine effects on chondrocyte survival, subchondral bone remodeling, and suppression of synovial macrophage activation [62]. Available evidence indicates that U-MSCs possess an excellent safety profile [63]. Owing to their immune-privileged phenotype, they exhibit minimal risk of immune rejection following allogeneic administration. Unlike autologous MSC therapies, U-MSCs eliminate donor-site morbidity, sparing patients from surgical tissue harvest and associated complications [55]. To date, no significant adverse events have been reported in veterinary trials, and long-term follow-up suggests stable engraftment without tumorigenicity.

(Table 1) provides an integrated comparative analysis of AD-MSCs and U-MSCs across biological, immunologic, manufacturing, regulatory, and clinical dimensions relevant to companion-animal OA. AD-MSCs, obtained through surgical excision or liposuction of adult adipose tissue for autologous use, are influenced by donor-specific factors such as age, obesity, and metabolic status that modulate cellular yield and functional potency. In contrast, U-MSCs originate from perinatal birth tissue (umbilical cord/Wharton's jelly) and are isolated non-invasively from healthy, donor-screened animals, enabling ethically sourced, allogeneic, banked cell lots with uniform critical quality attributes (CQAs). Immunologically, AD-MSCs display variable inducible expression of human leukocyte antigen-DR (HLA-DR) and costimulatory molecules (CD40, CD80, CD86) following inflammatory priming, potentially enhancing host immune recognition, whereas U-MSCs maintain intrinsically low HLA-DR and costimulatory profiles that confer a "younger," immune-tolerant phenotype with reduced rejection risk. Functionally, AD-MSCs mediate PGE_2 and COX-1/COX-2 dependent suppression of T-cell proliferation and partial macrophage M2 polarization, but these effects are context-sensitive. U-MSCs demonstrate broader, more potent immunomodulation characterized by up-regulation of indoleamine 2,3-dioxygenase 1 (IDO1), induction of tolerogenic dendritic cells (DCs) and regulatory T-cells (Tregs), and sustained dampening of synovial inflammation. Secretome (i.e., total set of bioactive factors secreted by cells) and EV analyses further delineate source-specific signatures: AD-MSCs secrete high levels of PGE_2 and tumor necrosis factor stimulated gene-6 (TSG-6) but may exhibit elevated interleukin-6 (IL-6) and interleukin-8 (IL-8) in senescent donors, whereas U-MSC secretomes (are enriched in anti-inflammatory and trophic mediators such as transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and reparative microRNAs (miR-

21, miR-146a), yielding a more chondroprotective profile. Clinically, AD-MSC administration produces transient pain and lameness improvement without consistent cartilage regeneration, while placebo-controlled randomized clinical trials (RCTs) of allogeneic U-MSCs report significant gains in peak vertical force (PVF) and Canine Brief Pain Inventory (CBPI) scores with favorable safety, though long-term structural data remain limited. Manufacturing and regulatory contrasts are equally salient: AD-MSC preparations exhibit batch-to-batch heterogeneity from individualized, clinic-based processing with inconsistent adherence to Good Manufacturing Practice (GMP) or International Society for Cellular Therapy (ISCT) guidelines, whereas U-MSC products manufactured under centralized GMP workflows align with Advanced Therapy Medicinal Product (ATMP) and U.S. FDA Center for Veterinary Medicine (CVM) regulatory frameworks requiring validated potency assays (e.g., IDO1 activity, PGE_2 output). Logistically, AD-MSC therapy necessitates operating-room (OR) anesthesia, tissue harvest, and weeks of ex vivo expansion prior to reinjection, whereas U-MSCs offer cryopreserved, "off-the-shelf" formulations for immediate, point-of-care use, reducing procedural morbidity, cost, and variability by an estimated 30 50 %. Collectively, the table underscores that while AD-MSCs remain a feasible autologous option, U-MSCs provide superior immunobiological stability, scalability, and translational consistency, positioning them as a next-generation platform for disease-modifying OA therapy in veterinary regenerative medicine.

