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REVIEW

How Selective are Nanomaterials to Treat Osteoarthritis

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Abstract: Osteoarthritis (OA) is now increasingly recognized as a disease that affects the entire joint, where synovial inflammation plays a key role in pain, cartilage degeneration, and structural progression. Synovial macrophages (SMs) are key regulators in this process due to their phenotypic plasticity and central roles in amplifying inflammation, disrupting immunometabolism, and interacting with other joint-resident cells. These characteristics make SMs attractive targets for disease-modifying interventions. However, conventional therapies are limited by poor intra-articular retention, low cellular selectivity, and inadequate control over complex pathogenic networks. This review summarizes the biological functions of SMs in OA and explains why they are a mechanistically important and therapeutically accessible target. Next, we provide a structured overview of nanomaterial-based strategies for SM-targeted OA therapy, covering major material platforms, receptor-guided delivery approaches, subset- and state-selective targeting, intracellular functional intervention, and multi-target combination designs. We highlight representative studies that show how nanomedicines can improve local retention, enhance macrophage-specific uptake, and modulate inflammation, metabolism, oxidative stress, and cell fate. Finally, we discuss the major barriers to clinical translation, such as macrophage heterogeneity, safety, pharmacokinetics, and chemistry, manufacturing, and controls (CMC), and outline future directions for biomarker-guided and precision nanotherapy in OA.

Keywords: osteoarthritis, synovial inflammation, synovial macrophages, nanomedicine, precision therapy, nanocarriers

Introduction

Osteoarthritis (OA) is a common degenerative joint disorder affecting millions worldwide, leading to significant socio-economic burdens, including chronic pain, reduced mobility, and rising healthcare costs.[1,2] OA is characterized by progressive cartilage degradation, subchondral bone remodeling, and chronic synovitis, manifesting as a multifactorial disease driven by mechanical, inflammatory, and metabolic factors.[3,4] Despite its high prevalence, especially in aging populations, current therapies—such as NSAIDs, intra-articular corticosteroids, and joint replacement—mainly provide symptomatic relief and do not halt disease progression, highlighting the urgent need for innovative approaches targeting the underlying pathophysiology.[5,6]

Synovial macrophages (SMs) are key immune effectors in the OA joint microenvironment, playing a central role in orchestrating inflammatory cascades, pain sensitization, and structural damage through their phenotypic plasticity, including transitions between pro-inflammatory M1 and reparative M2 states.[7,8] These cells amplify damage-associated molecular patterns (DAMPs), reactive oxygen species (ROS), and cytokine networks, thereby exacerbating synovitis and contributing to cartilage degradation.[9,10] Despite growing recognition of their critical role, targeting SMs for therapeutic purposes remains underexplored in OA, with traditional approaches limited by network redundancy and insufficient specificity for macrophage subtypes. Targeting SMs holds substantial therapeutic promise for concurrently

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mitigating pain, inflammation, and tissue remodeling.[11] However, conventional approaches, such as single-cytokine blockade or broad-spectrum anti-inflammatories, are limited by network redundancy, inadequate specificity for macrophage subsets, rapid joint clearance, and inconsistent efficacy across heterogeneous patient populations.[10,12] In recent years, nanomedicine has emerged as a transformative approach to overcome these challenges, offering engineered nanomaterials, such as lipid carriers, polymeric systems, and biomimetic platforms, that enable precise targeting of SMs in OA.[13,14] Nanomedicine bridges the gap between OA's inflammatory drivers and macrophage-centric interventions by facilitating receptor-mediated uptake, microenvironment-responsive release, and multifunctional modulation. This enhances intra-articular retention, minimizes off-target effects, and targets upstream hubs to achieve sustained disease modification.[15–17]

This review synthesizes mechanistic insights into synovial macrophage function in OA, explores nanomaterial designs for targeted SM delivery, and evaluates translational opportunities, aiming to position nanomedicine as a cornerstone for advanced OA management. By highlighting cutting-edge developments and clinical pathways—including stratified trials, biomarker integration, and safety profiling, we aim to guide future research toward clinically viable solutions that address OA's complexity and improve patient outcomes.

How Significant are Synovial Macrophages as Drug Targets

SMs as Central Regulators in OA

In OA, symptoms and structural progression are often partially dissociated. Synovitis frequently serves as an inflammatory hub that re-establishes the link between subjective pain and objective disease progression (Figure 1).[18] Therefore, this review focuses on SMs, targeting a central "pivot" that may concurrently account for pain, recurrent inflammation, and structural degeneration.[19,20] Recent population-based and imaging studies further corroborate this view. Ultrasound-detected synovitis is linked to both the presence of OA and the severity of symptoms in the knee and hand. Longitudinal analyses and Mendelian randomization (MR) studies suggest a bidirectional relationship between synovitis and OA,

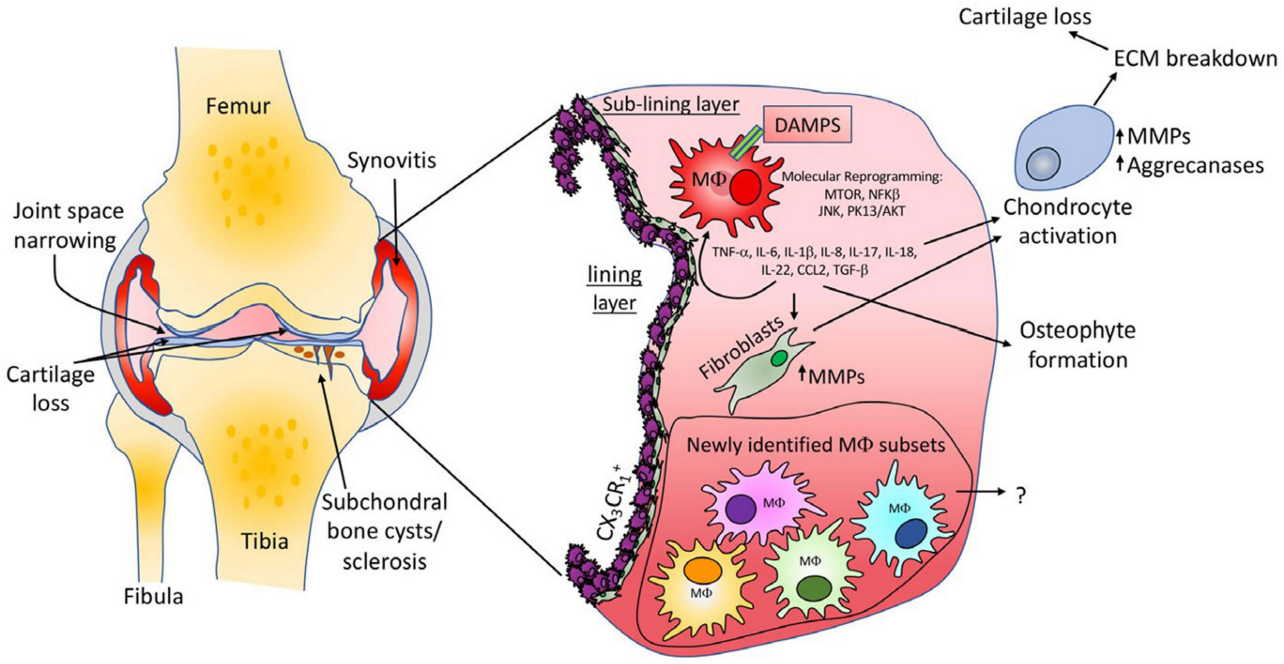

Figure 1 The role and mechanisms of SMs in OA are illustrated in the schematic overview of osteoarthritic joint changes, including synovitis, joint space narrowing, cartilage loss, and subchondral bone sclerosis/cysts, highlighting the central role of SMs. DAMPs, derived from damaged tissues, activate macrophages in the lining and sub-lining layers, triggering signaling reprogramming (eg, mTOR, NF-κB, JNK, PI3K/AKT) and the release of cytokines/chemokines (eg, TNF-α, IL-1β, IL-6, IL-8, IL-17/18/22, CCL2, TGF-β). These mediators enhance MMP/aggrecanase production, promote chondrocyte and fibroblast activation, accelerate ECM breakdown and cartilage degeneration, and contribute to osteophyte formation and subchondral remodeling. Different macrophage subsets may exert distinct effects during OA progression. Adapted from Thomson A, Hilkens CMU. Synovial Macrophages in Osteoarthritis: The Key to Understanding Pathogenesis? Front Immunol. Copyright © 2023by authors.[18]

indicating that synovitis may serve as both a risk factor and a consequence of the disease. This bidirectionality may partly explain why rheumatoid arthritis–style broad-spectrum anti-inflammatory or anti-cytokine strategies do not consistently provide benefits in OA.[20] Regarding structural outcomes, 4-year MRI data from the Osteoarthritis Initiative (OAI) cohort revealed that persistent synovitis is linked to faster progression of structural damage, including worsening meniscal pathology, bone marrow lesions, and cartilage degeneration scores. These findings suggest that synovitis is not merely an epiphenomenon but may accelerate structural degeneration.[19] Regarding pain outcomes, cross-sectional studies report a stronger correlation between synovitis and persistent pain. This relationship is observed even in early imaging stages, supporting the hypothesis that synovitis-driven sensitization and pain amplification can occur independently of purely mechanical wear.[21] Furthermore, ultrasound-guided synovial biopsy studies indicate that histological synovitis correlates with the extent of radiographic damage, suggesting that synovitis severity may serve as a marker of structural risk.[22] We propose the centrality of macrophages within the synovitis network, as monocyte–macrophage lineage cells are often abundant in OA synovium and synovial fluid. These cells exhibit significant plasticity and correlate with the distribution and activation states of other immune populations, supporting their role in shaping the local microenvironment.[23]

SMs exhibit heterogeneity. In the synovial lining, subsets like $CX3CR1^{+}TREM2^{+}$ cells appear to support barrier integrity and homeostasis, possibly through the expression of tight-junction–related molecules, thereby limiting inflammatory spread and preserving intra-articular homeostasis. When this barrier is disrupted, the persistent influx of damage-associated molecular patterns (DAMPs, such as cartilage fragments and matrix degradation products) can promote monocyte recruitment and the expansion of pro-inflammatory macrophages. This shift may drive the synovium toward low-grade, chronic inflammation and fibrosis.[18,24] At the cellular interaction level, macrophages and fibroblast-like synoviocytes (FLS) form a positive feedback loop. Macrophages release TNF- and IL-1–like signals and lipid mediators, which can induce an inflammatory, tissue-remodeling FLS phenotype. In turn, FLS promote monocyte recruitment and sustain macrophage survival and polarization through chemotactic programs (eg, the CCL2–CSF axis), thereby converting transient inflammation into tissue-level chronicity.[16,18,25] Along the macrophage–T cell axis, synovial fluid and synovial monocyte–macrophage subsets differ in their ability to stimulate T cells; some subsets show limited T cell activation but enhanced migratory potential. These observations suggest that OA is not devoid of immune interactions. Instead, immune interactions may be relatively low-intensity, heterogeneous, and spatiotemporally stratified, potentially contributing to inter-individual variability in pain and disease progression.[23,26] In innate immune synergy, neutrophils act as early amplifiers of inflammation. Their effector products— ROS, proteases, and neutrophil extracellular traps (NETs), can directly exacerbate tissue damage and amplify inflammatory signals that further activate or reprogram macrophage responses, potentially shifting synovitis from reversible to self-sustaining.[27,28] Mast cells may also contribute to sustained synovitis and neuroimmune coupling through degranulation mediators and cytokines, in conjunction with the inflammatory milieu of synovial fluid. In this context, mast cells may act as initiators and amplifiers of pain and inflammatory flares.[29,30] Therefore, targeting macrophages may provide broader benefits than inhibiting a single cytokine. Several conventional anti-inflammatory and biologic agents have failed to show consistent clinical benefit in OA trials, suggesting that single-pathway blockade may be inadequate to address the redundant inflammatory network of OA synovitis. Mechanistically, macrophages occupy an upstream hub that integrates DAMP sensing, intercellular communication, and the output of multiple inflammatory mediators. Therapeutic strategies that limit macrophage recruitment or promote functional reprogramming, for example, shifting macrophages from a pro-inflammatory to a pro-repair state via TREM2-related pathways—could, in principle, dampen multiple pain and tissue-injury pathways simultaneously. Such upstream modulation may also attenuate downstream inflammatory circuits involving FLS, T cells, neutrophils, and mast cells.[16,18,31,32]

Macrophage Ontogeny, Renewal, and Niche Dynamics in OA Synovitis

Understanding the ontogeny, renewal dynamics, and spatial niches of SMs is crucial not only for explaining how macrophages sustain OA synovitis, but also for addressing a key translational question: which macrophage populations are sufficiently stable, spatially constrained, and drug-accessible within the joint to enable truly targeted therapy (Figure 2).[25,33,34] Recent lineage-tracing and single-cell studies suggest that SMs arise from at least two major sources: long-lived, self-renewing tissue-resident macrophages (TRMs) and monocyte-derived macrophages, which are recruited

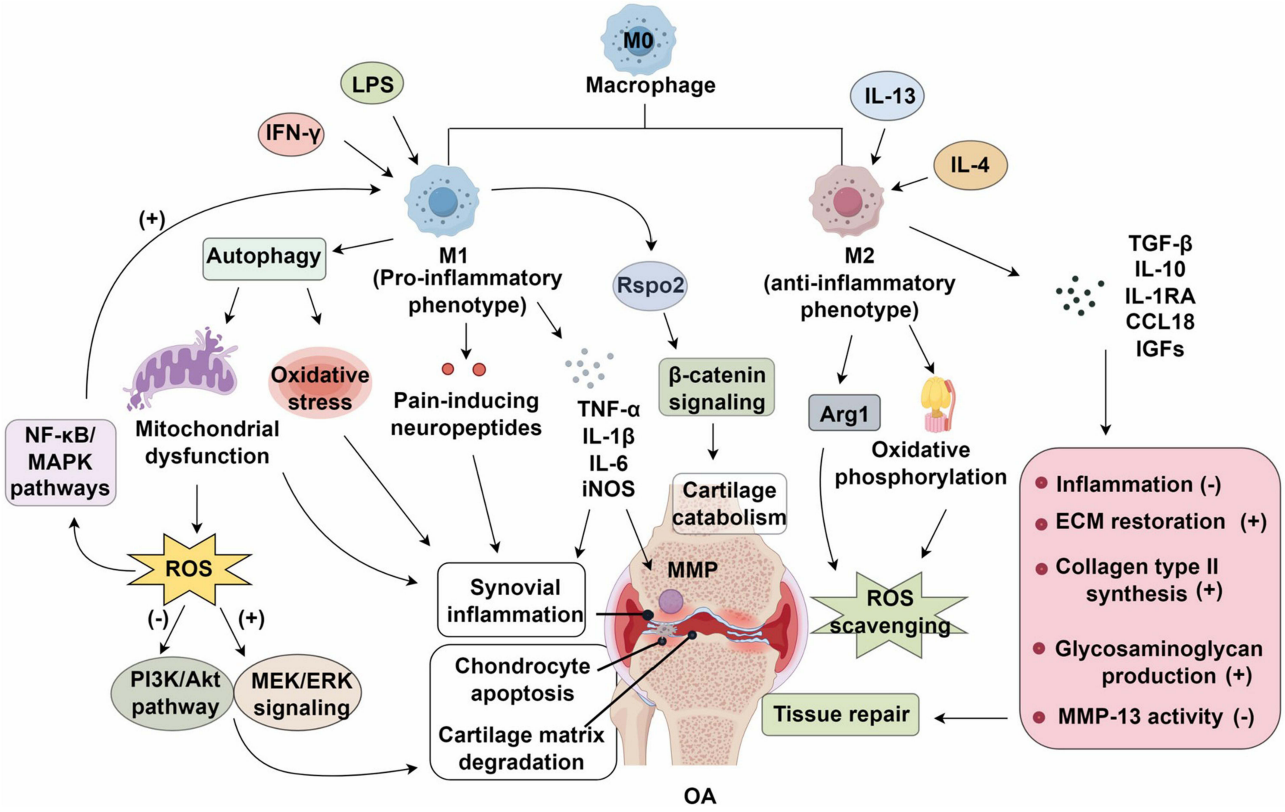

Figure 2 Origin, renewal, and functional polarization of SMs in OA. Schematic representation of the origin, renewal, and spatial–functional heterogeneity of SMs in OA. SMs arise from circulating monocytes (M0) and undergo dynamic polarization in response to microenvironmental cues. Pro-inflammatory stimuli (eg, LPS and IFN-γ) drive macrophages toward an M1 phenotype, characterized by activation of NF-κB/MAPK signaling, mitochondrial dysfunction, oxidative stress, and autophagy, leading to ROS production, synovial inflammation, chondrocyte apoptosis, cartilage matrix degradation, and pain-associated neuropeptide release. In contrast, IL-4 and IL-13 promote M2 polarization, which supports anti-inflammatory responses, ROS scavenging, tissue repair, and extracellular matrix restoration through factors such as TGF-β, IL-10, IL-1RA, CCL18, and IGFs. The balance between distinct macrophage subsets within specific synovial niches critically regulates inflammation, cartilage catabolism, and repair during OA progression. Adapted from Zhang K, Wang Z, He J et al Mechanisms of synovial macrophage polarization in osteoarthritis pathogenesis and their therapeutic implications. Front Immunol. Copyright © 2025 by authors.[25]

and differentiate in large numbers during inflammation or injury. Importantly, these lineages do not simply coexist in parallel; instead, synovial niche cues selectively permit monocyte entry, constrain differentiation, or promote the replacement of resident cells.[34,35] In mouse models, disruption of retention-supporting niches—such as the loss of resident macrophage homeostasis—facilitates the entry of circulating monocytes into the synovium. These monocytes can occupy vacated niches and differentiate into SMs, linking cellular "source replacement" to the histological persistence of chronic inflammation. These findings provide a mechanistic rationale for targeting macrophage renewal and replenishment pathways.[35] In OA, spatial localization closely correlates with function. Barrier-like macrophages in the synovial lining express CX3CR1 and TREM2 and are enriched in tight-junction–associated molecules (eg, claudin-5), forming an immunological boundary that limits the entry of peripheral immune cells into the joint cavity. Disruption of PRG4 (lubricin) signaling or increased oxidative stress can impair this barrier phenotype. Inhibition of xanthine oxidase (XO) attenuates ROS–HIF-1α signaling, restores barrier-associated markers, and is accompanied by a reduction in synovial thickness. Together, these observations suggest that the lining barrier is not irreversibly damaged and may be reconstructed through modulation of immunometabolic pathways.[24]

Consistently, PRG4 deficiency increases the overall abundance of SMs, biases them toward a pro-inflammatory phenotype, and enhances monocyte recruitment and the influx of inflammatory macrophages into the joint. Furthermore, macrophage depletion reduces markers of synovial hyperplasia and fibrosis, suggesting that macrophage origin, renewal, and phenotype are interdependent, rather than independent, determinants of synovial remodeling.[36] In post-traumatic OA (PTOA) models, SMs exhibit finer stratification and dynamic state transitions, accompanied by the activation of renewal

and survival programs, such as M-CSF (CSF1) signaling. These findings suggest that local growth-factor networks can drive macrophage expansion and phenotypic switching, making the blockade of renewal pathways—or reprogramming their direction—potentially actionable therapeutic strategies.[35,37] Single-cell atlases of human OA extend these niche concepts to disease classification. Knee OA synovium may display distinct transcriptional programs, consistent with inflammatory versus fibrotic phenotypes. This implies that the surrounding cellular and extracellular-matrix context—such as fibroblast states and vascular microenvironments—shapes macrophage recruitment, retention, and effector output, positioning spatial niche as a key factor in explaining heterogeneity and designing stratified therapies.[38,39] When the lining barrier is compromised or synovial exudation occurs, large numbers of mononuclear phagocyte-lineage cells appear in the joint cavity as multiple subpopulations. These subsets correlate with the distribution and activation of other immune cells, suggesting that barrier breach–associated exudation and cell trafficking may provide an observable window for peripheral immune modulation in OA.[39] Studies also suggest that after barrier disruption, resident SMs can migrate into synovial fluid and upregulate pro-fibrotic and pro-osteoclastogenic pathways (eg, sRANKL-associated programs) within the inflammatory fluid milieu. This links niche migration to mechanisms that may contribute to structural damage.[40] Aging-related immune remodeling may further shift therapeutic priorities. Recent studies report an increased burden of senescent-like macrophages in OA synovium, characterized by an amplified senescence-associated secretory phenotype (SASP), mitochondrial dysfunction, and impaired efferocytosis (clearance of apoptotic cells). In mice, interventions that modulate p53-driven senescence signaling via biomaterial-based delivery, along with strategies that enhance phagocytic clearance through the STAT3–ADAM17–MerTK axis, alleviate both trauma-induced and age-associated OA. These results suggest that renewal failure and senescent-cell accumulation represent modifiable niche states.[41]

DAMP Sensing and Macrophage Activation in OA: Mechanisms of Inflammation and Pain