Table 1: integrated comparative analysis of AD-MSCs and U-MSCs across biological, immunologic, manufacturing, regulatory, and clinical dimensions relevant to companion-animal OA.

Dimension	AD-MSCs	U-MSCs
Tissue source & harvest	Adult adipose; surgical harvest (biopsy/lipoaspirate); autologous common	Birth tissue (cord/Wharton's jelly); no patient harvest; donor-screened allogeneic
Baseline immunogenicity	Adult tissue phenotype; HLA-DR/costimulatory expression can be induced by inflammatory priming	Lower HLA-DR/costimulatory expression; "younger" phenotype favors immune tolerance
Immunomodulatory mechanisms	Robust PGE_2/COX-1–linked T-cell suppression in some assays; variable macrophage skewing (M2)	Strong tolerogenic DC induction, Treg promotion; potent IDO1 upregulation with licensing
Secretome/EV profile	Rich in PGE_2, TSG-6; in some settings higher basal IL-6/IL-8; EVs emphasize immune regulation	EV/secretome enriched for tissue-repair/anti-inflammatory cargos; lower pro-inflammatory signature in several reports
Clinical OA evidence	Short-term pain/lameness improvement; heterogeneity; durability inconsistent	Placebo-controlled canine RCTs show functional gains and favorable safety through 3–6 mo; long-term structure-modifying data still limited
Consistency & scalability	Donor-to-donor variability (age, obesity, comorbidities); batch expansion per patient	High scalability from one cord; banked lots with defined CQAs and release tests
Regulatory fit	Often clinic-specific processing; variable adherence to GMP/ISCT reporting	Streamlined GMP workflows; aligns with ATMP/new animal drug frameworks and potency expectations
Logistics/cost	OR/anesthesia, culture lead-times, repeat harvests for redosing	Off-the-shelf, point-of-care dosing; reduced procedure burden

HLA-DR: A class II major histocompatibility complex (MHC) molecule involved in antigen presentation to helper T-cells; PGE_2: prostaglandin E2; COX-1/COX-2: cyclooxygenase-1/2; M2 macrophages: Anti-inflammatory macrophage subset promoting tissue healing; DC: Dendritic cell; Treg: Regulatory T-cell; suppresses excessive immune responses; IDO1: Indoleamine 2,3-dioxygenase 1; an enzyme mediating tryptophan catabolism that inhibits T-cell proliferation; EV: Extracellular vesicle; TSG-6: Tumor necrosis factor stimulated gene-6 protein; IL-6/IL-8: Pro-inflammatory cytokines; CQA: Critical Quality Attribute; GMP: Good Manufacturing Practice; ISCT: International Society for Cellular Therapy; ATMP: Advanced Therapy Medicinal Product; EU classification for cell and gene therapies; FDA/CVM: U.S. Food and Drug Administration, Center for Veterinary Medicine; EMA: European Medicines Agency.

Comparative Analysis: AD-MSCs vs. U-MSCs

Both AD-MSCs and U-MSCs share canonical immunomodulatory and trophic functions; however, mounting comparative evidence delineates distinct mechanistic, molecular, and translational profiles that directly impact therapeutic outcomes in companion-animal OA. Mechanistically, both AD-MSCs and U-MSCs suppress T-cell activation, attenuate pro-inflammatory cytokine cascades, and reprogram macrophages toward an anti-inflammatory M2 phenotype through paracrine signaling [64,65] Yet, U-MSCs display a broader, more durable immunoregulatory repertoire. Their potency derives from a lower baseline immunogenicity, manifested by minimal HLA-DR and costimulatory marker expression, even under inflammatory priming, whereas AD-MSCs exhibit inducible upregulation of HLA-DR, CD40, and CD80/CD86 that can increase