Throughout the continuum from joint injury to clinical symptoms, recognition of DAMPs by synovial immune cells is often an early event and a significant amplifier of downstream pathology. Therefore, delineating the pathway from DAMP sensing to innate immune activation, and subsequently to inflammation, cartilage damage, and pain, helps explain why synovial macrophage–centered mechanisms represent feasible and modifiable therapeutic targets.[42–44] In synovial fluid from patients with joint injury or OA, alarmins such as HMGB1 and S100A8/A9 are often elevated early and seem to correspond to distinct inflammatory profiles. HMGB1 is more strongly associated with cartilage degradation biomarkers, whereas S100A8/A9 aligns more closely with pro-inflammatory cytokine modules. This pattern suggests that distinct DAMP signals may bias downstream programs toward tissue destruction via different inflammatory pathways.[45] Mechanistically, HMGB1—an OA-relevant DAMP—can trigger p65 nuclear translocation and activate NF-κB and MAPK signaling (eg, phosphorylation of IKKβ, JNK, and ERK) through a TLR4-dominant macrophage activation axis. This signaling promotes M1-like polarization and the release of inflammatory mediators such as TNF-α. In this context, NOD2 functions as a negative regulator of HMGB1–TLR4 signaling, helping to limit macrophage overactivation.[44] DAMP-triggered macrophage activation extends beyond a single-cytokine effect and propagates pathology across joint tissues via paracrine signaling. Macrophage-conditioned media enhance FLS invasion, migration, and adhesion programs (eg, p-FAK–associated phenotypes). It also shifts chondrocytes toward a catabolic transcriptional state, upregulating MMP3/MMP13 and ADAMTS4/5 while downregulating anabolic markers such as COL2A1, aggrecan, and SOX9. Collectively, these effects provide a mechanism by which synovitis can be translated into cartilage structural degeneration.[44] Moreover, macrophages not only produce inflammatory mediators but also amplify danger signaling through inflammatory cell-death pathways. In human OA samples and collagen-induced OA (CIOA) models, SMs exhibit gasdermin D (GSDMD)–dependent pyroptosis, accompanied by increased ROS, aberrant mTORC1 activation, and elevated MMP9. Together, these changes may form a self-reinforcing loop that links inflammation to matrix degradation[45] Under pyroptosis-associated mitochondrial stress, mitochondrial DNA leakage activates the cGAS–STING pathway. Targeted delivery of functionalized nanoparticles that simultaneously inhibit pyroptosis, reduce ROS, suppress cGAS–STING activation, and promote mitophagy has been shown to reduce synovial pathology and protect cartilage

in vivo. These results suggest that upstream nodes in the DAMP-to-innate-sensing cascade are pharmacologically addressable.[45] Notably, cytosolic DNA sensing is not confined to immune cells. In OA-like chondrocytes and in human and murine OA cartilage, cGAS and STING expression are upregulated, and STING deficiency alleviates cartilage damage and subchondral bone sclerosis. However, intra-articular administration of cGAMP exacerbates structural damage, suggesting that STING may act as a convergence point for DAMP-related sensing across joint tissue.[42] Importantly, STING links structural pathology to pain phenotypes. STING signaling regulates the expression of peripheral sensitization mediators in the synovium and meniscus, and genetic STING deficiency alleviates mechanical allodynia. Together, these findings provide a testable and modifiable mechanistic link between DAMP-triggered innate immune activation and OA pain.[42]

SMs as Targets for OA Treatment: Advancements in Targeted Nanotherapy and Immune Modulation

Accumulating evidence indicates that OA is not just a "wear-and-tear" disorder but involves an inflammatory phenotype, in which synovitis plays a central role. Consequently, leveraging macrophages for targeted intra-articular delivery of therapeutic materials has emerged as a key strategy for OA treatment.[46,47] Repeated setbacks in synovitis-focused therapies are evident in randomized trials where single-cytokine targeting (eg, IL-1 or TNF) has shown inconsistent or limited efficacy. This pattern suggests considerable redundancy and compensatory bypass within the inflammatory network, making single-node blockade unlikely to meaningfully alter the disease trajectory.[47,48] In this context, SMs act as upstream hubs within the joint immune network. By sensing DAMPs through pattern-recognition receptors and activating transcriptional programs such as NF-κB and MAPK, they can amplify cytokine/chemokine production and oxidative stress, promote FLS activation, and reinforce inflammatory circuitry. These downstream effects support catabolic cartilage metabolism and may contribute to neuroinflammatory processes, making macrophage-centered intervention a broader "lever" than targeting a single mediator (Figure 3).[46,48] Beyond their signaling roles, macrophages exhibit high phagocytic capacity and efficient uptake mediated by scavenger and Fc receptors. This makes them well-suited for selective targeting by biomaterials in local intra-articular delivery, reframing immune modulation from a purely pharmacological challenge to one of engineered delivery and cellular selectivity.[49,50] Compared with conventional OA treatments, such as NSAIDs, intra-articular corticosteroids, and hyaluronic acid supplementation, SM-targeted nanotherapeutic strategies are designed not only to relieve symptoms but also to more directly intervene in the inflammatory and metabolic drivers of disease progression.[51,52] In contrast to single-cytokine blockade or broad anti-inflammatory therapy, which may be limited by pathway redundancy and insufficient joint retention, nanomaterial-based systems can integrate local delivery, cell-selective uptake, sustained release, and multi-pathway modulation within a single platform. Moreover, compared with emerging regenerative or cell-based strategies that primarily focus on cartilage repair or tissue replacement, macrophage-targeted nanotherapy may offer a complementary advantage by simultaneously reshaping the synovial immune microenvironment, which contributes to persistent inflammation, oxidative stress, and structural deterioration.[53,54] Therefore, this strategy may be viewed not just as another anti-inflammatory approach, but as a bridge between symptom control, immune regulation, and disease-modifying intervention. For example, an "opsonization-trap" strategy coats nanocarriers with IgG to exploit preferential FcγR-mediated uptake by inflammatory (M1-like) macrophages. Intracellular drug release can then promote M1-to-M2 reprogramming, dampen inflammation, and improve tissue repair outcome.[49] Within the same delivery framework, subsequent studies have emphasized metabolic reprogramming. IgG/Fe-based CV nanoparticles targeting M1-like macrophages suppress HIF-1α/GLUT1-driven aerobic glycolysis and limit glutamine uptake, thereby shifting cellular energetics from glycolysis to oxidative phosphorylation. This metabolic shift helps rebalance M1/M2 states and reduce OA-related cartilage damage.[55]

A more biomimetic strategy utilizes macrophage-membrane coatings to confer inflammatory chemotaxis and partial immune-evasive properties. Membrane proteins and adhesion axes (eg, hyaluronic acid–CD44) enhance accumulation within inflamed synovium, enabling carriers to co-deliver multimodal cargos such as anti-inflammatory peptides and nucleic acids. This platform supports the parallel modulation of multiple pathways, potentially outperforming single-cytokine blockade.[48] Similarly, phosphatidylserine (PS) nanoliposomes, inspired by apoptotic bodies, engineer an "eat-

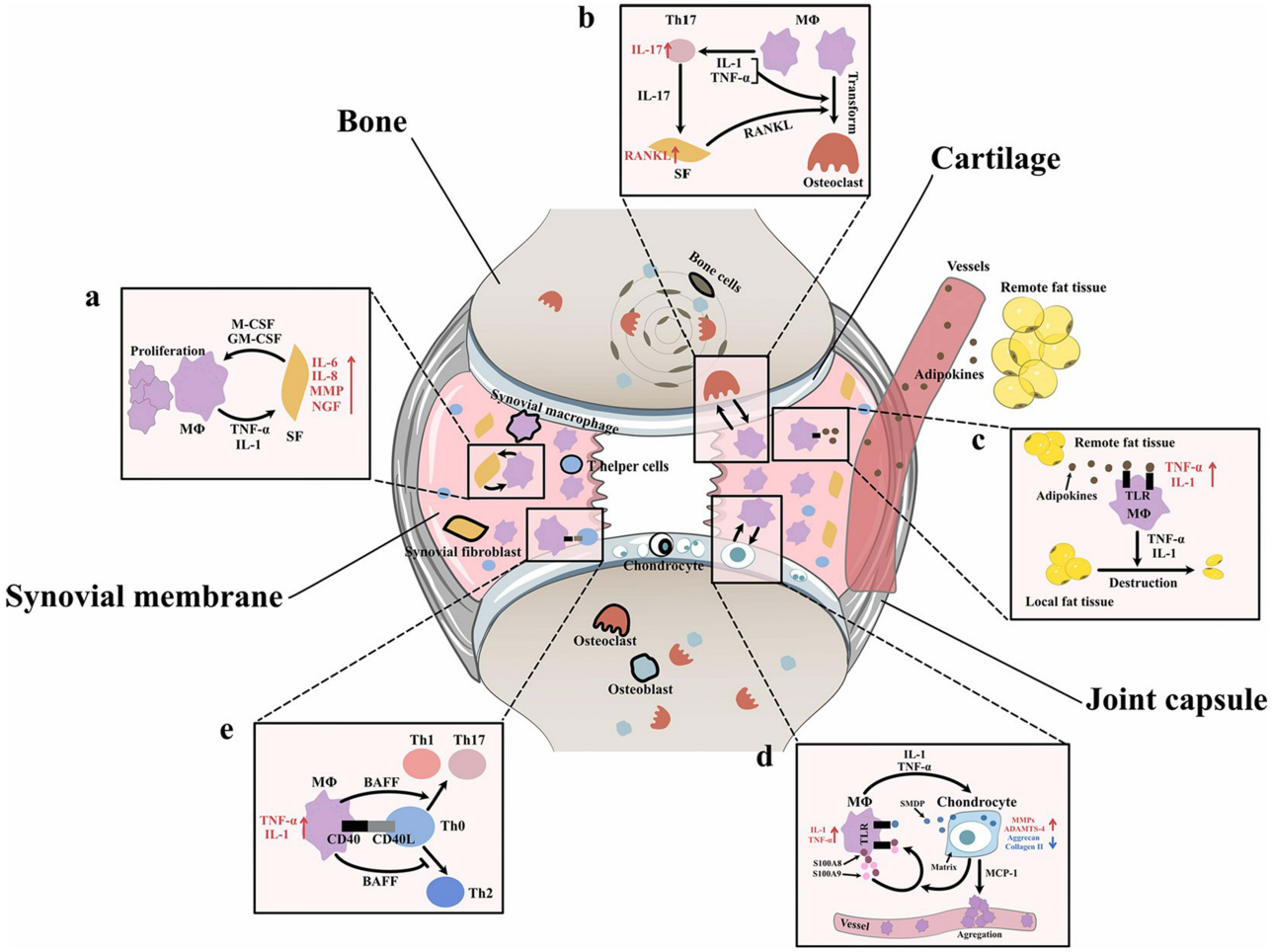

Figure 3 Interactions between synovial macrophages and other cells in OA pathogenesis. This diagram highlights the complex interplay between synovial macrophages and various cell types in OA. (**a**) In the synovial membrane, macrophages (MΦ), stimulated by M-CSF and GM-CSF, proliferate and produce pro-inflammatory cytokines (TNF-α, IL-1), as well as chemokines (IL-6, IL-8) and matrix metalloproteinases (MMP), which contribute to cartilage degradation. (**b**) Th17 cells, activated by IL-17, induce further macrophage polarization toward the M1 phenotype via the RANKL signaling pathway, enhancing the inflammatory cascade and promoting osteoclast differentiation, which accelerates bone destruction. (**c**) Remote fat tissue secretes adipokines that activate Toll-like receptors (TLRs) on macrophages, driving local inflammation and contributing to cartilage degradation through TNF-α and IL-1 production. (**d**) In cartilage, macrophage-secreted factors such as IL-1 and TNF-α exacerbate chondrocyte dysfunction, stimulating matrix degradation and cell apoptosis, ultimately contributing to OA progression. (**e**) Additionally, synovial macrophages engage in bidirectional signaling with T-helper cells (Th1 and Th17), activating the BAFF-CD40 pathway, which further amplifies the immune response and inflammatory environment. These interactions underscore the central role of synovial macrophages in driving OA inflammation and tissue destruction, highlighting potential therapeutic targets within these cellular crosstalks. Adapted from Zhao K, Ruan J, Nie L, Ye X, Li J. Effects of synovial macrophages in osteoarthritis. *Front Immunol.* Copyright © 2023by authors.[56]

me" signal, promoting preferential recognition and uptake by macrophages over fibroblast-like synoviocytes (FLS). These nanoliposomes also deliver the BRD4 inhibitor JQ1 to suppress M1 polarization and attenuate downstream pain-related programs, including TRPA1. Together, these effects highlight the translational potential of concurrently targeting epigenetic regulation, inflammation, and pain.[57] Furthermore, PGAM5 is upregulated in OA SMs. It promotes M1-like polarization via AKT–mTOR and p38/ERK signaling, while suppressing M2 polarization through the STAT6–PPARγ axis. Building on this mechanism, siPGAM5 was delivered using mannose-modified fluoropolymers to enable CD206-mediated uptake and selective silencing in SMs. This approach directly reverses pro-inflammatory polarization at a mechanistic level (Figure 4).[58]

In summary, the translational appeal of targeting SMs lies not in adding another anti-inflammatory target, but in focusing a highly redundant joint inflammatory network on a locally accessible cellular node. This node can be selectively targeted by engineered carriers and reprogrammed through complementary mechanisms spanning metabolism, epigenetics, and signal transduction. These features provide a biological rationale for designing selective and durable material-based interventions.[46,47,59,60]

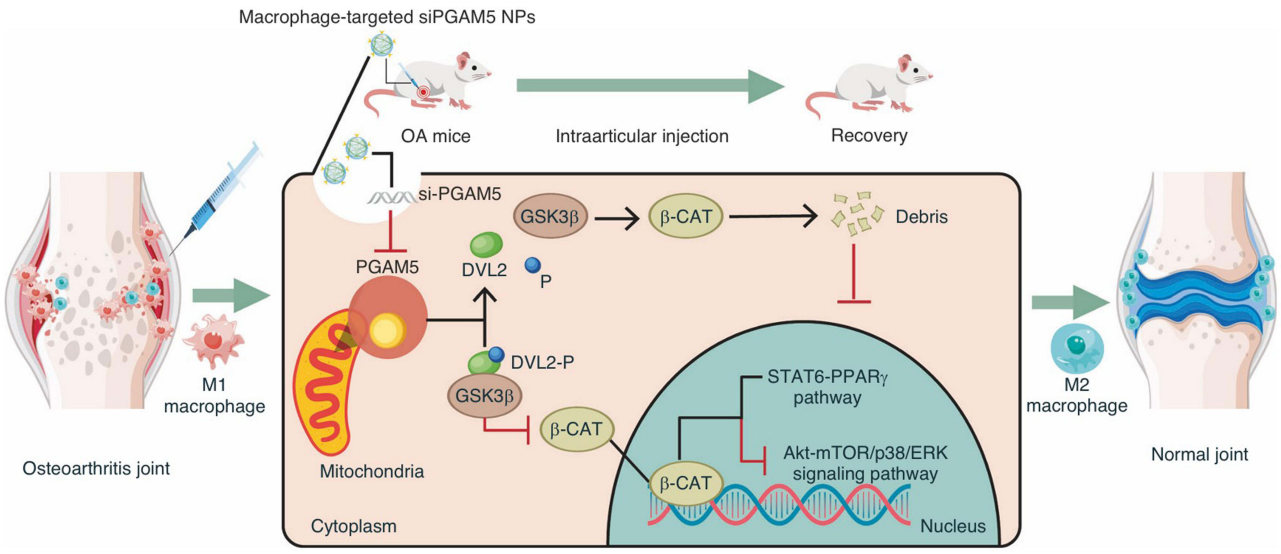

Figure 4 Mechanism of siPGAM5-mediated reversal of OA joint inflammation. In the OA model, macrophages (M1-type) are polarized via upregulation of PGAM5, which activates the AKT–mTOR and p38/ERK signaling pathways while inhibiting M2 polarization through the STAT6–PPARγ axis. Targeted delivery of siPGAM5 using mannose-modified fluoropolymers facilitates CD206-mediated uptake and selective silencing in synovial macrophages (SMs). This intervention leads to the suppression of PGAM5 activity, resulting in the reversal of pro-inflammatory M1-like polarization and the restoration of anti-inflammatory M2-like macrophage polarization, thus contributing to joint recovery and normalization of the OA-affected joint. Adapted from Liu Y, Hao R, Lv J et al Targeted knockdown of PGAM5 in synovial macrophages efficiently alleviates osteoarthritis. *Bone Res*. Copyright © 2024 by authors.[58]

How Nanomaterials Can Target Synovial Macrophages to Treat Osteoarthritis

In OA, SMs serve not only as major sources of pro-inflammatory cytokines and matrix-degrading signals but also as critical amplifiers of metabolic dysregulation within the joint microenvironment, including hypoxia, acidosis, oxidative stress, and nitric oxide accumulation.[25,56] Consequently, compared to interventions targeting a single cytokine or signaling pathway, nanotherapeutic strategies enabling cell-specific delivery and the simultaneous modulation of inflammatory and metabolic nodes within the synovial cavity are more likely to produce stable and reproducible therapeutic effects during disease progression. Additionally, SMs display pronounced phenotypic plasticity, characterized by dynamic transitions between M1 and M2 states at different stages of OA, rendering them both pathological drivers and reprogrammable therapeutic targets.[61] By regulating cellular uptake pathways, intracellular release, and microenvironment-responsive behavior, nanomaterials can precisely exploit this plasticity to broaden the therapeutic window without increasing systemic exposure. In recent years, nanotherapeutic systems targeting SMs have developed rapidly, with key distinctions arising from targeting strategies, payload composition, and material functionalization. To clarify the design principles and applicable contexts of these systems, we classify and summarize nanomaterials developed for targeting SMs in OA therapy (Figure 5).[52,62,63]

Lipid Based Nanocarriers Targeting SMs for Targeted Treatment of OA

Lipid-based carriers, such as liposomes and solid lipid nanoparticles, have been extensively investigated for OA therapy due to their biocompatibility and inherent ability to interact with cellular membranes. These systems can encapsulate anti-inflammatory agents, antioxidants, or gene modulators, facilitating their preferential uptake by synovial macrophages, which are key drivers of synovial inflammation in OA. The lipid bilayer structure mimics biological membranes, improving intra-articular retention and reducing systemic clearance, thereby enhancing local therapeutic concentrations at sites of inflammation.[64,65] Furthermore, surface modifications (eg, receptor-targeting ligands) can further enhance macrophage selectivity and attenuate inflammatory signaling pathways, mitigating synovial thickening and pro-inflammatory cytokine release—two hallmarks of OA pathogenesis. Lipid-based systems have been shown to effectively target synovial inflammatory responses and reduce oxidative stress within the joint microenvironment by delivering

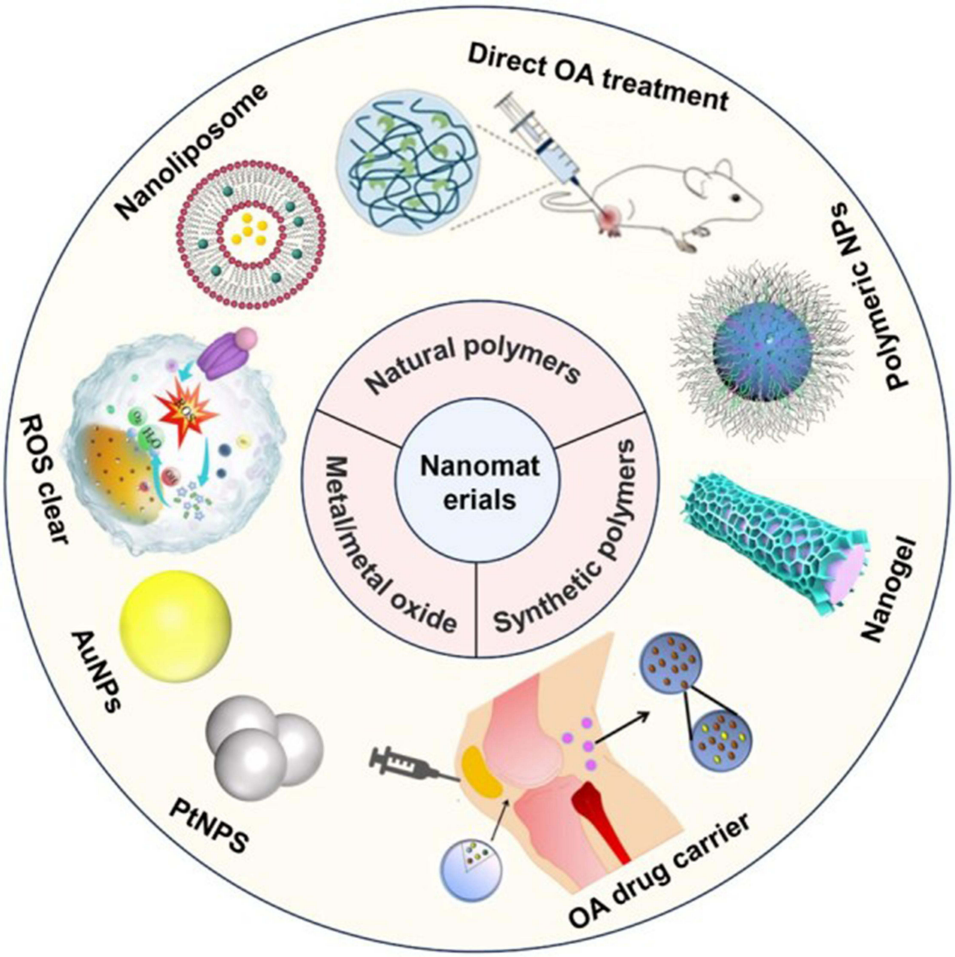

Figure 5 Classification of nanomaterials targeting SMs for the treatment of OA. This schematic illustrates the major classes of nanomaterials developed to target SMs in OA therapy, categorized according to their material composition, including natural polymers, synthetic polymers, and metal/metal oxide–based nanomaterials. Representative formulations such as nanoliposomes, polymeric nanoparticles, nanogels, metal-based nanoparticles (eg, AuNPs), and Prussian blue nanoparticles (PtNPs) are shown. These nanomaterials function either as direct intra-articular therapeutic agents or as drug delivery carriers, enabling targeted modulation of synovial inflammation through mechanisms such as reactive oxygen species (ROS) scavenging, controlled drug release, and macrophage phenotype regulation. By leveraging macrophage phagocytic properties and microenvironment-responsive behaviors, these nanoplatforms aim to remodel the inflammatory synovial microenvironment and improve OA outcomes. Adapted from Deng W, Wang T, Li L et al A review of nanomaterials in osteoarthritis treatment and immune modulation. Regen Biomater. Copyright © 2025 by authors.[52]

antioxidants and immunomodulators to macrophage populations.[66,67] For example, lipid carriers can further exploit membrane components and receptor axes (eg, efferocytosis pathways and Siglec-1/CD169) to enhance cell-selective delivery, shifting drug exposure from passive diffusion to receptor-guided uptake.[57,68] Within liposome-based approaches, a representative "material–mechanism–efficacy" paradigm is exemplified by phosphatidylserine (PS)-based apoptotic mimicry. Xu et al developed PS-containing nanoliposomes (PSLs) incorporating the BRD4 inhibitor JQ1 into the liposomal structure. By presenting PS as an "eat-me" cue, PSLs achieved preferential uptake by SMs over FLS and alleviated synovitis and pain in the anterior cruciate ligament transection (ACLT) model, primarily through suppression of M1 polarization. However, the challenge lies in fine-tuning surface modifications and stabilizing these formulations for clinical applications, particularly regarding immunogenicity and batch-to-batch consistency. In parallel, BRD4 inhibition downregulated TRPA1-related signaling in macrophages, linking inflammatory pain pathways and cartilage degeneration to a shared cellular target.[57] Collectively, these findings illustrate how liposomes can support both immune reprogramming and analgesic benefits within a single platform. We believe that integrating targeted surface modifications and optimizing lipid nanoparticle formulations will further enhance their clinical viability for OA treatment. We believe that integrating targeted surface modifications and optimizing lipid nanoparticle formulations will further enhance their clinical viability for OA treatment. Notably, this "programmable membrane" concept is not