host immune recognition under high IFN-γ or TNF-α conditions [66]. This phenotypic resilience of U-MSCs allows sustained anti-inflammatory signaling within the synovial microenvironment, promoting macrophage tolerance and cartilage matrix preservation. Functional divergence also arises in enzymatic and metabolic pathways [67]: AD-MSCs primarily mediate PGE_2 dependent COX-1/COX-2 suppression of T-cell proliferation [68], while U-MSCs rely on IDO1 linked tryptophan catabolism, leading to kynurenine accumulation, Treg induction, and DC tolerization [69]. Comparative proteomic and EV profiling further underscores that U-MSC secretomes are enriched in transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), VEGF, and anti-inflammatory microRNAs such as miR-21 and miR-146a, enhancing chondrocyte anabolism and angiogenic balance [70], AD-MSCs, conversely, often demonstrate elevated IL-6 and IL-8 in senescent or metabolically impaired donors, conferring variable inflammatory risk [55,71]. The secretomic landscape of each source is further modulated by

Summary. AD-MSCs have established clinical feasibility for palliative management of OA in companion animals; however, their therapeutic consistency is constrained by donor-linked heterogeneity, age-related senescence, and metabolic-inflammatory shifts that attenuate regenerative potency. Despite short-term improvements in pain, mobility, and owner-reported quality-of-life scores, AD-MSC therapy seldom achieves sustained cartilage restoration or long-term modification of the disease trajectory, reflecting limited control over donor variability, secretory phenotype, and in-vivo persistence. Age- and obesity-associated mitochondrial dysfunction and the senescence-associated secretory phenotype (SASP) drive pro-inflammatory cytokine output (IL-6, IL-8, MCP-1) and diminish trophic signaling, reducing the chondrotrophic and immunoregulatory efficacy of AD-MSCs.

U-MSCs, in contrast, represent a biologically younger, epigenetically stable, and immunoprivileged cell population that exhibits superior proliferative kinetics, higher clonogenic potential, and a more favorable cytokine and EV signature. The low basal expression of HLA-DR and costimulatory molecules, coupled with strong inducibility of IDO1 and prostaglandin E_2 under inflammatory licensing, endows U-MSCs with enhanced tolerance and context-responsive immunomodulation relative to adult-tissue sources. Their secretomes and EVs carry enriched profiles of anti-inflammatory and pro-regenerative cargos (e.g., TGF-β, HGF, VEGF, and miRNAs regulating NF-κB, Wnt, and mTOR pathways) positioning them as mechanistically potent candidates for structural and symptomatic OA repair. When integrated with advanced biomaterial delivery systems (e.g., hyaluronan-gel matrices, self-assembling hydrogels, and nanofiber scaffolds), U-MSCs achieve improved intra-articular persistence, localized factor release, and mechanotransductive stimulation that together prolong therapeutic efficacy. The future trajectory of veterinary regenerative orthopedics should therefore shift from empirical application toward mechanism-guided, evidence-based development. Priority objectives include:

i. Multicenter, randomized controlled trials (RCTs) directly comparing AD-MSCs and U-MSCs using blinded kinetic and imaging endpoints (force-plate PVF, MRI T_2 mapping, quantitative synovial cytokine and EV biomarkers) to define source-specific efficacy profiles and durability.

ii. Standardized chemistry-manufacturing-control (CMC) frameworks operating under GMP with validated potency panels encompassing IDO1 enzymatic activity, PGE_2 quantification, NF-κB suppression, and EV functional bioassays, as well as stability, identity (CD73/CD90/CD105), and sterility testing to ensure lot-to-lot reproducibility.

iii. Harmonized cross-species outcome frameworks linking veterinary and human OA assessment tools to create OH-aligned regulatory and translational pathways that enable bidirectional learning and accelerate clinical adoption [72-76].

In this integrated paradigm, U-MSCs and their cell-free derivatives (EVs, conditioned media) provide a scalable, ethically sourced, and biologically consistent platform that unites cellular immunology, biomaterials science, and translational bioengineering. Such convergence will not only elevate the rigor of regenerative therapy for companion-animal OA but also serve as a predictive and ethically efficient preclinical bridge to human OA therapeutics, advancing the shared goals of the OH framework toward sustainable, cross-species musculoskeletal regeneration.

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