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confined to PS. For example, Xu et al compared macrophage uptake of sialic acid (SA)-modified versus PS-modified liposomes, suggesting that both glycan ligands and apoptotic-mimicry cues can serve as modular surface designs. This provides a reusable chemical toolbox for active targeting of synovial $CD169^{+}$ macrophages.[68] This perspective highlights the potential of liposomes as an adaptable and targeted delivery system for OA treatment; however, further research is necessary to address their clinical translation challenges. Solid lipid nanoparticles (SLNs) are often considered a more pharmaceutical-development-friendly option. Their solid lipid cores (eg, stearic acid and monoglycerides) support high loading of hydrophobic drugs and slower release kinetics, which align with intra-articular needs for fewer injections and longer maintenance. For example, Ayesha et al optimized diacerein-loaded SLNs for intra-articular administration using response surface methodology. By tuning lipid composition and process parameters, they achieved formulation stability and prolonged drug action, highlighting manufacturability and scalability for chronic OA management.[69] In next-generation lipid nanoparticle (LNP) systems, a key advantage is their capacity to co-deliver small molecules, nucleic acids, or other regulatory cargos for intracellular delivery. Yi et al developed pH-responsive LNPs@UA to achieve better-matched release in the acidic joint microenvironment. In vitro, these LNPs reduced ROS and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and promoted M2 polarization. Transcriptomic analyses suggested coupling to NF-κB suppression and pathways related to mitochondrial homeostasis, autophagy, and ferroptosis. In the ACLT model, LNPs@UA reduced OA progression, illustrating that LNP design can integrate organelle stress responses and immuno-metabolic pathways—not just drug loading—into therapeutic mechanisms.[70] In addition, LNP surface ligands enable joint-directed delivery via multicellular targeting. Yang et al reported a dual-targeted LNP that uses folate (FA) to engage activated immune cells and a type II collagen–binding peptide (WYRGRL) to target the cartilage matrix, enabling co-delivery of miR-330-3p and kartogenin (KGN). In temporomandibular joint OA, this design concurrently modulated the immune microenvironment and supported cartilage-repair signaling, highlighting the systems-level potential of LNPs to address both immunologic and structural endpoints.[71]

From a translational perspective, an additional source of confidence in lipid platforms is their industrial maturity. An article notes that lipid nanocarriers are widely regarded as a gold standard for RNA delivery, and multiple LNP-based RNA therapeutics have received regulatory approval. This track record implies that raw-material supply chains, large-scale manufacturing, and quality-control workflows are well-established, providing a practical reference for chemistry, manufacturing, and controls (CMC) planning and safety evaluation for intra-articular administration in OA.[72] This translational spillover is beginning to extend to musculoskeletal applications. For example, Kong et al administered intra-articular FGF18 mRNA encapsulated in LNPs, achieving deeper tissue penetration and more sustained expression in cartilage, accompanied by activation of the FOXO3a–autophagy protective axis. In DMM and age-associated OA models, this approach improved pain, synovitis, and OARSI scores. These findings suggest that LNP-mediated nucleic acid delivery is not limited to vaccines and may represent a feasible option for local biologic delivery in OA.[73] Therefore, when the goal is to target SMs, liposomes serve as precision tools for programmable membrane signaling and phagocytosis-guided targeting. SLNs provide a pharmaceutical foundation for long-acting release and manufacturability. LNPs further integrate immune reprogramming, nucleic acid modulation, and an established industrialization pathway within a single materials paradigm, positioning them as particularly promising platforms for bridging basic discoveries to clinical translation.[57,69,70,73] But, while liposomes and solid lipid nanoparticles offer significant advantages in targeting SMs, the scalability and large-scale manufacturing processes of these systems remain key challenges, particularly when aiming for consistent production and long-term stability.

Polymeric Nanocarriers for Targeted OA Therapy with SMs Reprogramming and Sustained Drug Release

Polymeric nanosystems are one of the most structurally stable platform backbones for OA nano-immunotherapy targeting SMs. Because OA is characterized by persistent synovial inflammation and increased oxidative stress, polymeric nanoparticles can be designed to maintain therapeutic levels over time, reducing repetitive dosing and peak-trough fluctuations in drug concentration. Moreover, polymer matrices can be engineered to respond to pathological cues such as low pH or elevated ROS, enabling on-demand drug release where inflammatory intensity and oxidative stress are highest

within the joint. These features allow polymeric nanosystems to address osteoarthritic inflammation and oxidative dysregulation simultaneously, improving therapeutic efficacy against macrophage-mediated degeneration.[74]

Their key advantage lies in integrating controllable drug release (temporal dimension), intra-articular retention and tissue penetration (spatial dimension), and cell-selective uptake with immune reprogramming (cellular dimension) into a single engineered carrier, aligning more closely with clinical requirements for dosing frequency and safety.[75,76] Among these systems, PLGA/PEG-based formulations (including PEGylated surfaces or PLGA–PEG copolymers) represent the most translationally advanced approach. PLGA offers predictable biodegradation and low immunogenicity, and PLGA-based intra-articular microsphere formulations (eg, triamcinolone acetonide–loaded PLGA products) already serve as regulatory precedents. These features provide clear advantages in CMC development and safety assessment for local OA administration.[77] I In a representative study, Ma et al encapsulated hydrophobic rapamycin into PLGA nanoparticles (RNPs, ~250–450 nm), using sustained release to overcome rapid intra-articular clearance—an important limitation of local OA therapy. In the DMM model, this approach concurrently improved synovitis, cartilage structural damage, and pain-related phenotypes, indicating that the platform functions not only as a carrier but also as a lever for translational goals such as reduced injection frequency with sustained therapeutic exposure. Mechanistically, RNPs provide continuous suppression of mTORC1-associated stress, mitigating inflammation- and oxidative stress–driven cellular senescence and metabolic dysregulation, weakening the coupling between inflammatory amplification and tissue degeneration at the whole-joint level. This stress-node-to-whole-joint outcome pathway helps explain why PLGA-based sustained-release systems often yield more consistent structural benefits than freely administered drugs.[77] PEGylation (or introduction of a hydrophilic brush layer) further reduces nanoparticle aggregation and nonspecific protein adsorption, prolongs intra-articular retention, and improves tissue distribution in protein-rich synovial fluid. These properties favor preferential uptake by highly phagocytic SMs, providing a materials-based rationale for macrophage targeting.[75] We believe that PLGA-based systems, while effective, need further refinements in surface modification to enhance their ability to target different macrophage subpopulations, which will be essential for optimizing their therapeutic effects in OA. For active targeting, recognition ligands can be incorporated into the polymer shell. For example, Zerrillo et al developed hyaluronic acid (HA)–grafted PLGA nanoparticles that exploit CD44 and related receptors to enhance localization to inflamed synovium and uptake by immune cells. This HA-shell/PLGA-core architecture balances biocompatibility with scalable manufacturing and aligns well with clinical requirements for reproducibility and batch consistency.[78] From our perspective, HA-grafted PLGA systems provide an excellent balance between targeting precision and clinical applicability, making them a strong candidate for further clinical investigation. For nucleic acid or peptide delivery, polycationic platforms (eg, PEI) facilitate cargo loading via electrostatic complexation and promote endosomal escape through the proton sponge effect, converting delivery into functional intracellular activity. This feature is particularly important for strategies requiring gene silencing or signaling reset in SMs.[16,32] Zhou et al constructed an M2 macrophage–membrane biomimetic nanosystem in which PEI condensed the anti-inflammatory peptide KAFAK and shRNA targeting LEPR, followed by HA-mediated surface charge reversal and membrane coating. This design promoted macrophage reprogramming from M1 to M2, attenuated synovial inflammation, and alleviated joint damage, highlighting the advantages of combining polycationic delivery, membrane biomimicry, and receptor-mediated adhesion for immune intervention.[48] Another class of polycation-based systems focuses on materials with intrinsic therapeutic activity, embedding microenvironmental regulation directly into the carrier structure. For example, Wang et al incorporated ε-polylysine/spinel MnCoO nanoenzymes into an injectable HA hydrogel. Through sustained ROS scavenging and induction of M1-to-M2 polarization, this system downregulated TNF-α, IL-1β, iNOS, and MMP-13 in synovial fluid and synovium, while upregulating cartilage markers COL2 and SOX9 and inhibiting osteophyte formation. This carrier-as-efficacy-amplifier design is advantageous for clinical translation, as it extends therapeutic efficacy from a single drug entity to material-driven modulation of the immune microenvironment.[79] In addition, dendritic macromolecules offer an alternative strategy characterized by precise molecular architecture, high payload capacity, and multivalent interactions. Sun et al loaded catalase (CAT) and quercetin (Que) onto G2 hydroxyl-terminated phosphate dendrimers, synergistically promoting macrophage M2 polarization by alleviating hypoxia, oxidative stress, and mitochondrial dysfunction. This platform alleviated synovitis and cartilage degeneration in OA models and reprogrammed mononuclear/macrophage-like

cells derived from OA patient synovial effusions, underscoring the strength of dendritic systems in achieving mechanistic closure from ROS and hypoxia modulation to immune reprogramming, with supporting human validation.[80]

Polysaccharide-Based Nanocarriers for OA Therapy and SMs Targeting

Natural polysaccharides and other bioderived polymers play an important role among materials designed to target SMs in OA because they combine intra-articular biocompatibility with receptor-mediated interactions. They can act as carriers while enabling selective uptake by macrophages in inflamed synovium and subsequent immune reprogramming, aligning with clinical priorities for safety and reproducibility.[81] Meanwhile, HA, for example, not only serves as a lubricant and shock absorber in healthy joints but, when formulated as a nanocarrier, can enhance the delivery of anti-inflammatory agents and stabilize the joint microenvironment. These systems have been shown to reduce pro-inflammatory cytokine levels and oxidative stress in OA models by promoting M2-like macrophage polarization and enhancing cartilage matrix synthesis. Polysaccharide nanocarriers can thus directly modulate synovial macrophage activity and mitigate inflammatory and oxidative pathways that drive cartilage degradation. The key advantage of polysaccharide-based systems, including HA and chitosan, lies in their biocompatibility and ability to interact with specific immune cell receptors, making them promising platforms for clinical translation.[82] However, challenges remain in optimizing the release profiles and improving the scalability of these systems for long-term therapeutic applications. Hyaluronic acid (HA) provides a representative example. HA is widely used clinically as a viscoelastic supplement for intra-articular injection, and this established clinical use provides a practical starting point for translating HA into a drug- and nanodelivery matrix.[81] Importantly, the HA–CD44 axis provides a well-established binding mechanism on inflammation-associated cells, including inflammatory macrophages. This feature enables HA-based systems to incorporate modules for synovitis targeting and enhanced cellular uptake.[83] In OA models, a modified HA (P-HA) hydrogel loaded with rapamycin prolongs intra-articular retention and controlled release, enabling sustained inhibition of mTORC1-associated pro-inflammatory signaling. This treatment promotes SM polarization from M1 toward M2, reduces inflammatory mediators (TNF-α, IL-1β, and IL-6), and attenuates cartilage damage in vivo, illustrating a coherent causal chain linking the HA matrix to immunometabolic targets.[84] More recently, immune-engineering devices have been developed. While the immune-engineering devices hold great promise, we believe further efforts are needed to improve their stability and predictability in the clinical setting. Microfluidic hydrogel microspheres based on HAMA-SA (hyaluronic acid methacrylate–streptavidin) and ChSMA (chondroitin sulfate methacrylate) can recruit, capture, and reprogram inflammatory macrophages within the joint space, thereby reducing synovitis and protecting extracellular matrix integrity. These results highlight that polysaccharide networks can be formatted into structured microspheres to implement macrophage regulation as a locally executable engineering process.[85]

Chitosan (CS)-based systems offer distinct platform advantages, including intrinsic charge, chemical modifiability, and the ability to form gels or microspheres. For example, an injectable composite system consisting of kartogenin (KGN)-conjugated chitosan porous microspheres (CSK-PMS) embedded in a DMOG-loaded hydrolyzed chitin (HPCH) hydrogel exhibited immunomodulatory effects both in vivo and in vitro. This system promoted M2-associated phenotypes and a reparative microenvironment in osteochondral repair models, suggesting that CS-based platforms can not only deliver therapeutics but also orchestrate repair processes through structural design and immune compatibility.[86] We believe that chitosan-based systems, with their unique ability to promote macrophage reprogramming, offer a promising approach for OA therapy; however, their clinical application needs to overcome challenges related to formulation stability and consistency. From a clinically practical formulation perspective, thermosensitive hydroxybutylchitosan (HBC) gels enable poorly soluble natural anti-inflammatory compounds, such as curcumin, to achieve sustained intra-articular efficacy, highlighting the translational value of CS derivatives in terms of injection convenience, prolonged release, and safety.[87] In addition, a key feature of dextran/dextran sulfate (DXS) systems is their capacity to be engineered as recognition motifs preferentially taken up by inflammatory macrophages. DXS has been reported to bind receptors such as scavenger receptor class A (SR-A), which is highly expressed on activated macrophages at inflammatory sites, providing a materials-based route for preferential drug accumulation in macrophages and inflamed tissues.[88] Although fewer studies have directly applied DXS systems to target SMs in OA, work in inflammatory joint diseases has shown that self-assembled micelles of DXS–cis-aconitic anhydride–dexamethasone conjugates selectively

recognize and deliver drugs to activated macrophages. These findings provide a materials rationale for extending DXS-based strategies to OA through shared receptor axes.[89] We believe that dextran-based systems, while less commonly studied in OA, offer significant potential for macrophage targeting and drug delivery due to their ability to bind to activated macrophage receptors, making them a promising avenue for future exploration in OA therapy. Dextran has also been incorporated into injectable Schiff-base hydrogels for intra-articular OA therapy, in which HA-ADH and aldehyde-modified dextran (Dex-ALH) form a dynamic network. This platform enables delivery of ROS-degradable micelles and dexamethasone, improving joint retention while providing synergistic antioxidant and anti-inflammatory effects, positioning dextran as a structural backbone for injectable, degradable HA-based systems in OA.[90]

More broadly, gelatin and gelatin methacrylate (GelMA) systems provide microenvironments that closely resemble the extracellular matrix and offer favorable biological processing conditions. GelMA hydrogels functionalized with mesenchymal stem cell (MSC)-derived extracellular matrix enhance immunoregulation and modulate macrophage polarization in OA-associated inflammatory environments, demonstrating the plasticity of natural matrix cues and gelatin-based networks in shaping the synovial immune microenvironment.[91] In addition, oxidized alginate–gelatin composite nanohydrogels formed via Schiff-base reactions enhance mechanical integrity and ROS-scavenging capacity. In OA animal models, these systems reduce inflammatory mediators and osteophyte formation while protecting cartilage, indicating that a gelatin-as-network, nano-component-as-function design is a reproducible structural strategy.[92] Finally, HA–gelatin combinations have been applied in injectable, dynamically cross-linked drug microsphere strategies closer to clinical translation. In particular, borate-ester-cross-linked HA hydrogels loaded with gelatin microspheres enable responsive drug release and enhanced lubrication. This approach underscores the ability of polysaccharide/gelatin platforms to simultaneously address immune regulation, drug retention, and mechanical lubrication, representing a key practical advantage of natural polymer systems in OA translation.[93]

Inorganic and Hybrid Nanomaterials for OA Therapy and Macrophage Modulation

Inorganic and hybrid nanomaterials, including metal-organic frameworks (MOFs), mesoporous silica, and metal oxide nanoparticles (eg, cerium oxide), provide multifunctional platforms that combine drug delivery with intrinsic catalytic or redox activity. Their high surface area and tunable pore architecture allow dual functions: they can deliver therapeutic payloads such as anti-inflammatory drugs or siRNA while simultaneously scavenging ROS — a major contributor to oxidative stress and macrophage activation in OA. For instance, ROS-scavenging nanomaterials can attenuate oxidative damage in synovial macrophages and chondrocytes, reducing downstream inflammatory cascades and matrix degradation. Moreover, inorganic hybrid platforms functionalized with targeting ligands can accumulate preferentially in inflamed synovium, enabling focused intervention at pathological sites.[94,95] Porous platforms, exemplified by mesoporous silica, can integrate adsorption, clearance, and immune reprogramming into a single mechanistic continuum. For example, Shi et al developed cationic mesoporous silica nanoparticles (MSN-PEI) functionalized with PEI and cross-linked via diselenide bonds. The cationic surface enabled high-affinity capture of hazardous mediators such as cell-free DNA within the joint space. Diselenide linkages also confer antioxidant and ROS-responsive properties. In surgical and collagenase-induced models, these features were associated with reduced synovitis and cartilage protection, in part through suppression of macrophage M1 polarization.[94] We believe that mesoporous silica nanoparticles, with their ability to capture hazardous mediators and provide ROS-responsive features, represent a promising approach for OA therapy. However, more work is needed to enhance their clinical translation, particularly regarding consistent drug loading and release profiles. A translational advantage of this multi-target hazardous-mediator clearance concept is that efficacy can be tuned by quantifiable physicochemical parameters (eg, pore size, surface charge, and linker chemistry), rather than relying solely on drug loading and release.[94] Moreover, scalable synthesis and surface modification of silica materials facilitate GMP-compatible consistency and inter-batch stability. From our perspective, while mesoporous silica offers excellent potential, there is still a need to refine its fabrication process to improve reproducibility and scalability for clinical applications. Cerium oxide (CeO_2) exemplifies the inorganic nanozyme approach because reversible Ce^{3+}/Ce^{4+} redox cycling confers SOD- and CAT-like ROS-scavenging activity. In OA models, Ren et al showed that intra-articular cerium oxide nanoparticles (CeNPs) reduced synovial ROS and inhibited NF-κB–associated inflammation and SASP, thereby slowing disease progression along a synovial senescence–inflammation–cartilage breakdown axis.[96] While CeO_2

nanoparticles show great promise in ROS scavenging and inflammation regulation, their long-term safety, pharmacokinetics, and potential toxicity need to be rigorously studied before clinical use. Further tissue targeting can be achieved using hybrid surface shells. Specifically, Zhuang et al PEGylated CeO_2 nanoparticles and grafted the cartilage-targeting peptide WYRGRLGK, which prolonged intra-articular retention and attenuated excessive PI3K/AKT and MAPK activation, thereby reducing oxidative cartilage damage. This inorganic-core/bioligand design preserves an engineering interface for future incorporation of macrophage-targeting ligands (eg, FR-β– and scavenger receptor–directed ligands).[97] Notably, CeO_2 may also modulate macrophage phenotype. Under inflammatory conditions, CeO_2 nanoparticles downregulate pro-inflammatory markers such as iNOS and upregulate anti-inflammatory gene programs, suggesting that they function not only as ROS scavengers but may also reshape synovial macrophage reactivity via immunometabolic and transcriptional networks.[98] This makes CeO_2 systems a promising option for not only ROS scavenging but also for modulating macrophage function in OA, though more studies are needed on its long-term therapeutic potential. Metal–organic frameworks (MOFs), such as UiO-66-NH_2, extend pore-based drug storage, surface recognition, and even organelle-level delivery. Huang et al loaded baicalein onto folic acid–modified UiO-66-NH_2 (Bai@FA-UiO-66-NH_2), enabling selective uptake by LPS-stimulated macrophages via folate receptor–mediated recognition. The platform then gradually released the payload and reduced intracellular ROS, promoting M1-to-M2 repolarization and alleviating synovitis while improving OA phenotypes in vivo—an example of how the material platform can embody the targeting logic.[95] Layered double hydroxides (LDHs) and LDH-based hybrid hydrogels highlight the combination of structural ions, antioxidant polyphenols, and inflammation-adaptive release. In vitro, Liu et al developed an LDH@TAGel system that engaged the Nrf2/Keap1 and PI3K/AKT pathways to counter inflammation-induced oxidative stress and apoptosis and to reduce MMPs and other catabolic markers. In the ACLT model, LDH@TAGel significantly reduced OARSI scores, and its release behavior adapted to the degree of inflammation. This provides a verifiable prototype for pathology-responsive dosing based on disease intensity.[99] Gold-based materials can serve as inert or catalytic cores for multifunctional applications (eg, photothermal therapy and ROS catalysis). Hong et al reported cartilage-targeting Au@Pt nanospheres that enhanced the Pt catalytic interface and incorporated the WYRGRL peptide, promoting OA recovery in preclinical models. These studies also underscore potential thrombosis and immune-related risks at higher doses, emphasizing the need for systematic toxicology and clearance-kinetics assessments before clinical translation of precious-metal platforms.[100,101]

Notably, early clinical evidence for intra-articular gold-based interventions has begun to emerge. Rasmussen et al used HA as a carrier for intra-articular injection of gold particles (20–40 μm) in a knee OA cohort, and most participants reported subjective improvement after two years of follow-up. Ongoing, more rigorous clinical studies will further inform feasibility and regulatory considerations for inorganic particle strategies in OA.[102,103] Overall, successful clinical translation of inorganic and hybrid platforms depends not only on efficacy but also on establishing a closed loop among structure, mechanism, and safety. Engineered porosity and surface chemistry can anchor therapeutic effects to core circuits involving ROS, DAMPs, and macrophage polarization, while traceable residence time, degradation/excretion profiles, and immunotoxicity datasets can reduce regulatory uncertainty and support clinical adoption.[95,100,102]

Biomimetic Nanocarriers for Targeted OA Therapy and Immune Modulation

Biomimetic nanocarriers using cell membranes (eg, macrophage or platelet membranes) or exosomes derived from immune or stem cells have emerged as highly selective platforms for OA therapy. These systems inherently express surface proteins that facilitate homing to inflamed tissues and can fuse with macrophage membranes to deliver therapeutic cargos efficiently.[104] Because synovial inflammation involves aberrant macrophage signaling and cytokine production, biomimetic carriers can both dampen pro-inflammatory signaling and transfer regulatory molecules (eg, IL-10, miRNAs) that promote macrophage reprogramming toward anti-inflammatory phenotypes. Such systems thus integrate targeted delivery with immune modulation, directly addressing pathological inflammation and restoring tissue homeostasis within OA joints.[105,106] A central rationale for macrophage membrane–coated nanoparticles is that the membrane retains adhesion- and chemotaxis-related molecules as well as receptors for inflammatory mediators. This facilitates adhesion to inflamed synovium and enables sequestration or neutralization of mediators such as TNF-α and IL-6 via membrane-surface receptors. Consequently, the coating can confer an intrinsic broad-spectrum anti-inflammatory

capacity.[107] For example, Xu et al developed macrophage membrane–wrapped curcumin "nanosponges" (CM@Cur-NPs) built on a drug-loaded polymeric core with a biomimetic membrane shell. In vitro and in vivo, CM@Cur-NPs reduced TNF-α and IL-6 levels and suppressed iNOS and ROS. Markers of ferroptosis (eg, ACSL4, MDA, and Fe^{2+}) were downregulated, whereas SLC7A11 and GPX4 were upregulated. In OA models, these effects translated into cartilage protection and slowed disease progression, suggesting synergism between the membrane-mediated anti-inflammatory effect and the payload's antioxidant/anti-ferroptotic activity.[108] In our view, this demonstrates that membrane-coated systems are not just carriers, but can function as sophisticated delivery platforms with significant potential for modulating immune responses and providing therapeutic benefits. Relative to drug-loaded membrane encapsulation, macrophage membrane decoys (nanosponges) function as a receptor library: their membrane receptor networks sequester a broad spectrum of inflammatory factors. For example, Teo et al encapsulated gold nanoparticles (Au-M2 NPs) in M2 macrophage membranes and showed that M2-derived coatings outperformed M0/M1 membrane controls in anti-inflammatory effects and cartilage-matrix protection. This indicates that membrane source and polarization state are design variables that shape receptor composition and immunomodulatory bias.[109] We believe that using macrophage membrane decoys has a distinct advantage in their versatility for targeting a broad range of inflammatory mediators, making them particularly promising for clinical applications. A further biomimetic strategy is to construct cell-like "artificial macrophages". Ma et al proposed a yolk–shell artificial M2 macrophage (AM2M) in which a macrophage membrane forms the outer shell and an inflammation-responsive gel core (gelatin–chondroitin sulfate) serves as the "yolk". Matrix metalloproteinases (MMPs) in the inflamed joint trigger rapid payload release during the acute phase to suppress inflammation, followed by sustained release under lower-inflammatory conditions to support repair. In OA models, AM2M targeted inflamed lesions while preserving joint integrity, highlighting that material architecture, release kinetics, and disease-stage timing can be co-engineered for optimal matching.[110] This approach illustrates that artificial macrophages can mimic the immune system's functionality, offering an effective and flexible strategy for targeted OA therapy.

As an example of membrane wrapping coupled with active cargos, Zhou et al developed M2H@RPK. iRGD/KAFAK and shRNA targeting LEPR were condensed with PEI into a polyplex and then assembled via HA-mediated electroporation to achieve membrane encapsulation. After accumulating in inflamed synovium, this nanosystem simultaneously inhibited pro-inflammatory signaling via the KAFAK–MK2 axis and inactivated leptin signaling through LEPR down-regulation. It also promoted M1-to-M2 repolarization, reducing synovitis and joint structural damage. These results demonstrate that the biomimetic shell functions not only as a "stealth" cloak but also as an amplifier of intra-articular localization and immune reprogramming.[48] Compared with membrane-coated carriers, exosomes offer inherent nanoscale size, low immunogenicity, and the capacity to transport protein and nucleic acid cargos that can gently modulate immune-cell states. These properties make exosomes well-suited for reshaping inflammatory ecosystems dominated by SMs.[111] Wu et al further addressed manufacturability by modulating exosome biogenesis. TNF-α pretreatment of infrapatellar fat pad MSCs (IPFP-MSCs) activated PI3K/AKT–CREB signaling and upregulated ATG16L1, increasing exosome secretion and enriching LRP1 in the exosomal cargo. In OA mice, these exosomes improved gait and joint pathology. These findings suggest that controllable external stimulation can jointly optimize exosome yield and therapeutic potency.[112] Song et al embedded M2 macrophage–derived exosomes (M2-Exo) in a thermosensitive, dynamically cross-linked HA/Pluronic F-127 injectable hydrogel to achieve sustained intra-articular release. This system promoted lymphatic endothelial cell proliferation and migration, increased synovial lymphangiogenesis, enhanced lymphatic drainage, and slowed OA progression. Together, these results suggest that combining exosomal cargos with injectable, joint-resident materials is a practical strategy for clinical delivery.[113]

From a clinical translation perspective, the main barriers for biomimetic systems lie in biopharmaceutical considerations, including raw-material consistency (eg, membrane or exosome source and cellular state), scalable and reproducible assembly, characterization of membrane-protein fidelity and orientation, sterility assurance, and robust inter-batch quality control. Nonetheless, recent reviews have outlined systematic process-development and quality-control frameworks—such as large-scale separation and filtration workflows and standardized characterization panels—as a roadmap toward GMP manufacturing and clinical validation.[107]

Functionalized Nanomaterials for Stimuli-Responsive Targeted OA Therapy

Functionalized nanomaterials incorporate bioactive or bioinspired modifications that endow carriers with sustained therapeutic functions.[114] By incorporating functional groups or ligands responsive to these cues, these materials can trigger localized drug release at sites of pathology, maximizing therapeutic action while minimizing off-target effects. Functionalization strategies have enabled nanocarriers to selectively release anti-inflammatory or antioxidative agents in response to heightened ROS levels in synovial fluid, directly combating oxidative stress — a key driver of macrophage activation and cartilage breakdown in OA. These smart release systems provide dynamic and adaptive therapeutic delivery aligned with pathological features, enabling more precise modulation of synovial inflammation and oxidative stress.[43] In OA, where inflammatory intensity fluctuates and intra-articular clearance is rapid, stimuli-responsive and smart-release materials offer particular value for targeting SMs.[115] Accordingly, their application in OA warrants further discussion. Stimuli-responsive, smart-release materials can align the timing and location of drug release with the synovitis microenvironment and concentrate therapeutic action on a pathological hub—SMs and their paracrine networks. This targeting may enable more stable immune reprogramming and structural benefit at lower doses and with fewer injections.[116] Mechanistically, OA synovial fluid and synovium present material-readable cues, including mild acidification, ROS overload, and protease activation (eg, MMPs). Accordingly, multi-stimulus platforms—or high-sensitivity single-stimulus systems—can shift nanocarriers from passive delivery to lesion-sensing, on-demand release within the joint.[70,116] We believe that multi-stimulus systems, while promising, require further optimization to balance responsiveness and sustained therapeutic exposure. For example, Yi et al developed pH-responsive lipid nanoparticles (LNPs@UA) that exploit acidic inflammatory/lysosomal microenvironments to trigger release and support mitochondrial targeting. In cells, urolithin A more effectively reduced mtROS, promoted mitophagy, and inhibited ferroptosis. These effects also biased macrophages toward an M2-like phenotype and downregulated NF-κB–associated inflammatory transcription, alleviating synovitis and cartilage degeneration in the ACLT model (Figure 6).[70] Using dual cues of acidity and immune-cell surface receptors, Huang et al loaded baicalin onto UiO-66-NH_2 and functionalized the MOF with folate to promote active uptake by M1-like macrophages, consistent with FR-β expression on inflammatory macrophages. The UiO-66 scaffold provided sustained release and scavenged ROS (·OH, $\cdot O_2^-$, and H_2O_2) under acidic conditions (pH ≈ 5). In rats, this strategy reduced inflammation and tissue damage, accompanied by ROS reduction and M1-to-M2 polarization.[95] Our perspective on this approach is that combining dual signals for targeting macrophages and modulating inflammation holds great promise, but further studies are needed to optimize the coordination of these signals in vivo. Along a ROS-triggered axis closely linked to macrophage inflammatory metabolism, Wang et al modified HA and PVA with phenylboronic acid (PBA) to form a dynamic cross-linked network that is cleavable by ROS. They encapsulated siMMP-13 nanocarriers containing PEI–PEG–Fe_3O_4 to accelerate RNAi release under high-ROS conditions. This system prolonged intra-articular retention, inhibited synovitis, osteophyte formation, and cartilage degradation, and improved locomotor activity and pain-related behaviors in DMM mice.[117] Tao et al further modularized responsiveness by incorporating phenylboronic acid ester motifs into a macrophage-targeted nanomicellar system with ROS-scavenging and H_2S-releasing properties, thereby enabling ROS-triggered activation and oxidative-stress scavenging, while achieving long-term release from porous GelMA microspheres. In parallel, folate moieties supported sustained in situ macrophage targeting and enabled intracellular H_2S release to suppress p-STAT3 and p-ERK signaling. This shifted polarization away from M1 and toward M2, yielding synergistic anti-inflammatory and cartilage-protective effects in DMM rats.[118] We view this approach as highly promising for OA treatment due to its dual-action mechanism and sustained release, which could be instrumental in overcoming some of the limitations of current therapies.

Moving beyond modest reprogramming, Qi et al designed MMP9-targeted peptide-modified rapamycin-loaded mesoporous Prussian blue nanoparticles (RAPA@MPB-MMP9) to target crosstalk between pyroptosis and mitophagy in SMs. Through Prussian blue-mediated ROS scavenging and rapamycin release (mTORC1 inhibition), this system enhanced mitophagy and suppressed NLRP3-driven inflammatory amplification and pyroptosis. In the collagenase-induced OA (CIOA) model, it concomitantly reduced synovitis and cartilage destruction, illustrating a smart nano strategy that uses inflammatory programmed cell death as both a trigger and an intervention target.[43] Stimuli-responsive systems do not necessarily require complex pharmacological payloads. For example, Wang et al reported that chondroitin sulfate-coated

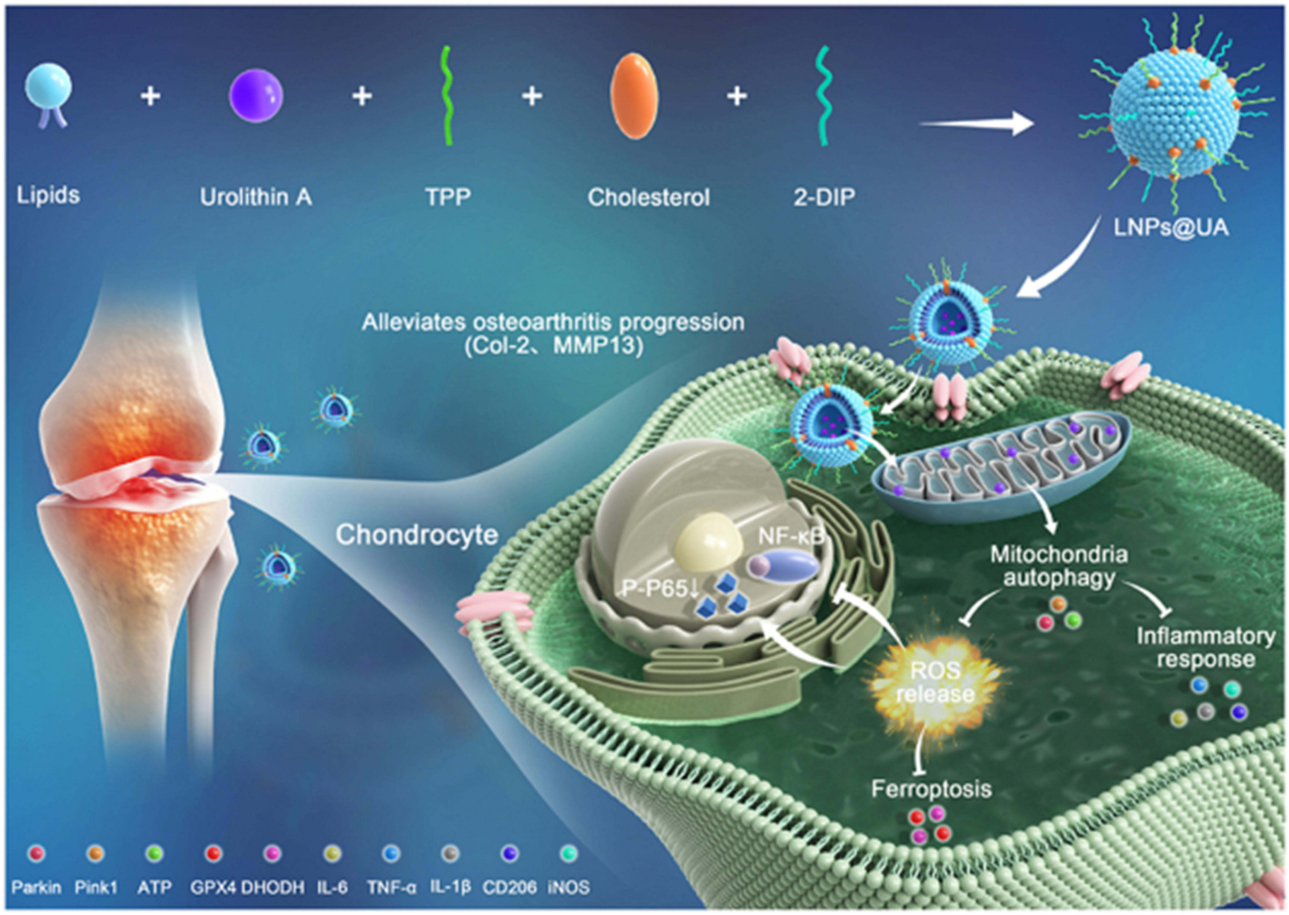

Figure 6 Design and therapeutic mechanism of LNPs@UA for alleviating OA. LNPs@UA are constructed by co-assembling lipids with urolithin A (UA), cholesterol, triphenylphosphonium (TPP), and 2-DIP to form multifunctional lipid nanoparticles. After intra-articular administration, LNPs@UA are taken up by chondrocytes and preferentially accumulate in mitochondria via TPP-mediated targeting. UA delivery promotes mitochondrial autophagy (mitophagy), reduces excessive reactive oxygen species (ROS) production, and suppresses ferroptosis. Concurrently, LNPs@UA inhibit NF-κB signaling and downstream inflammatory responses, leading to reduced expression of pro-inflammatory mediators (eg, TNF-α, IL-1β, iNOS) and matrix-degrading enzymes (eg, MMP13), while preserving cartilage matrix components such as type II collagen (Col-2). Through coordinated regulation of mitochondrial function, oxidative stress, inflammation, and cell death pathways, LNPs@UA ultimately slow OA progression and protect cartilage integrity. Adapted fromYi, G., Li, M., Zhou, J., Li, J., Song, X., Li, S., Liu, J., Zhang, H., and Chen, (Z) (2025). Novel pH-responsive lipid nanoparticles deliver UA-mediated mitophagy and ferroptosis for osteoarthritis treatment. Materials today. Bio. Copyright © 2025 by authors.[70]

ROS-scavenging nanoparticles improve tissue compatibility and local efficacy via polysaccharide interfaces, protecting cartilage in vivo through sustained attenuation of oxidative stress. These results suggest that material chemistry leveraging pathological cues as reaction or consumption substrates can itself constitute an active therapeutic component.[119] For protease-triggered delivery, Xiang et al constructed HAMA hydrogel microspheres incorporating an MMP13-substrate peptide and noncovalently anchored celecoxib-loaded cationic liposomes within the network. As MMP13 increases during OA progression, peptide cleavage accelerates microsphere degradation and drug release, enabling closed-loop control, in which higher inflammatory activity drives faster local delivery. This design concentrates COX-2 inhibition within the joint and may reduce risks associated with long-term systemic exposure.[120] From a translational perspective, a shared advantage of triggerable or smart-release platforms is the shift from peak-trough pharmacokinetics to lesion-adaptive drug supply, which could reduce injection frequency and widen the safety window. Clinical deployment will also require scalable, reproducible manufacturing, robust validation of trigger thresholds across patients and disease stages, and systematic evaluation of degradation products, residence time, and long-term intra-articular safety.[116,121]

Advances in Macrophage-Targeted Nanotherapies for Osteoarthritis Treatment and Disease Modification

SMs Targeting Strategies in OA Therapy for Enhanced Inflammation Modulation

Within the inflammatory network of the OA joint, SMs act as amplifiers of pro-inflammatory signals (eg, TNF-α and IL-1β) and as a key hub that governs whether dysregulated M1/M2 balance can be restored.[25] Accordingly, prioritizing nanomedicine delivery to SMs aims to regain upstream control of inflammatory cascades, rather than intervening only at end-stage cartilage pathology. SMs also possess robust phagocytic and foreign-body-clearing capacity.[63] If a material presents appropriate phagocytic cues within the joint (eg, opsonization by endogenous factors, a cell-membrane-like surface, or "eat-me" signals), it can bias uptake toward macrophages. This increases effective intracellular exposure in target cells while reducing off-target uptake by chondrocytes and other resident cells (Table 1).[49] A representative example is the opsonization-based nanoparticle strategy. Sang et al designed nanoparticles that preferentially bind opsonins after intra-articular administration, enhancing uptake by macrophages in synovial fluid and synovium via Fc receptor–mediated phagocytosis. In OA models, this approach modulated macrophage polarization, reduced inflammatory mediators, and improved joint pathology, illustrating how innate phagocytic programs can be leveraged for targeting.[49] Hyaluronic acid (HA)-based nanosystems represent another targeted material class. Kang et al reported that unloaded, self-assembled HA nanoparticles act primarily through the HA–CD44 axis, protecting cartilage after intra-articular injection in vivo. Mechanistically, these particles inhibited CD44-induced NF-κB activation and downstream catabolic gene programs. Because CD44-expressing cells in inflamed synovium actively internalize HA, HA serves as a natural ligand that supports preferential endocytosis by SMs, combining biocompatibility with receptor affinity.[122] E Emphasizing cellular mimicry, Zhou et al developed activated macrophage membrane-coated nanoparticles (M2 membrane-camouflaged; M2H@RPK). Interactions between membrane-surface proteins and the inflammatory microenvironment promoted enrichment in inflamed synovium and preferential uptake by macrophages. In vitro and in vivo, this system downregulated pro-inflammatory mediators, alleviated synovitis, and reduced joint damage, indicating that membrane-mediated immune recognition can drive uptake more effectively than a single ligand.[48] A representative example of combining biomimetic targeting with ligand-mediated recognition is provided by Deng et al Their apoptotic neutrophil membrane-camouflaged liposomes (NM@Lip) presented apoptosis-associated "eat-me" signals (eg, phosphatidylserine) and retained a broad repertoire of inflammatory adhesion molecules. NM@Lip showed high uptake by M1 macrophages and activated synovial fibroblasts in vitro (supported by endocytosis-inhibition assays) and achieved intra-articular retention for up to 28 days in vivo. When loaded with triamcinolone acetonide, NM@Lip promoted M1-to-M2 reprogramming and reduced pro-inflammatory cytokines/chemokines and matrix-degradation mediators, in part via PI3K/Akt inhibition. In rodent OA models, these effects translated into sustained improvements in pain and structural degeneration.[123]

Within the OA synovial microenvironment, SMs function as both inflammatory amplifiers and versatile therapeutic entry points. Accordingly, receptor-ligand active targeting that enhances nanocarrier delivery and cellular internalization can increase local effective exposure while reducing off-target tissue uptake. It may also enable future precision therapy stratified by inflammatory phenotypes.[25,129] Commonly exploited receptors on SMs include CD44 (well-matched to HA platforms for intra-articular delivery and retention), FR-β/FOLR2 (useful for targeting and imaging-based stratification of activated macrophages), FcγRs (leveraged by IgG/opsonin strategies to enhance preferential uptake by inflammatory macrophages), and scavenger receptors such as SR-A/MR (supporting uptake of anionic ligands, eg, dextran sulfate).[55,122,124] First, in the CD44-HA axis, unloaded self-assembled hyaluronic acid nanoparticles (HA-NPs) can enter joint-resident cells via CD44-mediated uptake and inhibit CD44-NF-κB-driven catabolic and inflammatory transcriptional programs. In a mouse OA model, intra-articular HA-NPs alleviated cartilage degeneration, suggesting that receptor-guided HA materials may extend beyond lubrication supplementation to pathway-level anti-inflammatory intervention.[122] Building on HA's material advantages, NO-scavenging HA nanoparticles (HA-NSCs) reduced intracellular NO and inflammatory mediators in LPS-activated RAW264.7 macrophages and alleviated pain while reducing cartilage damage in MIA-induced OA rat models. Given HA's established intra-articular use and chemical tunability, CD44-compatible HA platforms are well-positioned for engineering optimization of safety, manufacturability, and joint

Table 1 Application and Clinical Translation of Receptor Ligand Active Targeting of SMs

Target Receptor (Enriched Cell Population/Targeting Rationale)	Ligand/Key Material Motif	Representative Material Implementation (Examples)	Mechanistic Basis for Enhanced Macrophage Uptake	Best-fit OA Use Scenarios	Translational Considerations	Ref.
CD44 (expressed on SMs and other joint-resident cells; often functionally engaged in inflamed synovium)	Hyaluronic acid (HA); HA coating / HA self-assembled nanoparticles	Self-assembled HA nanoparticles (HA-NPs) for intra-articular therapy; NO-scavenging HA nanoparticles (HA-NSc)	CD44–HA binding triggers receptor-mediated endocytosis and can increase intra-articular retention; HA-based systems may concurrently attenuate inflammatory transcriptional programs (eg, NF-κB-linked cascades) and inflammatory mediators (eg, NO)	Intra-articular delivery where local retention and biocompatibility are priorities; suitable when broad "inflamed synovium" targeting is acceptable	HA has a comparatively favorable translational profile (prior clinical use in joints), but cell-type specificity is limited (CD44 is not macrophage-exclusive); optimization typically requires tuning ligand density, size, charge, and residence time	[122,124]
FRβ / FOLR2 (preferentially associated with activated monocyte–macrophage subsets; useful for "inflammation-high" phenotypes)	Folate (FA); FA conjugation / FA decoration	FA-functionalized MOF nanocarriers (eg, FA-UIO-66-NH_2 loading baicalin) to enhance uptake by M1-like macrophages; human macrophage subtype FRβ profiling to support target selection	FA–FRβ high-affinity recognition enables receptor-mediated internalization; frequently coupled with anti-inflammatory/anti-oxidative payloads to reduce ROS and bias M1→M2 repolarization	OA with prominent synovitis; scenarios where targeted therapy plus potential imaging-based stratification is desirable	FRβ is closer to an "inflammation-associated macrophage" entry point; however, clinical translation requires validating spatiotemporal FRβ expression in human OA synovium, and ensuring reproducible ligand presentation and scalable manufacture	[95,125,126]
Fcγ receptors (FcγRs) (canonical phagocyte receptors; can be exploited via opsonization/IgG motifs)	IgG / Fc motifs; antibody-like opsonization surfaces	IgG/Fe-CV nanosystems that enhance M1 macrophage uptake and drive metabolic reprogramming	Fc–FcγR engagement amplifies phagocytic uptake; can be integrated with macrophage metabolic modulation (eg, glycolysis-related programs) to promote phenotypic rebalancing (M1→M2)	When a strong "phagocytosis switch" is needed to maximize macrophage internalization following intra-articular administration	IgG-based motifs are closer to established biopharmaceutical paradigms, but local immune context and protein corona effects may alter opsonization efficiency; safety evaluation should include immune-complex–related risks and long-term joint tolerability	[55]
Scavenger receptor A (SR-A / MSR1) (phagocytic receptor on activated macrophages; binds polyanionic ligands)	Dextran sulfate (DS) and other polyanionic polysaccharides	DS–dexamethasone conjugate micelles (macrophage-targeted anti-inflammatory delivery platform; translatable design logic for OA)	DS–SR-A binding promotes uptake by activated macrophages; supports local delivery of glucocorticoids with reduced systemic exposure	OA where activated SMs are abundant and the goal is localized steroid-sparing or dose-sparing anti-inflammatory therapy	Polysaccharide chemistry is generally scalable, but OA-specific translation needs joint retention/clearance profiling and assessment of complement/coagulation-related interactions, depending on formulation	[89,127]
Companion diagnostics / stratification use (target validation and patient selection)	FR-targeted radiotracers (eg, ^68Ga-labeled folate conjugates)	^68Ga–folate conjugates for preclinical visualization of inflammatory foci	Receptor-targeted imaging can quantify macrophage-associated inflammatory burden, supporting enrichment strategies and pharmacodynamic endpoints	Patient stratification (identify "macrophage-high" synovitis) and response monitoring in trials of macrophage-targeted nanomedicines	Enables measurable target engagement; OA-specific translation requires correlation of imaging readouts with synovial pathology and clinical outcomes	[126,128]

https://doi.org/10.2147/IJN.S601362

residence time during translation.[124] For the FR-β/FOLR2 (folate, FA) axis, FR-β expression varies across human monocyte-derived macrophage subsets and can be modulated by glucocorticoid exposure. FR-β has been exploited for macrophage imaging and targeting in inflammatory joint diseases, including OA; thus, FR-β targeting is particularly suitable when synovitis is prominent and when targeted delivery, patient stratification, and response monitoring are desired concurrently.[125] Mechanistic studies indicate that FR-β-targeted strategies can promote rapid inflammation resolution by selectively acting on activated monocytes/macrophages, supporting FR-β as a functional delivery entry point rather than merely a biomarker.[130] Huang et al reported Bai@FA-UiO-66-NH_2, a folic acid-modified MOF loaded with baicalin, which uses FA to promote preferential uptake by folate receptor-high, M1-like macrophages. The platform enabled sustained release, intracellular ROS scavenging, and M1-to-M2 polarization, alleviating synovitis and improving OA outcomes—an illustrative paradigm that couples receptor targeting with immunometabolic/oxidative-stress regulation (Figure 7).[95] A clinically aligned nuclear medicine example is provided by Petrosova et al, who developed ^{68}Ga-labeled folate conjugates to visualize inflammatory foci with prominent macrophage involvement. These results suggest that FR-targeted tracers could support quantitative imaging of OA synovitis, enabling actionable criteria for trial inclusion and response assessment based on macrophage-driven inflammation.[126] Beyond ligand recognition, FcγR-mediated uptake has also been leveraged in OA. Chen's group reported an IgG/Fe CV nanosystem that enhanced uptake by inflammatory macrophages via IgG–FcγR interactions and induced metabolic reprogramming by inhibiting HIF-1α–GLUT1-driven glycolysis and glutamine metabolism. This promoted M1-to-M2 transition, reduced inflammation, and protected cartilage, exemplifying the concept of using immune receptors as phagocytic switches.[55] Finally, the

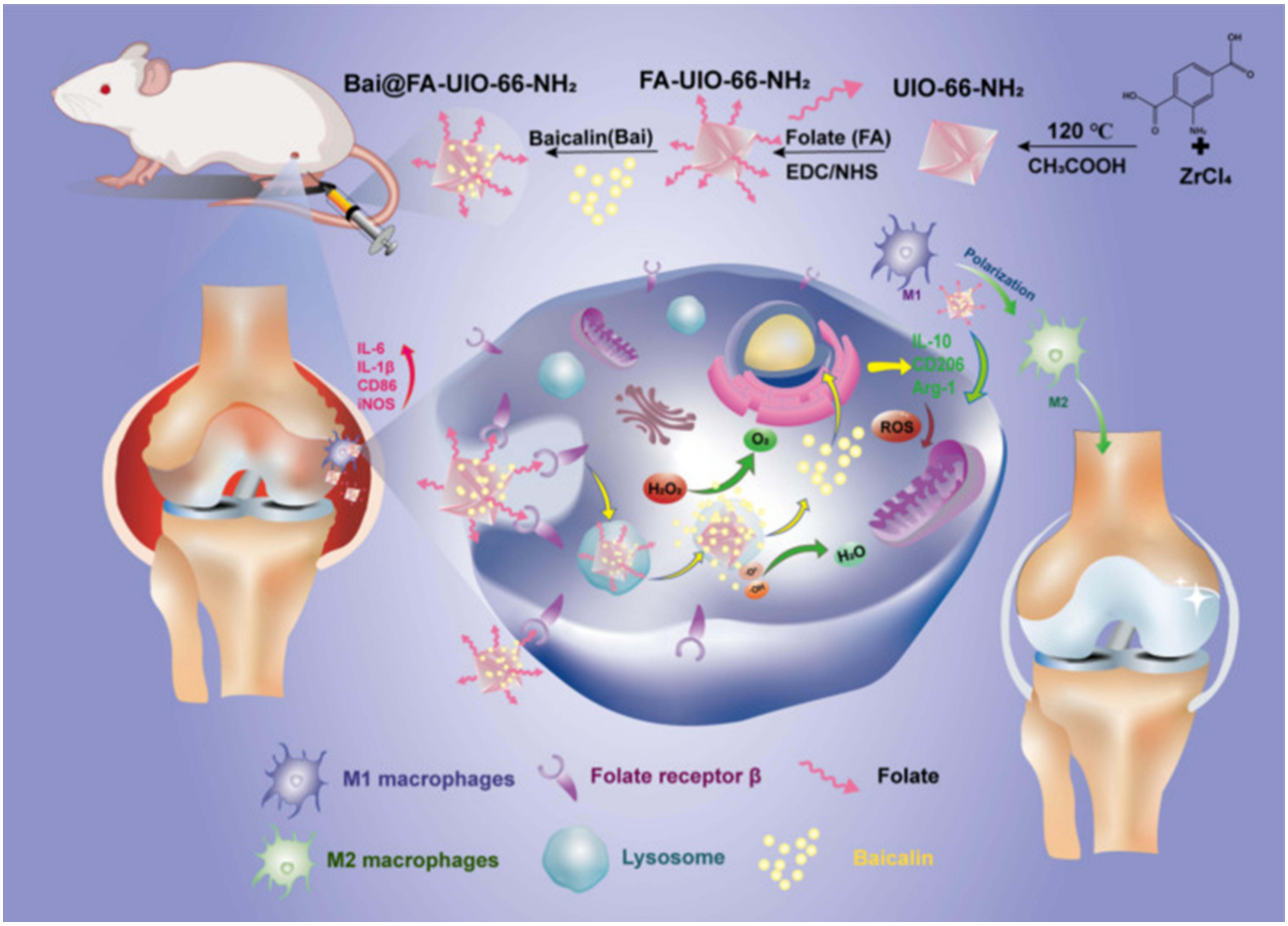

Figure 7 Schematic overview of how Bai@FA-UIO-66-NH_2 reduces oxidative stress and modulates macrophage polarization to enhance osteoarthritis therapy. This M1 macrophage–targeted delivery platform (Bai@FA-UIO-66-NH_2) synergistically scavenges excess ROS and drives M1-to-M2 repolarization, thereby alleviating inflammatory synovitis. Adapted from Huang L, Yao Y, Ruan Zet al Baicalin nanodelivery system based on functionalized metal-organic framework for targeted therapy of osteoarthritis by modulating macrophage polarization. J Nanobiotechnology. Copyright © 2024 by authors.[95]

dextran sulfate (DS)-scavenger receptor axis leverages scavenger receptors (eg, SR-A, MR) on activated macrophages as phagocytic entry points. Prior studies suggest that this axis can support targeted anti-inflammatory delivery in OA, particularly when SMs are highly activated and localized release of conventional anti-inflammatory agents is desired.[89]

From a translational perspective, selective nanotherapies are more likely to be integrated with current OA treatment strategies than to replace them. For example, HA-based targeted nanosystems may be incorporated into existing intra-articular treatment frameworks, while macrophage-selective platforms may serve as steroid-sparing or dose-sparing approaches by enhancing local efficacy and reducing systemic exposure.[78,131] In addition, FR-β-targeted systems may be particularly suitable for patients with inflammation-dominant OA, in whom imaging- or biomarker-guided stratification could support treatment selection.[132,133]

State-Selective SMs Targeting for OA Therapy

In the OA synovial microenvironment, indiscriminate depletion or inhibition of macrophages risks damaging resident barrier-like macrophages that maintain homeostasis. Therefore, a more rational strategy is state- and subset-selective intervention: prioritize pathogenic recruited subsets and inflammatory metabolic states while preserving, or even supporting, reparative and barrier-like macrophages. This approach may improve efficacy, widen the safety window, and strengthen translational rationale (Table 2).[27,134] This approach is especially relevant to OA because clinical cohort studies report marked heterogeneity and state stratification of mononuclear/macrophage lineage cells in knee OA (KOA) synovial effusions. These data support the feasibility of future patient stratification, companion diagnostics, and subset-guided therapy at the population level.[23] A central theme is to target inflammatory phenotype markers, such as iNOS-associated M1 states and CCR2-associated recruited populations. Qadri et al used flow cytometry to show enrichment of iNOS and IL-6 in $CD86^+$ pro-inflammatory subsets in synovium from Prg4-deficient models. Conversely, Prg4 over-expression limited accumulation of pro-inflammatory macrophages and reduced recruited inflammatory infiltration. Together, these findings support functional separability between pathogenic inflammatory subsets and homeostatic maintenance subsets, providing a biological coordinate for subset-selective materials delivery.[36] Ozkan et al encapsulated the CCR2 antagonist RS504393 into PLGA polymer microplates (μPLs) for sustained intra-articular release, targeting CCR2-dependent recruitment of inflammatory monocytes/macrophages. In the DMM-induced post-traumatic OA (PTOA) model, this formulation provided greater cartilage protection and reduced synovial hyperplasia compared with the free drug. These results demonstrate how materials can impose spatial confinement and temporal programming to suppress recruitment-driven inflammation.[135] As a complementary strategy, materials can also target phenotype-specific uptake and regulation of $iNOS^+$ inflammatory macrophages. For example, Zhang et al used apoptosis-inspired, phosphatidylserine-mimetic nanoliposomes to deliver the BRD4 inhibitor JQ1 (JQ1@PSLs). Given the reported high BRD4 expression in $iNOS^+$ M1 macrophages in OA synovium, this carrier favored macrophage uptake and inhibited M1 polarization, thereby reducing synovitis and pain and delaying cartilage degeneration. This represents a paradigm of targeting pathogenic macrophage states using phenotype markers coupled with epigenetic transcriptional modulation.[57] In parallel, resident barrier-like macrophages can be pursued as reparative targets because they help maintain the synovial barrier and homeostasis, potentially through tight-junction–related molecular programs. PRG4-related studies further suggest that modulating macrophage homeostasis and inflammatory infiltration can influence the trajectory of synovitis and tissue remodeling.[36] Mechanistically, Elsaid et al proposed that PRG4 modulates synovial inflammation by regulating the xanthine oxidase (XO)–HIF-1α axis in SMs. They also reviewed $CX3CR1^+TREM2^+$, claudin-5–associated barrier-like macrophage subsets in the synovium. These insights provide actionable biological targets and translational endpoints for materials designed to reinforce barrier integrity and restore homeostasis—for example, by locally releasing homeostatic factors or metabolic correctors.[24]

From a metabolic-state perspective, Chen et al proposed that M1 macrophages rely more heavily on aerobic glycolysis, whereas M2 macrophages preferentially use oxidative phosphorylation (OXPHOS). Building on this concept, an IgG-coated self-assembled nanoparticle system (IgG/Fe CV NPs) preferentially targeted inflammatory macrophages and inhibited key glycolytic nodes, including HIF-1α and GLUT1, thereby promoting M1-to-M2 polarization. In vivo, this intervention reduced synovitis and protected cartilage, illustrating a materials-executable route for reprogramming pathogenic macrophages based on metabolic state.[55] Extending the inflammation–metabolism–cell-fate coupling

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Table 2 Nanomaterials Targeting Distinct Subgroups and Functional States of SMs in OA

Targeted Macrophage Subgroup/State	Hallmark Markers/Axes	Nanomaterial Design Strategy	Representative Formulation	Key experimental Evidence/Functional Outcome in OA Models	Translational Significance	Refs.
Recruited inflammatory macrophages (reduce monocyte influx and inflammatory amplification)	CCR2–CCL2 axis (recruitment/ accumulation of inflammatory monocytes → macrophages)	Intra-articular depot and sustained release to maintain local CCR2 blockade while minimizing systemic exposure	RS504393-loaded PLGA polymeric microplates (μPLs)	Local, sustained CCR2 inhibition improved synovitis-related pathology and protected cartilage compared with free drug in post-traumatic OA settings	Clinically aligned with intra-articular therapy: improves exposure control, reduces off-target immunosuppression, and supports dose-sparing strategies	[135]
iNOS$^+$ / CD86$^+$ inflammatory phenotype (reprogram "pathogenic M1-like" states)	iNOS, IL-6; CD86$^+$ (pro-inflammatory activation signature linked to synovitis progression)	Apoptotic-mimicking surfaces (eg, phosphatidylserine-like "eat-me" cues) to bias uptake by inflammatory macrophages	Apoptotic body-inspired nanotherapeutics (PS-mimetic) delivering JQ1 (JQ1@PSLs)	Preferential macrophage uptake and suppression of BRD4-regulated inflammatory polarization reduced synovitis/pain and slowed cartilage degeneration	"State-aware" targeting can widen the therapeutic window by focusing on pathogenic polarization programs rather than ablating macrophages broadly	[57]
Homeostatic / barrier-like resident macrophages (preserve/restore synovial lining barrier and joint immune homeostasis)	Cx3CR1$^+$ TREM2$^+$; claudin-5 (CLDN5) (lining barrier-associated macrophages; protective compartment)	Microenvironment restoration via local delivery/augmentation of homeostatic regulators rather than cytotoxic depletion	Mechanistic framework: PRG4 (lubricin)-linked regulation of macrophage inflammatory tone	Evidence supports that restoring homeostatic macrophage regulation can mitigate synovitis and remodel inflammatory circuits	Provides a rationale for "do no harm" designs: preserve barrier macrophages while targeting recruited inflammatory states; suggests measurable endpoints (barrier markers, lining integrity)	[24,36]
Metabolic inflammatory state: glycolysis-high macrophages (suppress pathogenic immunometabolism)	HIF-1α / GLUT1; glycolysis dependence (inflammation-supporting metabolic program)	Opsonization/IgG-mediated phagocytic routing + metabolic reprogramming payload logic	IgG/Fe-CV nanoparticles (opsonization strategy with immunometabolic modulation)	Enhanced uptake by inflammatory macrophages and downregulation of glycolysis-associated pathways promoted M1→M2 shift and improved OA outcomes	Offers biomarker-driven translation: metabolic markers can support stratification and pharmacodynamic readouts in trials	[55]
Acidic/hypoxic-adaptive inflammatory state (collapse "stress-adapted" pathogenic persistence)	CA9 (carbonic anhydrase IX; acid/hypoxia adaptation), NO burden	Dual-function nanomedicine: NO scavenging + gene silencing of metabolic adaptation node	NO-scavenging + siCA9 nanomedicine (NAHA-CaP /siCA9)	Reduced inflammatory activation and promoted reparative polarization; attenuated OA progression by targeting stress-adaptive immunometabolism	Mechanism is "state-selective": exploits metabolic dependencies that are amplified in inflamed synovium, improving specificity beyond generic anti-inflammatories	[57]
Cell-death/mitochondrial quality-control state (block pyroptosis-driven inflammation; restore mitochondrial homeostasis)	Pyroptosis; ROS–mTORC1; mitophagy (damage-amplifying inflammatory cell death and mitochondrial dysfunction)	Stimuli-/pathway-directed nanotherapy to suppress pyroptosis and normalize mitophagy	RAPA@MPB-MMP9 nanoparticles (rapamycin-loaded, MMP9-targeted mesoporous Prussian blue platform)	Reduced macrophage pyroptosis and inflammatory signaling; improved synovitis and cartilage protection via ROS control and mitophagy support	Expands "state targeting" beyond M1/M2: focuses on tractable, druggable programs with clear PD biomarkers (ROS, pyroptosis markers, mitophagy flux)	[43]
Pathogenic macrophage enrichment via innate phagocytosis rules (increase delivery into "disease-driving" macrophages in situ)	FcγR/opsonization pathways (phagocyte uptake bias)	Opsonized nanoparticles to preferentially enter inflammatory macrophages and modulate polarization	Opsonized nanoparticle platform regulating polarization in OA	Higher macrophage uptake and improved inflammatory control with cartilage protection in OA models	Translationally attractive as a modular "delivery layer" that can be combined with different payloads; requires robust control of corona/opsonization consistency	[49]
Inflamed-synovium–homing and macrophage-education via biomimicry (multi-signal recognition and immune modulation)	Activated-macrophage membrane protein repertoire (context-dependent recognition)	Activated macrophage membrane coating to enhance inflammatory-site interactions and macrophage uptake	Activated macrophage membrane-coated nanoparticles (eg, M2H@RPK)	Reduced synovitis and joint damage by reshaping macrophage polarization in OA models	Powerful targeting but higher CMC/regulatory complexity (membrane source, batch consistency, safety), demanding early translational planning	[48]

framework, Qi et al constructed rapamycin-loaded mesoporous Prussian blue nanoparticles modified with an MMP9-targeting peptide (RAPA@MPB-MMP9 NPs). Supported by evidence from OA patients and collagenase-induced OA (CIOA) models implicating synovial macrophage pyroptosis and ROS–mTORC1 dysregulation, interventions that inhibit pyroptosis, reduce ROS, and enhance mitophagy can attenuate inflammation and limit cartilage degradation. This suggests that "attacking" pathogenic macrophages can extend beyond surface phenotype to include cell-death programs and mitochondrial quality-control states.[43] Kou et al applied an opsonization-inspired design to promote direct macrophage uptake. Their Bb@BRPL nanoparticles enhanced phagocytosis by inflammatory macrophages and facilitated polarization modulation, leading to cartilage protection and reduced inflammation in OA models. These findings indicate that leveraging immune recognition and phagocytic pathways can strengthen delivery to pathogenic macrophage states.[49] In addition, Zhou et al used activated macrophage membrane encapsulation to construct biomimetic nanoparticles (M2H@RPK). In OA models, the system alleviated synovitis, preserved joint structure, and improved pain, suggesting that biomimetic membranes can serve as a modular strategy to enhance macrophage uptake and promote immune remodeling within the intra-articular microenvironment. Such modules are readily combinable with subset/state-selective payloads.[48]

From a clinical translation perspective, these studies converge on three actionable translational opportunities. First, intra-articular delivery combined with sustained-release materials (eg, μPLs) can reduce systemic exposure and immune-related adverse effects, aligning with the long-term management needs of OA.[35,135] Second, phenotype- or metabolic-state-guided reprogramming (eg, JQ1@PSLs and IgG/Fe CV systems) can anchor efficacy to quantifiable biological readouts—such as iNOS, HIF-1α/GLUT1, synovitis scores, and pain-related behaviors—thereby facilitating companion diagnostics and dose-response modeling.[55,57] Third, the lineage complexity revealed in patient samples supports future trial designs with stratified enrollment, mechanism-aligned delivery, and consistent endpoints. This can accelerate nanomedicine development toward verifiability, regulatory oversight, and scalability.[23,136]

In addition, these selective nanotherapies may be more realistically integrated with current OA treatment strategies than used as stand-alone replacements.[137] For example, macrophage-targeted intra-articular nanosystems could be combined with existing approaches such as hyaluronic acid injection, corticosteroid-based symptom control, and rehabilitation programs to improve local efficacy while reducing reinjection frequency or systemic drug exposure.[138] In this way, selective nanotherapy may function as a targeted extension of current clinical management, particularly in patients with persistent synovitis or inflammation-dominant OA phenotypes.

Functional Nanomedicines for Disease Modification in OA Through Targeted SMs Intervention

Once preferential uptake by SMs is achieved, the design of the functional payload largely determines whether a nanomedicine can progress beyond transient anti-inflammatory effects to achieve disease modification. This requires precise intracellular intervention in inflammatory transcription, cellular stress responses, and cell-death programs, reshaping the synovial microenvironment and indirectly protecting cartilage. For example, phosphatidylserine (PS) nanoliposomes, which mimic apoptotic bodies, exploit SM recognition and phagocytosis of PS to deliver the BRD4 inhibitor JQ1 into inflammatory SMs. This reduces $iNOS^{+}$ M1 polarization and alleviates pain and synovitis in vivo, emphasizing transcriptional regulation as a central intervention axis.[57] A complementary microenvironment-metabolism coupling strategy uses NAHA CaP/siCA9 nanoparticles to scavenge NO via o-phenylenediamine groups and silence CA9 in SMs, mitigating acidosis/hypoxia-associated metabolic stress. This promotes M1-to-M2 reprogramming and slows disease progression in progressive OA models, illustrating that functional interventions can jointly target inflammatory mediators and metabolic nodes (Figure 8).[12] In synovial environments enriched with free radicals and reactive nitrogen species, hyaluronic acid-based NO-scavenging nanoparticles (HA-NSCs) further demonstrate the feasibility of inherent material pharmacology. By continuously removing inflammatory NO and modulating macrophage phenotype, HA-NSCs improve synovitis and chondrocyte pathology in vivo, potentially enabling a simpler CMC pathway for drug-free or low-loading translation.[124] Biomimetic membrane encapsulation can also repurpose conventional small molecules into more targeted functional therapies. Apoptotic neutrophil membrane-camouflaged liposomes (NM@Lip) delivered

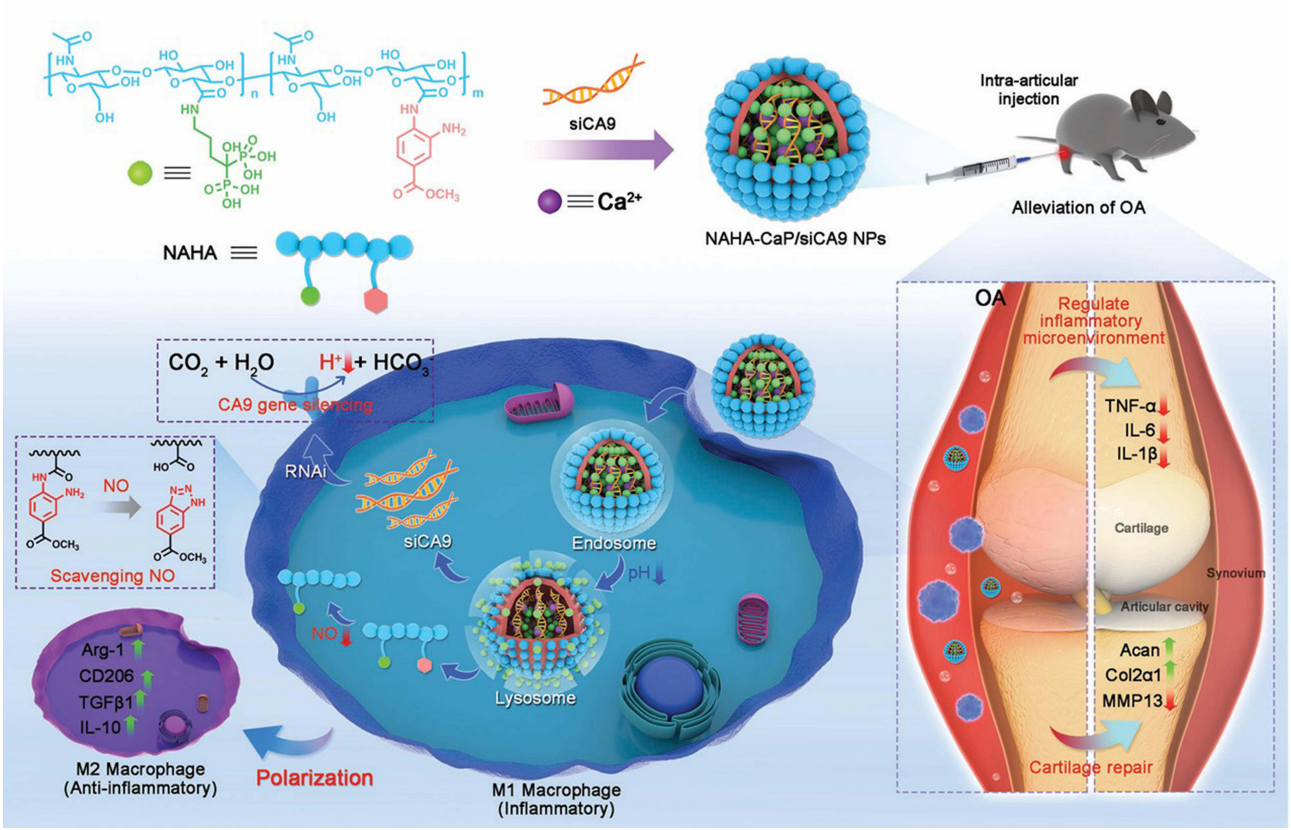

Figure 8 Design and proposed therapeutic mechanism of NAHA–CaP/siCA9 nanoparticles for OA via microenvironment–metabolism coupling. NAHA–CaP/siCA9 NPs are assembled by complexing NAHA with CaP to encapsulate siCA9, while *o*-phenylenediamine moieties enable nitric oxide (NO) scavenging. Following intra-articular injection, the nanoparticles preferentially accumulate in SMs, where endosomal/lysosomal processing facilitates siCA9 release to silence carbonic anhydrase IX (CA9). Concurrent NO clearance and CA9 knockdown alleviate acidosis/hypoxia-associated metabolic stress, reprogramming pro-inflammatory M1 macrophages toward an anti-inflammatory M2 phenotype. This remodeling of the inflammatory microenvironment suppresses cytokine production (TNF-α, IL-6, IL-1β), enhances cartilage anabolic markers (Acan, Col2a1), reduces matrix catabolism (MMP13), and ultimately slows OA progression while promoting cartilage protection and repair. Adapted from Yan Y, Lu A, Dou Yet al Nanomedicines Reprogram Synovial Macrophages by Scavenging Nitric Oxide and Silencing CA9 in Progressive Osteoarthritis. *Adv Sci (Weinh)*. Copyright © 2023 by authors.[12]

triamcinolone acetonide (TA) and inhibited PI3K/Akt-associated inflammatory amplification by targeting both SMs and activated synovial fibroblasts (SFs). This achieved more durable analgesic and anti-synovitis effects, suggesting that functional interventions can extend from single-cell targeting to modulation of intercellular networks.[123] At the cell-fate level, the MMP-9-responsive rapamycin-loaded mesoporous Prussian blue system (RAPA@MPB-MMP9) uses arthritis-associated protease activity as a release switch. Local drug release suppresses macrophage pyroptosis and reduces synovitis and cartilage damage, exemplifying pathology-triggered functional intervention.[43] Another strategy focuses on immunometabolic rewiring. IgG/Fe CV self-assembled nanoparticles exploit Fc-mediated uptake by M1-like SMs and jointly inhibit HIF-1α/GLUT1-driven glycolysis while limiting glutamine availability. This promotes metabolic M1-to-M2 conversion and protects cartilage in vivo, indicating that targeting cellular energetics can directly shape macrophage phenotype.[55]

pH-responsive lipid nanoparticles delivering urolithin A (LNPs@UA) target the mitochondrial ferroptosis–inflammation cascade. By inducing macrophage mitophagy and attenuating ferroptosis-associated injury, this strategy improves synovitis and structural joint outcomes, suggesting that restoring mitochondrial homeostasis can help interrupt chronic inflammatory circuits.[70] In recent years, senescent-like SMs have been implicated as a key source of refractory synovitis. pH-responsive chloroquine polymer/superoxide dismutase nanoparticles (pCQ/SOD NPs) integrate lysosomal–autophagy modulation with ROS scavenging to reduce SASP-like inflammatory outputs in senescent SMs. This provides a clinically relevant, stratified approach, particularly for older patients or those with metabolic dysfunction.[41] In parallel, ultrasmall

Prussian blue nanoenzymes (USPB NPs) remove ROS and modulate macrophage phenotype via multi-enzyme–like catalytic activity. This supports the concept that catalytic materials can sustainably dampen oxidative stress–inflammation positive feedback and may better match the long-term safety requirements of intra-articular administration.[139] From a translational perspective, these functional nanomaterials are well suited to intra-articular injection, and an increasing number of studies employ clinically familiar material systems (eg, Prussian blue, hyaluronic acid, and liposomes) to mitigate toxicity and regulatory risk. However, further evidence chain supplementation is still needed in large animal models, repeated administration safety, joint cavity retention/clearance kinetics, and efficacy endpoint design linked with imaging/biomarkers, in order to translate the advantage of "rewriting the inflammatory program within cells" into verifiable clinical benefits.[123,140] In clinical practice, such selective nanotherapies may be most feasibly integrated as an adjunct to current OA management rather than as a stand-alone replacement. In the future, this integration may be particularly valuable for patients with persistent synovitis, microenvironments dominated by oxidative stress, or inadequate response to traditional intra-articular therapies.[66,137]

Multi-Mechanism Nanotherapies for Targeted OA Treatment and SMs Modulation

In OA, chronic synovitis driven by synovial macrophages often co-occurs with dysregulated cartilage metabolism, cytokine cascades, and metabolic reprogramming. Consequently, single-agent or single-target therapies may offer short-term analgesic or anti-inflammatory benefits but rarely prevent structural progression. This limitation has shifted nanomaterial design from single-drug delivery to integrated platforms that enable multi-mechanistic collaboration and multicellular targeting within the joint cavity.[48,55] A representative strategy is to co-deliver an immunomodulator with an inhibitor of a key signaling axis within a single carrier. For example, an M2 macrophage membrane–coated nanocarrier (M2H@RPK) co-loaded the anti-inflammatory, cell-penetrating peptide KAFAK and shRNA targeting LEPR (to inhibit leptin receptor signaling). Enrichment in inflamed synovium was achieved via hyaluronic acid (HA) and membrane biomimicry. In OA rat models, this formulation reduced pro-inflammatory mediators, alleviated synovitis, and mitigated structural joint damage, supporting synergy between anti-inflammatory activity and tissue protection.[48] Another approach integrates dual targeting of SMs and synovial fibroblasts with established drugs. Apoptotic neutrophil membrane–camouflaged liposomes (NM@Lip) deliver triamcinolone acetonide (TA) and exploit apoptotic "eat-me" cues to enhance macrophage uptake. This design enriches drug exposure in inflammatory synovial cell populations, improves suppression of synovitis, and ameliorates OA pathology in animal models. These findings suggest that conventional glucocorticoids may achieve dose reduction with improved efficacy and a more controllable safety window through targeting and controlled release.[123] Beyond drug co-delivery, multi-module designs aim to simultaneously remodel the inflammatory microenvironment and alter cell fate. NAHA CaP/sicA9 integrates nitric oxide (NO) scavenging and CA9 gene silencing within a single nanocarrier, thereby reprogramming SMs by lowering NO burden and attenuating acidification- and hypoxia-associated inflammatory amplification. Across multiple models (eg, MIA and DMM), this platform confers anti-inflammatory effects, cartilage protection, and indications of repair. This microenvironment–gene–immune triad may provide greater robustness against OA heterogeneity.[48] In parallel, modulator–immunoglobulin (IgG) "trap" strategies leverage an outer IgG layer to promote preferential phagocytosis by inflammatory M1 macrophages via Fc receptor–mediated uptake. Drug release is then triggered by an inner reactive oxygen species (ROS)–responsive component, creating spatiotemporal synergy: targeted entry into pathogenic macrophages followed by intracellular activation. For example, IgG/Bb@BRPL clears ROS and inhibits NF-κB signaling, promoting M1-to-M2 polarization and improving the function of adjacent chondrocytes. This result illustrates a mechanistic synergy between phagocytic preference and stimulus-responsive release.[49] Metabolic co-targeting can further enhance synergy. IgG/Fe-CV NPs co-deliver chrysin and V-9302, block glutamine uptake, and inhibit the HIF-1α/GLUT1 glycolytic axis. Together, these actions shift SMs from a glycolysis-dependent inflammatory state toward a more reparative metabolic program, while suppressing inflammation and protecting cartilage in vivo. This suggests that dual-pathway immunometabolic modulation may be more robust than reliance on a single polarizing factor.[55] In addition, Yang et al's study targeted PGAM5 through experiments and found that it promotes M1 polarization of synovial macrophages in OA, and exacerbates inflammatory responses through the AKT mTOR and p38/ERK signaling pathways. By using siRNA to inhibit PGAM5, researchers successfully reversed the polarization of M1 macrophages, promoting their shift towards M2 and reducing joint damage

caused by OA. This indicates that targeting PGAM5 can effectively regulate the function of synovial macrophages, providing a new target for the treatment of OA. At the same time, this also suggests that by precisely targeting the polarization state of synovial macrophages, it may effectively inhibit the inflammatory response and osteochondral damage of OA, opening up the potential for multi-target combination therapy (Figure 9).[15]

In addition, intra-articular strategies can combine targeted, controlled release with multifunctional reactions at the material level. For example, GelMA@FPLBD enables folate receptor-mediated targeting of macrophages, combines ROS scavenging with H_2S release, and uses GelMA microspheres to prolong intra-articular residence. This synchronous modulation of inflammatory signaling and the tissue microenvironment provides more durable anti-inflammatory and structural benefits in OA models.[118] From a translational perspective, these multi-target and multi-mechanism platforms offer a key advantage: they minimize systemic exposure by using local intra-articular (IA) administration, while employing biomimetic membranes, IgG "traps", or microenvironment-responsive designs to concentrate active agents on key effector cells, such as SMs. Collectively, these features offer materials-based approaches to reduce dose, decrease reinjection frequency, and improve the durability of therapeutic effects.[48,55,123] However, the translational threshold remains significant. The consistency of CMC in composite systems, especially variability in membrane source, orientation, and inter-batch differences—along with scalable manufacturing, sterile quality control, and long-term biosafety evaluation, often determines whether promising animal results can translate to GMP production and clinical trials. This challenge has been highlighted in reviews on the translation of macrophage membrane-coated nanosystems.[107] Therefore, near-term clinical development will likely rely on mature material backbones (eg, PLGA, HA, GelMA, and liposomes) and prioritize combination nanomaterials that are synergistic, manufacturable, and regulator-ready. Progression into large-animal studies and early clinical evaluation should be guided by explicit patient stratification (inflammatory phenotype and synovitis burden) and quantifiable endpoints (MRI/ultrasound-assessed synovitis, inflammatory biomarkers, and structural progression).[48,107,118] In addition, these selective nano-therapeutic strategies may be more realistically integrated with current OA care than used as stand-alone replacements.[137] For example, they may be incorporated into treatment pathways already based on exercise and rehabilitation, weight management, oral or topical NSAIDs, intra-articular corticosteroid injection, and hyaluronic acid injection.[114,141] In this setting, selective intra-articular nanotherapies could be used to enhance local anti-inflammatory efficacy, prolong symptom control after injection, reduce repeated corticosteroid exposure, or improve outcomes in patients with persistent synovitis and inadequate response to conventional intra-articular treatment.

Challenges and Future Prospective

Challenges

Although multidimensional nanomaterial approaches targeting SMs show therapeutic potential in OA, substantial barriers remain for clinical translation. For example, accumulating evidence shows that SMs can act as pro-inflammatory amplifiers while also supporting synovial barrier function and tissue homeostasis in OA. Accordingly, nanomedicines that broadly inhibit or deplete macrophages risk an inherent efficacy-safety trade-off and should shift toward interventions selective for specific SM subpopulations or activation states.[23,24] A primary challenge is population- and tissue-level heterogeneity; large-cohort studies of knee OA (KOA) effusions reveal complex, stratified monocyte-macrophage lineages. Without patient or cellular subtyping in clinical trials, the benefit of targeted strategies may be diluted by averaging across heterogeneous subgroups.[23] Moreover, the absence of harmonized cell nomenclature and analysis pipelines across single-cell and spatial-omics studies impedes reusable annotation and cross-cohort integration, thereby weakening the ability to establish verifiable links between target populations and clinical endpoints.[142] A second tension arises from the coexistence of pathogenic SM subsets and protective, barrier-like subsets. Barrier-like SMs characterized by $Cx3CR1^{+}TREM2^{+}$ phenotypes and expression of the tight-junction protein claudin-5 have been linked to joint homeostasis, and their ablation has been associated with arthritis development. These findings imply that future materials should not only enhance uptake but also avoid irreversible injury to barrier-like resident SMs, and should incorporate barrier integrity or restoration of homeostasis as efficacy endpoints.[24] A third translational bottleneck concerns the dynamics of intra-articular delivery. Conventional small molecules are often cleared rapidly and limited by tissue barriers

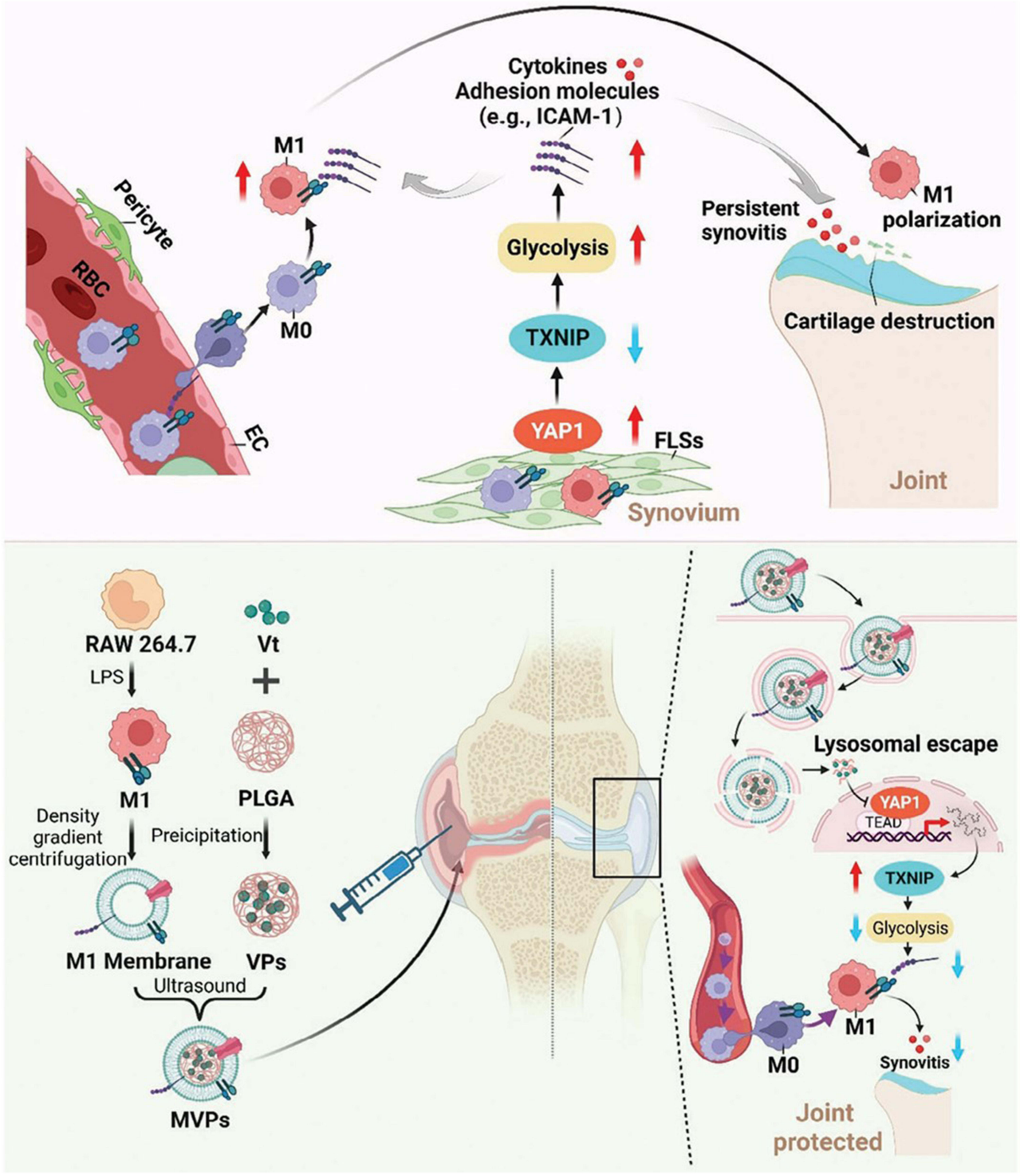

Figure 9 Mechanism of YAP1 and TXNIP-mediated macrophage polarization and cartilage destruction in OA, and the therapeutic approach via MVPs. The upper panel illustrates the role of YAP1 and TXNIP in mediating M1 macrophage polarization in the synovium. In response to cytokines and adhesion molecules (eg, ICAM-1), glycolysis is upregulated, leading to the activation of TXNIP and YAP1. This process enhances persistent synovitis and promotes cartilage destruction via M1 polarization. The lower panel depicts the experimental strategy of targeting M1 macrophages using multi-vesicular particles (MVPs). RAW 264.7 cells, treated with LPS to induce M1 polarization, are subjected to density gradient centrifugation and precipitation to isolate M1 membranes. These M1 membrane vesicles (MVs) are then encapsulated in PLGA and administered through ultrasound for joint protection. Upon lysosomal escape, MVPs selectively inhibit YAP1 signaling in macrophages, suppressing glycolysis and TXNIP activation, ultimately preventing M1 polarization and alleviating synovitis. This approach presents a promising strategy for modulating macrophage behavior in OA therapy. Adapted from Yang J, Li S, Li Zet al Targeting YAP1-regulated Glycolysis in Fibroblast-Like Synoviocytes Impairs Macrophage Infiltration to Ameliorate Diabetic Osteoarthritis Progression. Adv Sci (Weinh). Copyright © 2024 by authors.[15]

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after intra-articular administration, whereas nanoparticles can prolong residence, enable controlled release, and increase local exposure. However, pharmacokinetics and biodistribution across joint states—such as variations in effusion volume, synovitis severity, and lymphatic drainage—require systematic, quantitative comparisons within standardized evaluation frameworks.[75] An additional, often underappreciated variable is the protein corona and opsonization effect. In particular, for biomimetic membrane–based and immunoglobulin-related platforms, in vivo protein adsorption and immune clearance can substantially alter targeting behavior and safety profiles. Therefore, protein corona characterization, complement activation assays, phagocytosis-related readouts, and efficacy measures should be incorporated as early translational screening criteria.[143] A fourth practical challenge is CMC feasibility and process controllability for complex biomimetic systems. Reviews have repeatedly noted limitations of macrophage membrane–coated nanoparticles, including low membrane-extraction yield and reproducibility, inter-batch coating variability, potential immunogenicity, and long-term accumulation with biosafety risk. Collectively, these issues may constitute a hard barrier to progressing from animal studies to an investigational new drug (IND) application.[107] A major limitation is the insufficient human evidence base and the risk of over-extrapolating from animal models. Although rodent OA studies have reported transcriptional and epigenetic immune reprogramming via SM targeting (eg, BRD4 inhibition suppressing M1-like programs and improving synovitis and pain), selectivity, optimal dosing windows, and long-term safety in human OA synovium—especially across patient subgroups—remain to be validated in explants, organoids, and large-animal models.[57,143] Similarly, nanotherapies combining microenvironmental and metabolic modulation (eg, NO scavenging combined with CA9 silencing to counter acidic and hypoxic adaptation and reprogram SMs) have performed well in animals. For clinical translation, it will be essential to identify patients with sufficiently strong acidity/hypoxia and metabolic dependence, and whether measurable biomarkers can define eligibility and dose-response relationships.[10,12]

The Future Prospective

Although recent years have seen progress in nanomedicines targeting SMs for OA, substantial challenges remain for translation from bench to bedside. We propose several priorities that could accelerate this translational trajectory. Nanomedicine has shown significant promise in cartilage regeneration by enabling precise delivery of therapeutic agents, enhancing tissue repair, and promoting chondrocyte survival.[144] For example, nano-engineered scaffolds and drug carriers have been demonstrated to facilitate localized, sustained release of growth factors and anti-inflammatory agents that improve regenerative outcomes in cartilage defects.[145,146] Nanomaterials such as polymeric nanoparticles and nanocomposite hydrogels have been shown to improve site-specific therapeutic delivery and promote chondrogenesis and extracellular matrix deposition, overcoming the inherently limited self-healing ability of articular cartilage.[147,148] First, selective targeting of SM subpopulations and functional states is likely to become central to future OA therapy. Current strategies often aim to broadly inhibit or deplete SMs; however, this may also injure barrier-like, protective macrophages and increase adverse effects[41,142] Collaboration between biomaterials scientists, clinicians, and biologists will be essential to optimize these targeting strategies and ensure their clinical relevance. Future work should prioritize robust criteria to distinguish pathogenic from reparative SMs and leverage nanomaterials to target these subsets with high specificity.[23] For example, metabolic-state targeting has shown efficacy in animal models by suppressing glycolysis-dependent, inflammatory M1-like programs while promoting oxidative phosphorylation–associated, reparative M2-like programs. This approach may improve efficacy while reducing off-target immunosuppression, supporting its translational potential.[41,149]

Second, advances in macrophage-membrane biomimicry offer new routes for SM targeting.[104,150] Using macrophage membranes as coatings or carriers can exploit innate homing properties to enhance targeting while minimizing perturbation of non-target immune cells.[151] Future work should optimize fabrication of macrophage membrane–encapsulated nanoparticles, with particular attention to inter-batch consistency, long-term immunogenicity, and scalable manufacturing.[63,152,153] Additionally, controlling the oriented presentation of membrane proteins and preserving membrane integrity under clinically relevant conditions will be critical for translation. Third, combination therapy and multi-target synergy are likely essential for OA nanotherapy. Single-agent regimens often fail to address the multifactorial pathology of OA.[154,155] Accordingly, future designs should integrate complementary mechanisms, including immunomodulation, metabolic reprogramming, and apoptosis regulation. For example, functionalized nanoparticles that

concurrently modulate SM metabolism, suppress inflammatory signaling, and promote cartilage repair have shown efficacy in multiple animal models.[78,99] Such cross-mechanism, multi-target strategies enable precise intra-articular delivery and sustained local exposure, reducing systemic toxicity. However, key translation challenges remain. Variation in biodistribution and pharmacokinetics across joint pathological states requires systematic datasets and standardized frameworks to quantify intra-articular retention and release kinetics.[156] In addition, companion diagnostics could enable personalized therapy by stratifying patients using imaging and biomarkers, and by tailoring regimens to immunometabolic phenotypes.[157]

Safety remains a major constraint in translating nanomedicines into clinical practice. Long-term biocompatibility—particularly risks from metabolites and immune-related adverse effects—requires rigorous chronic in vivo safety studies and standardized toxicology testing.[52,114] In large-scale CMC requirements demand standardized, reproducible processes to ensure product consistency, stability, and clinical safety.[158] Overall, future efforts will likely emphasize multi-target collaboration, combination regimens, and personalized strategies. With mechanism-informed interventions, optimized nanocarrier engineering, and rigorous preclinical validation, these approaches may progress toward clinical implementation and ultimately provide safer and more effective options for OA patients.[131,137,159]

Conclusion

This review highlights the pivotal role of SMs in the synovitis-pain-structural progression axis of OA. It systematically summarizes how nanotherapy targeting SMs overcomes the limitations of traditional drugs, such as short-term anti-inflammatory and analgesic effects, and their inability to halt structural degeneration. This is achieved through intra-articular administration, cell-biased enrichment, and microenvironment-responsive release. More broadly, nanomaterials play a crucial therapeutic role in OA by serving not only as drug-delivery vehicles but also as multifunctional platforms that improve intra-articular retention, enhance cell-selective targeting, enable stimulus-responsive release, and support coordinated regulation of inflammation, metabolism, oxidative stress, and tissue repair. In this context, nanomedicine offers a versatile strategy to link disease mechanisms with therapeutic intervention, thereby expanding the possibility of disease-modifying treatments for OA. Overall, future designs with high translational potential will shift from broad-spectrum macrophage clearance or inhibition to subpopulation- or state-selective regulation. This approach inhibits pathogenic inflammatory programs and metabolic abnormalities while maximizing protection of resident SMs that maintain barrier and homeostatic functions. Simultaneously, robustness against OA heterogeneity can be enhanced by synergistically employing multiple mechanisms, including immune regulation, metabolic reprogramming, microenvironment repair, and cell fate regulation. However, clinical translation is limited by several key challenges: inconsistent classification and cross-cohort annotation standards for human-derived SMs; lack of comparable evaluation frameworks for pharmacokinetics (PK) and distribution of nanosystems across different joint pathological states; potential alterations in targeting and safety due to protein corona or regulatory effects; and difficulties in ensuring CMC consistency, large-scale sterile production, and long-term biosafety of complex biomimetic systems. Therefore, a more feasible near-term approach is to employ mature frameworks, such as PLGA, HA, GelMA, or liposomes, to implement synergistic yet manufacturable and regulable combination strategies. This should be followed by validation in large-animal models and early clinical trials, guided by clear population stratification (eg, inflammatory phenotype or synovitis burden) and quantitative endpoints (eg, imaging of synovitis, inflammatory biomarkers, and structural progression). Such efforts will accelerate the translation of SM-targeted nanotherapy from laboratory research to a viable disease-modifying strategy for OA.

Abbreviations

OA, Osteoarthritis; SMs, Synovial Macrophages; DAMPs, Damage-Associated Molecular Patterns; ROS, Reactive Oxygen Species; TNF-α, Tumor Necrosis Factor Alpha; IL-1β, Interleukin 1 Beta; NF-κB, Nuclear Factor Kappa B; MAPK, Mitogen-Activated Protein Kinase; M1, M1 Macrophage (pro-inflammatory); M2, M2 Macrophage (anti-inflammatory); M-CSF, Macrophage Colony-Stimulating Factor; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; MMP, Matrix Metalloproteinases; CCL2, C-C Motif Chemokine Ligand 2; TGF-β, Transforming Growth Factor Beta; PI3K/AKT, Phosphoinositide 3-Kinase/Protein Kinase B; AKT-mTOR, AKT/mammalian Target of

Rapamycin; STAT6, Signal Transducer and Activator of Transcription 6; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; siRNA, Small Interfering RNA; TXNIP, Thioredoxin-Interacting Protein; YAP1, Yes-Associated Protein 1; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; CX3CR1, C-X3-C Motif Chemokine Receptor 1; FcγR, Fc Gamma Receptor; HA, Hyaluronic Acid; FR-β, Folate Receptor Beta; PEG, Polyethylene Glycol; PLGA, Poly(lactic-co-glycolic acid); LNPs, Lipid Nanoparticles; MVPs, Multi-Vesicular Particles; M0, Resting Macrophage; M2H@RPK, M2 Macrophage Membrane-Coated Nanoparticles.

Data Sharing Statement

No new data has been generated, all references are cited in the manuscript.

Consent for Publication

All the authors were consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests associated with the manuscript.

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393:1745–1759.
2. Cao F, Xu Z, Li XX, et al. Trends and cross-country inequalities in the global burden of osteoarthritis, 1990–2019: a population-based study. *Ageing Res Rev*. 2024;99:102382. doi:10.1016/j.arr.2024.102382
3. Yao Q, Wu X, Tao C, et al. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. *Signal Transduct Target Ther*. 2023;8(1):56. doi:10.1038/s41392-023-01330-w
4. Hu H, Zhou C, Jiang B, et al. Expression and clinical significance of LncRNA Kcnq1ot1 in type 2 diabetes mellitus patients with osteoarthritis. *BMC Endocr Disord*. 2025;25:131. doi:10.1186/s12902-025-01915-2
5. Wu CJ, Liu RX, Huan SW, et al. Senescent skeletal cells cross-talk with synovial cells plays a key role in the pathogenesis of osteoarthritis. *Arthritis Res Ther*. 2022;24:59. doi:10.1186/s13075-022-02747-4
6. Xie J, Huang Z, Yu X, Zhou L, Pei F. Clinical implications of macrophage dysfunction in the development of osteoarthritis of the knee. *Cytokine Growth Factor Rev*. 2019;46:36–44. doi:10.1016/j.cytogfr.2019.03.004
7. Haubruck P, Pinto MM, Moradi B, Little CB, Gentek R. Monocytes, macrophages, and their potential niches in synovial joints – therapeutic targets in post-traumatic osteoarthritis? *Front Immunol*. 2021;12:763702. doi:10.3389/fimmu.2021.763702
8. Wu CL, Harasymowicz NS, Klimak MA, Collins KH, Guilak F. The role of macrophages in osteoarthritis and cartilage repair. *Osteoarthritis Cartilage*. 2020;28(5):544–554. doi:10.1016/j.joca.2019.12.007
9. Cui SH, Yan Y, Lu A, et al. Nanomedicines promote cartilage regeneration in osteoarthritis by synergistically enhancing chondrogenesis of mesenchymal stem cells and regulating inflammatory environment. *ACS Nano*. 2024;18(11):8125–8142. doi:10.1021/acsnano.3c11848
10. Xue C, Tian J, Cui Z, et al. Reactive oxygen species (ROS)-mediated M1 macrophage-dependent nanomedicine remodels inflammatory microenvironment for osteoarthritis recession. *Bioact Mater*. 2024;33:545–561. doi:10.1016/j.bioactmat.2023.10.032
11. DiNicola ES, Martinez AV, Burnikel BC, Mercuri JJ. Cigarette smoke extract alters the inflammatory secretome of osteoarthritis-affected synovium increasing joint tissue oxidative stress in an indirect co-culture model. *J Orthop Res*. 2026;44(4):e70184. doi:10.1002/jor.70184
12. Yan Y, Lu A, Dou Y, et al. Nanomedicines reprogram synovial macrophages by scavenging nitric oxide and silencing CA9 in progressive osteoarthritis. *Adv Sci*. 2023;10(11):2207490. doi:10.1002/advs.202207490
13. Deng C, Xiao Y, Zhao X, et al. Sequential targeting chondroitin sulfate-bilirubin nanomedicine attenuates osteoarthritis via reprogramming lipid metabolism in M1 macrophages. *Adv Sci*. 2025;12(9):2411911. doi:10.1002/advs.202411911
14. Yuan YS, Li HY, Lu H, et al. Reprogramming mitochondrial metabolism to enhance macrophages polarization by ROS-responsive nanoparticles for osteoarthritis. *Biomaterials*. 2025;322:123395. doi:10.1016/j.biomaterials.2025.123395

15. Yang J, Li S, Li Z, et al. Targeting YAP1-regulated glycolysis in fibroblast-like synoviocytes impairs macrophage infiltration to ameliorate diabetic osteoarthritis progression. *Adv Sci*. 2023;11(5):2304617. doi:10.1002/advs.202304617
16. Zhang H, Cai D, Bai X. Macrophages regulate the progression of osteoarthritis. *Osteoarthritis Cartilage*. 2020;28(5):555–561. doi:10.1016/j.joca.2020.01.007
17. Shao H, Xu S, Zeng F, et al. Metal–organic framework-integrated nanoplatform orchestrates osteochondral-synovial homeostasis for osteoarthritis therapy. *ACS Nano*. 2025;19(36):32744–32766. doi:10.1021/acsnano.5c10692
18. Thomson A, Hilkens CMU. Synovial macrophages in osteoarthritis: the key to understanding pathogenesis? *Front Immunol*. 2021;12:678757. doi:10.3389/fimmu.2021.678757
19. Ramezanpour S, Kanthawang T, Lynch J, et al. Impact of sustained synovitis on knee joint structural degeneration: 4-year MRI data from the osteoarthritis initiative. *J Magn Reson Imaging*. 2023;57(1):153–164. doi:10.1002/jmri.28223
20. Jiang T, Weng Q, Liu K, et al. Bidirectional association identified between synovitis and knee and hand osteoarthritis: a general population-based study. *Lancet Reg Health West Pac*. 2024;50:101169. doi:10.1016/j.lanwpc.2024.101169
21. Philpott HT, Birmingham TB, Pinto R, et al. Synovitis is associated with constant pain in knee osteoarthritis: a cross-sectional study of OMERACT knee ultrasound scores. *J Rheumatol*. 2022;49(1):89–97. doi:10.3899/jrheum.210285
22. Rubortone P, De Lorenzis E, Leone F, et al. Histological synovitis and radiographic damage in knee osteoarthritis: insights from a comprehensive analysis of ultrasound-guided synovial biopsies in 161 patients. *RMD Open*. 2025;11(3):e006011. doi:10.1136/rmdopen-2025-006011
23. Mikulkova Z, Gallo J, Manukyan G, et al. Complexity of synovial fluid-derived monocyte-macrophage-lineage cells in knee osteoarthritis. *Cell Rep*. 2024;43(12):115011. doi:10.1016/j.celrep.2024.115011
24. Elsaid KA, Zhang LX, Zhao T, et al. Proteoglycan 4 (Lubricin) and regulation of xanthine oxidase in synovial macrophage as a mechanism of controlling synovitis. *Arthritis Res Ther*. 2024;26:214. doi:10.1186/s13075-024-03455-x
25. Zhang K, Wang Z, He J, et al. Mechanisms of synovial macrophage polarization in osteoarthritis pathogenesis and their therapeutic implications. *Front Immunol*. 2025;16:1637731. doi:10.3389/fimmu.2025.1637731
26. Kriegova E, Manukyan G, Mikulkova Z, et al. Gender-related differences observed among immune cells in synovial fluid in knee osteoarthritis. *Osteoarthritis Cartilage*. 2018;26(9):1247–1256. doi:10.1016/j.joca.2018.04.016
27. Trajerova M, Kriegova E, Mikulkova Z, Savara J, Kudelka M, Gallo J. Knee osteoarthritis phenotypes based on synovial fluid immune cells correlate with clinical outcome trajectories. *Osteoarthritis Cartilage*. 2022;30(12):1583–1592. doi:10.1016/j.joca.2022.08.019
28. Mehrani Y, Junqani RR, Morovati S, et al. The importance of neutrophils in osteoarthritis: current concepts and therapeutic perspectives. *Immuno*. 2023;3(3):250–272. doi:10.3390/immuno3030017
29. Hao G, Han S, Xiao Z, Shen J, Zhao Y, Hao Q. Synovial mast cells and osteoarthritis: current understandings and future perspectives. *Heliyon*. 2024;10(24):e41003. doi:10.1016/j.heliyon.2024.e41003
30. Loucks A, Maerz T, Hankenson K, Moeser A, Colbath A. The multifaceted role of mast cells in joint inflammation and arthritis. *Osteoarthritis Cartilage*. 2023;31(5):567–575. doi:10.1016/j.joca.2023.01.005
31. Fang C, Zhong R, Lu S, et al. TREM2 promotes macrophage polarization from M1 to M2 and suppresses osteoarthritis through the NF-κB/CXCL3 axis. *Int J Biol Sci*. 2024;20(6):1992–2007. doi:10.7150/ijbs.91519
32. Yin X, Wang Q, Tang Y, Wang T, Zhang Y, Yu T. Research progress on macrophage polarization during osteoarthritis disease progression: a review. *J Orthop Surg Res*. 2024;19(1):584. doi:10.1186/s13018-024-05052-9
33. Tu J, Hong W, Guo Y, et al. Ontogeny of synovial macrophages and the roles of synovial macrophages from different origins in arthritis. *Front Immunol*. 2019;10:1146. doi:10.3389/fimmu.2019.01146
34. Huang QQ, Doyle R, Chen SY, et al. Critical role of synovial tissue–resident macrophage niche in joint homeostasis and suppression of chronic inflammation. *Sci Adv*. 2021;7(2):eabd0515. doi:10.1126/sciadv.abd0515
35. Knights AJ, Farrell EC, Ellis OM, Song MJ, Appleton CT, Maerz T. Synovial macrophage diversity and activation of M-CSF signaling in post-traumatic osteoarthritis. *Elife*. 2025;12:RP93283. doi:10.7554/eLife.93283
36. Qadri M, Jay GD, Zhang LX, Schmidt TA, Totonchy J, Elsaid KA. Proteoglycan-4 is an essential regulator of synovial macrophage polarization and inflammatory macrophage joint infiltration. *Arthritis Res Therapy*. 2021;23(1):241. doi:10.1186/s13075-021-02621-9
37. Knights AJ, Farrell EC, Ellis OM, et al. Synovial fibroblasts assume distinct functional identities and secrete R-spondin 2 in osteoarthritis. *Ann Rheum Dis*. 2023;82(2):272–282. doi:10.1136/ard-2022-222773
38. Nanus DE, Badoume A, Wijesinghe SN, et al. Synovial tissue from sites of joint pain in knee osteoarthritis patients exhibits a differential phenotype with distinct fibroblast subsets. *eBioMedicine*. 2021;72:103618. doi:10.1016/j.ebiom.2021.103618
39. Damerau A, Rosenow E, Alkhoury D, Buttgereit F, Gaber T. Fibrotic pathways and fibroblast-like synoviocyte phenotypes in osteoarthritis. *Front Immunol*. 2024;15. doi:10.3389/fimmu.2024.1385006
40. Cyndari KI, Scorza BM, Zacharias ZR, et al. Resident synovial macrophages in synovial fluid: implications for immunoregulation. *Clin Immunol*. 2025;271:110422. doi:10.1016/j.clim.2024.110422
41. Liu Y, Duan J, Dang Y, et al. Remodeling of senescent macrophages in synovium alleviates trauma- and aging-induced osteoarthritis. *Bioact Mater*. 2026;55:42–56. doi:10.1016/j.bioactmat.2025.09.016
42. Shin Y, Cho D, Kim SK, Chun JS. STING mediates experimental osteoarthritis and mechanical allodynia in mouse. *Arthritis Res Therapy*. 2023;25(1):90. doi:10.1186/s13075-023-03075-x
43. Qi W, Jin L, Huang S, et al. Modulating synovial macrophage pyroptosis and mitophagy interactions to mitigate osteoarthritis progression using functionalized nanoparticles. *Acta Biomater*. 2024;181:425–439. doi:10.1016/j.actbio.2024.05.014
44. Li C, Ouyang Z, Huang Y, et al. NOD2 attenuates osteoarthritis via reprogramming the activation of synovial macrophages. *Arthritis Res Ther*. 2023;25:249. doi:10.1186/s13075-023-03230-4
45. Aulin C, Larsson S, Vogl T, et al. The alarmins high mobility group box protein 1 and S100A8/A9 display different inflammatory profiles after acute knee injury. *Osteoarthritis Cartilage*. 2022;30(9):1198–1209. doi:10.1016/j.joca.2022.06.009
46. Wang W, Chu Y, Zhang P, et al. Targeting macrophage polarization as a promising therapeutic strategy for the treatment of osteoarthritis. *Int Immunopharmacol*. 2023;116:109790. doi:10.1016/j.intimp.2023.109790

47. Kloppenburg M. Synovial inflammation in osteoarthritis. A treatable target? *Semin Arthritis Rheumatism*. 2024;64:152326. doi:10.1016/j.semarthrit.2023.152326
48. Zhou K, Yang C, Shi K, et al. Activated macrophage membrane-coated nanoparticles relieve osteoarthritis-induced synovitis and joint damage. *Biomaterials*. 2023;295:122036. doi:10.1016/j.biomaterials.2023.122036
49. Kou L, Huang H, Tang Y, et al. Opsonized nanoparticles target and regulate macrophage polarization for osteoarthritis therapy: a trapping strategy. *J Control Release*. 2022;347:237–255. doi:10.1016/j.jconrel.2022.04.037
50. Wang H, Zhang H, Fan K, et al. Frugoside delays osteoarthritis progression via inhibiting miR-155-modulated synovial macrophage M1 polarization. *Rheumatology*. 2021;60(10):4899–4909. doi:10.1093/rheumatology/keab018
51. Richard MJ, Driban JB, McAlindon TE. Pharmaceutical treatment of osteoarthritis. *Osteoarthritis Cartilage*. 2023;31(4):458–466. doi:10.1016/j.joca.2022.11.005
52. Deng W, Wang T, Li L, et al. A review of nanomaterials in osteoarthritis treatment and immune modulation. *Regen Biomater*. 2025:12:rbaf048. doi:10.1093/rb/rbaf048
53. Liu B, Liu T, Li Y, Tan C. Innovative biotherapies and nanotechnology in osteoarthritis: advancements in inflammation control and cartilage regeneration. *Int J Mol Sci*. 2024;25(24):13384. doi:10.3390/ijms252413384
54. Jang S, Lee K, Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. *Int J Mol Sci*. 2021;22(5):2619. doi:10.3390/ijms22052619
55. Chen R, Zheng S, Zhao X, et al. Metabolic reprogramming of macrophages by a nano-sized opsonization strategy to restore M1/M2 balance for osteoarthritis therapy. *J Control Release*. 2025;380:469–489. doi:10.1016/j.jconrel.2025.02.005
56. Zhao K, Ruan J, Nie L, Ye X, Li J. Effects of synovial macrophages in osteoarthritis. *Front Immunol*. 2023;14:1164137. doi:10.3389/fimmu.2023.1164137
57. Xu YD, Liang XC, Li ZP, et al. Apoptotic body-inspired nanotherapeutics efficiently attenuate osteoarthritis by targeting BRD4-regulated synovial macrophage polarization. *Biomaterials*. 2024;306:122483. doi:10.1016/j.biomaterials.2024.122483
58. Liu Y, Hao R, Lv J, et al. Targeted knockdown of PGAM5 in synovial macrophages efficiently alleviates osteoarthritis. *Bone Res*. 2024;12:15. doi:10.1038/s41413-024-00318-8
59. Yuan Z, Jiang D, Yang M, et al. Emerging roles of macrophage polarization in osteoarthritis: mechanisms and therapeutic strategies. *Orthop Surg*. 2024;16(3):532–550. doi:10.1111/os.13993
60. Sun Y, Zuo Z, Kuang Y. An Emerging Target in the Battle against Osteoarthritis: macrophage Polarization. *Int J Mol Sci*. 2020;21(22):8513. doi:10.3390/ijms21228513
61. Warmink K, Vinod P, Korthagen NM, Weinans H, Rios JL. Macrophage-driven inflammation in metabolic osteoarthritis: implications for biomarker and therapy development. *Int J Mol Sci*. 2023;24(7):6112. doi:10.3390/ijms24076112
62. Hao X, Jiang B, Wu J, et al. Nanomaterials for bone metastasis. *J Control Release*. 2024;373:640–651. doi:10.1016/j.jconrel.2024.07.067
63. Ummarino A, Gambaro FM, Kon E, Torres Andón F. Therapeutic manipulation of macrophages using nanotechnological approaches for the treatment of osteoarthritis. *Nanomaterials*. 2020;10(8):1562. doi:10.3390/nano10081562
64. Patel SK, Billingsley MM, Mukalel AJ, et al. Bile acid-containing lipid nanoparticles enhance extrahepatic mRNA delivery. *Theranostics*. 2024;14(1):1–16. doi:10.7150/thno.89913
65. Bordon G, Berenbaum F, Distler O, Luciani P. Harnessing the multifunctionality of lipid-based drug delivery systems for the local treatment of osteoarthritis. *Biomed Pharmacother*. 2023;168:115819. doi:10.1016/j.biopha.2023.115819
66. Keshari R, Muddala G, Rajput A, Balakrishnan B, Kaur N, Srivastava R. Theranostic nanoparticles for osteoarthritis: converging drug delivery and imaging toward personalised joint healthcare. *J Drug Delivery Sci Technol*. 2026;115:107796. doi:10.1016/j.jddst.2025.107796
67. Eichaker LR, Cho H, Duvall CL, Werfel TA, Hasty KA. Future nanomedicine for the diagnosis and treatment of osteoarthritis. *Nanomedicine*. 2014;9(14):2203–2215. doi:10.2217/nnm.14.138
68. Xu Z, Li J, Yan N, Liu X, Deng Y, Song Y. Phosphatidylserine and/or sialic acid modified liposomes increase uptake by tumor-associated macrophages and enhance the anti-tumor effect. *AAPS Pharm Sci Tech*. 2024;25(5):125. doi:10.1208/s12249-024-02837-3
69. Ayesha BT, Erum A, Shahid N, Tulain UR, Saleem U. An effective approach in osteoarthritis: diacerein-loaded solid lipid nanoparticles, preparation and evaluation for targeted therapy. *J Drug Delivery Sci Technol*. 2025;108:106856. doi:10.1016/j.jddst.2025.106856
70. Yi G, Li M, Zhou J, et al. Novel pH-responsive lipid nanoparticles deliver UA-mediated mitophagy and ferroptosis for osteoarthritis treatment. *Mater Today Bio*. 2025;32:101697. doi:10.1016/j.mtbio.2025.101697
71. Yang K, Zhao Y, Wang C, et al. Dual-targeted lipid nanoparticles system for synergistic anti-inflammation and cartilage repair in the treatment of temporomandibular joint osteoarthritis. *Chem Eng J*. 2024;481:148769. doi:10.1016/j.cej.2024.148769
72. Nele V, Campani V, Alia Moosavian S, De Rosa G. Lipid nanoparticles for RNA delivery: self-assembling *vs* driven-assembling strategies. *Adv Drug Delivery Rev*. 2024;208:115291. doi:10.1016/j.addr.2024.115291
73. Kong K, Li B, Chang Y, et al. Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. *J Nanobiotechnology*. 2025;23:34. doi:10.1186/s12951-025-03103-9
74. Mei H, Sha C, Lv Q, et al. Multifunctional polymeric nanocapsules with enhanced cartilage penetration and retention for osteoarthritis treatment. *J Control Release*. 2024;374:466–477. doi:10.1016/j.jconrel.2024.08.031
75. Wen J, Li H, Dai H, et al. Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management. *Mater Today Bio*. 2023;19:100597. doi:10.1016/j.mtbio.2023.100597
76. Yu G, Xu Q, Lei Z, Lu Y, Xu W, Wu R. Novel polymeric platform produced by photodegradation-induced rearrangement for a multifunctional negative photoresist. *Polym Adv Technol*. 2023;34(2):597–604. doi:10.1002/pat.5911
77. Ma JC, Luo T, Feng B, et al. Exploring the translational potential of PLGA nanoparticles for intra-articular rapamycin delivery in osteoarthritis therapy. *J Nanobiotechnol*. 2023;21(1):361. doi:10.1186/s12951-023-02118-4
78. Zerrillo L, Gigliobianco MR, D'Atri D, et al. PLGA nanoparticles grafted with hyaluronic acid to improve site-specificity and drug dose delivery in osteoarthritis nanotherapy. *Nanomaterials*. 2022;12(13):2248. doi:10.3390/nano12132248
79. Wang H, Li Z, Liu J, et al. Nanozyme-enhanced injectable hyaluronic acid-based hydrogel for the treatment of osteoarthritis. *Int J Biol Macromol*. 2024;282(Pt 2):136819. doi:10.1016/j.ijbiomac.2024.136819

80. Sun H, Zhan M, Zou Y, et al. Bioactive phosphorus dendrimers deliver protein/drug to tackle osteoarthritis *via* cooperative macrophage reprogramming. *Biomaterials*. 2025;316:122999. doi:10.1016/j.biomaterials.2024.122999
81. Costa FR, Marques MRC, Costa VC, et al. Intra-articular hyaluronic acid in osteoarthritis and tendinopathies: molecular and clinical approaches. *Biomedicines*. 2023;11(4):1061. doi:10.3390/biomedicines11041061
82. Shi S, Zhang L, Jiang K. Polysaccharide nanosystems for osteoarthritis therapy: mechanisms, combinations, and future directions. *Int J Biol Macromol*. 2024;279:135146. doi:10.1016/j.ijbiomac.2024.135146
83. Salathia S, Gigliobianco MR, Casadidio C, et al. Hyaluronic acid-based nanosystems for CD44 mediated anti-inflammatory and antinociceptive activity. *Int J Mol Sci*. 2023;24(8):7286. doi:10.3390/ijms24087286
84. Chen B, Wang J, Jin X, et al. Rapamycin incorporating hydrogel improves the progression of osteoarthritis by inducing synovial macrophages polarization and reducing intra-articular inflammation. *Mater Des*. 2023;225:111542. doi:10.1016/j.matdes.2022.111542
85. Xiao P, Han X, Huang Y, et al. Reprogramming macrophages via immune cell mobilized hydrogel microspheres for osteoarthritis treatments. *Bioact Mater*. 2024;32:242–259. doi:10.1016/j.bioactmat.2023.09.010
86. Ji X, Shao H, Li X, et al. Injectable immunomodulation-based porous chitosan microspheres/HPCH hydrogel composites as a controlled drug delivery system for osteochondral regeneration. *Biomaterials*. 2022;285:121530. doi:10.1016/j.biomaterials.2022.121530
87. Zhou Y, Li S, Huang Z, et al. A novel thermosensitive curcumin-loaded hydrogel that modulates macrophage M1/M2 polarization for osteoarthritis therapy. *Gels*. 2025;12(1):7. doi:10.3390/gels12010007
88. Ramasundaram S, Saravanakumar G, Sobha S, et al. Dextran sulfate nanocarriers: design, strategies and biomedical applications. *Int J Mol Sci*. 2022;24(1):355. doi:10.3390/ijms24010355
89. Han J, Na R, Zhao N, et al. Macrophage-targeted dextran sulfate-dexamethasone conjugate micelles for effective treatment of rheumatoid arthritis. *Molecules*. 2023;28(2):591.
90. Zhou T, Xiong H, Wang SQ, et al. An injectable hydrogel dotted with dexamethasone acetate-encapsulated reactive oxygen species-scavenging micelles for combinatorial therapy of osteoarthritis. *Mat Today Nano*. 2022;17:100164. doi:10.1016/j.mtnano.2021.100164
91. Chen Z, Pang Q, Zhan J, et al. MSCs-derived ECM functionalized hydrogel regulates macrophage reprogramming for osteoarthritis treatment by improving mitochondrial function and energy metabolism. *Mater Today Bio*. 2024;29:101340. doi:10.1016/j.mtbio.2024.101340
92. Chen Q, Jin Y, Chen T, et al. Injectable nanocomposite hydrogels with enhanced lubrication and antioxidant properties for the treatment of osteoarthritis. *Mater Today Bio*. 2024;25:100993. doi:10.1016/j.mtbio.2024.100993
93. Guo Q, Nan R, Du Y, et al. Hyaluronic acid composite hydrogel with enhanced lubrication and controllable drug release for the mitigation of osteoarthritis. *Int J Biol Macromol*. 2025;308:142677. doi:10.1016/j.ijbiomac.2025.142677
94. Shi T, Zhao J, Long K, et al. Cationic mesoporous silica nanoparticles alleviate osteoarthritis by targeting multiple inflammatory mediators. *Biomaterials*. 2023;303:122366. doi:10.1016/j.biomaterials.2023.122366
95. Huang L, Yao Y, Ruan Z, et al. Baicalin nanodelivery system based on functionalized metal-organic framework for targeted therapy of osteoarthritis by modulating macrophage polarization. *J Nanobiotechnol*. 2024;22(1):221. doi:10.1186/s12951-024-02494-5
96. Ren X, Zhuang H, Jiang F, et al. Ceria nanoparticles alleviated osteoarthritis through attenuating senescence and senescence-associated secretory phenotype in synoviocytes. *Int J Mol Sci*. 2023;24(5):5056.
97. Zhuang H, Ren X, Li H, Zhang Y, Zhou P. Cartilage-targeting peptide-modified cerium oxide nanoparticles alleviate oxidative stress and cartilage damage in osteoarthritis. *J Nanobiotechnology*. 2024;22:784. doi:10.1186/s12951-024-03068-1
98. Wei F, Neal CJ, Sakthivel TS, Kean T, Seal S, Coathup MJ. Multi-functional cerium oxide nanoparticles regulate inflammation and enhance osteogenesis. *Mater Sci Eng*. 2021;124:112041. doi:10.1016/j.msec.2021.112041
99. Liu C, Sun Y, Li D, et al. A multifunctional nanogel encapsulating layered double hydroxide for enhanced osteoarthritis treatment via protection of chondrocytes and ECM. *Mater Today Bio*. 2024;26:101034. doi:10.1016/j.mtbio.2024.101034
100. Hong Y, Ji M, Su Y, Song C. Cartilage-targeted Au@Pt nanospheres with enhanced photothermal effect for promoting the recovery of osteoarthritis via ROS catalysis. *Colloids Surf B Biointerfaces*. 2025;256(Pt 2):115036. doi:10.1016/j.colsurfb.2025.115036
101. Morici L, Allémann E, Rodríguez-Nogales C, Jordan O. Cartilage-targeted drug nanocarriers for osteoarthritis therapy. *Int J Pharm*. 2024;666:124843. doi:10.1016/j.ijpharm.2024.124843
102. Rasmussen S, Petersen KK, Aboo C, et al. Intra-articular injection of gold micro-particles with hyaluronic acid for painful knee osteoarthritis. *BMC Musculoskelet Disord*. 2024;25:211. doi:10.1186/s12891-024-07321-4
103. Study details | NCT07202390 | intraarticular gold microparticles for knee osteoarthritis | clinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT07202390. Accessed January 17, 2026.
104. Li W, Liu Y, Wei M, et al. Functionalized biomimetic nanoparticles targeting the IL-10/IL-10Rα/glycolytic axis in synovial macrophages alleviate cartilage degeneration in osteoarthritis. *Adv Sci*. 2025;12(27):2504768. doi:10.1002/advs.202504768
105. Wang L, Wang K, Zheng H. Macrophage membrane-coated nanocarriers in myocardial infarction: a paradigm shift in targeted cardiac therapy. *Int J Nanomed*. 2025;20:13499–13525. doi:10.2147/IJN.S546817
106. Sultana P, Kim YK, Cho SJ, Asadujjaman M, Jee JP. Advances in cell membrane-coated nanoparticles: multifunctional platforms for targeted drug delivery, precision phototherapy, and enhanced immunotherapy. *Biomater Sci*. 2025;13(19):5232–5259. doi:10.1039/d5bm00660k
107. Hou Y, Wu R, Zhou Y, et al. Macrophage membrane-coated nanoparticles in inflammatory diseases: from bioinspired design to translational potential. *J Nanobiotechnology*. 2025;24:37. doi:10.1186/s12951-025-03921-x
108. Xu H, Liu S, Wei Y, et al. Curcumin-loaded biomimetic nanosponges for osteoarthritis alleviation by synergistically suppressing inflammation and ferroptosis. *Chem Eng J*. 2024;491:152132. doi:10.1016/j.cej.2024.152132
109. Teo KYW, Sevencan C, Cheow YA, Zhang S, Leong DT, Toh WS. Macrophage polarization as a facile strategy to enhance efficacy of macrophage membrane-coated nanoparticles in osteoarthritis. *Small Sci*. 2022;2(4):2100116. doi:10.1002/smsc.202100116
110. Ma Y, Yang H, Zong X, et al. Artificial M2 macrophages for disease-modifying osteoarthritis therapeutics. *Biomaterials*. 2021;274:120865. doi:10.1016/j.biomaterials.2021.120865
111. Liao HJ, Chang CH, Huang CYF, Chen HT. Potential of using infrapatellar–fat–pad–derived mesenchymal stem cells for therapy in degenerative arthritis: chondrogenesis, exosomes, and transcription regulation. *Biomolecules*. 2022;12(3):386. doi:10.3390/biom12030386
112. W J, X W, G Y, et al. Engineering exosomes derived from TNF-α preconditioned IPFP-MSCs enhance both yield and therapeutic efficacy for osteoarthritis. *Heart Lung*. 2024;69:208–216. doi:10.1016/j.hrtlng.2024.10.015

113. Wu J, Wu J, Xiang W, et al. Engineering exosomes derived from TNF-α preconditioned IPFP-MSCs enhance both yield and therapeutic efficacy for osteoarthritis. *J Nanobiotechnology*. 2024;22:555. doi:10.1186/s12951-024-02795-9
114. Yi X, Leng P, Wang S, Liu L, Xie B. Functional nanomaterials for the treatment of osteoarthritis. *Int J Nanomed*. 2024;19:6731–6756. doi:10.2147/IJN.S465243
115. Huang H, Lou Z, Zheng S, et al. Intra-articular drug delivery systems for osteoarthritis therapy: shifting from sustained release to enhancing penetration into cartilage. *Drug Deliv*. 2022;29(1):767–791. doi:10.1080/10717544.2022.2048130
116. Li J, Zhang H, Han Y, Hu Y, Geng Z, Su J. Targeted and responsive biomaterials in osteoarthritis. *Theranostics*. 2023;13(3):931–954. doi:10.7150/thno.78639
117. Wang Q, Feng K, Wan G, et al. A ROS-responsive hydrogel encapsulated with matrix metalloproteinase-13 siRNA nanocarriers to attenuate osteoarthritis progression. *J Nanobiotechnol*. 2025;23(1):18. doi:10.1186/s12951-024-03046-7
118. Tao J, Deng H, Li Z, Cao L, Rao Y, Yin Z. Macrophage-targeted, ROS-removing and H2S-releasing nanomicelle encapsulated in hydrogel microspheres for the treatment of osteoarthritis. *Chem Eng J*. 2025;507:160345. doi:10.1016/j.cej.2025.160345
119. Wang Z, Xiong H, Zhai Z, et al. Reactive oxygen species-scavenging nanoparticles coated with chondroitin sulfate protect cartilage against osteoarthritis in vivo. *Nano Res*. 2022;16(2):2786–2797. doi:10.1007/s12274-022-4934-x
120. Xiang H, Zhang C, Xiong Y, et al. MMP13-responsive hydrogel microspheres for osteoarthritis treatment by precise delivery of celecoxib. *Mater Des*. 2024;241:112966. doi:10.1016/j.matdes.2024.112966
121. Yang F, Zhang Y, Niu X, Han G. Design strategies of biomaterial-based intra-articular drug delivery system for osteoarthritis therapy. *J Control Release*. 2026;389:114496. doi:10.1016/j.jconrel.2025.114496
122. Kang LJ, Yoon J, Rho JG, et al. Self-assembled hyaluronic acid nanoparticles for osteoarthritis treatment. *Biomaterials*. 2021;275:120967. doi:10.1016/j.biomaterials.2021.120967
123. Deng C, Chen Y, Zhao X, et al. Apoptotic neutrophil membrane-camouflaged liposomes for dually targeting synovial macrophages and fibroblasts to attenuate osteoarthritis. *ACS Appl Mater Interfaces*. 2023;15(33):39064–39080. doi:10.1021/acsami.3c05861
124. Nah Y, Sobha S, Saravanakumar G, Kang BY, Yoon JB, Kim WJ. Nitric oxide-scavenging hyaluronic acid nanoparticles for osteoarthritis treatment. *Biomater Sci*. 2024;12(6):1477–1489. doi:10.1039/D3BM01918G
125. Warmink K, Siebelt M, Low PS, et al. Folate receptor expression by human monocyte–derived macrophage subtypes and effects of corticosteroids. *Cartilage*. 2022;13(1):19476035221081469. doi:10.1177/19476035221081469
126. Petrosova KA, Lunev AS, Rakhimov MG, et al. Preclinical evaluation of 68Ga-labeled folic acid conjugates for visualization of inflammatory foci. *Nucl Med Biol*. 2025;142-143:108991. doi:10.1016/j.nucmedbio.2024.108991
127. Józefowski S, Biedroń R, Śróttek M, Chadzińska M, Marcinkiewicz J. The class A scavenger receptor SR-A/CD204 and the class B scavenger receptor CD36 regulate immune functions of macrophages differently. *Innate Immun*. 2014;20(8):826–847. doi:10.1177/1753425913510960
128. Fani M, Wang X, Nicolas G, et al. Development of new folate-based PET radiotracers: preclinical evaluation of ^{68}Ga-DOTA-folate conjugates. *Eur J Nucl Med Mol Imaging*. 2011;38(1):108–119. doi:10.1007/s00259-010-1597-8
129. Zou X, Xu H, Qian W. Macrophage polarization in the osteoarthritis pathogenesis and treatment. *Orthop Surg*. 2024;17(1):22–35. doi:10.1111/os.14302
130. Lu YJ, Wheeler LW, Chu H, et al. Targeting folate receptor beta on monocytes/macrophages renders rapid inflammation resolution independent of root causes. *Cell Rep Med*. 2021;2(10):100422. doi:10.1016/j.xcrm.2021.100422
131. Wu M, Chen Z, Song B, Wang X, Liang W. Current status and future perspectives of research on intra-articular drug delivery systems for osteoarthritis therapy. *Acta Biomater*. 2025;203:59–77. doi:10.1016/j.actbio.2025.07.057
132. Tsuneyoshi Y, Tanaka M, Nagai T, et al. Functional folate receptor beta-expressing macrophages in osteoarthritis synovium and their M1/M2 expression profiles. *Scand J Rheumatol*. 2012;41(2):132–140. doi:10.3109/03009742.2011.605391
133. Daghestani HN, Huang Z, Kraus VB. Characterization of folate receptor beta expression on cells of bone origin. *Osteoarthritis Cartilage*. 2015;23:A131. doi:10.1016/j.joca.2015.02.858
134. Hsueh MF, Zhang X, Wellman SS, Bolognesi MP, Kraus VB. Synergistic roles of macrophages and neutrophils in osteoarthritis progression. *Arthritis Rheumatol*. 2021;73(1):89–99. doi:10.1002/art.41486
135. Ozkan H, Di Francesco M, Willcockson H, et al. Sustained inhibition of CC-chemokine receptor-2 via intraarticular deposition of polymeric microplates in post-traumatic osteoarthritis. *Drug Delivery Transl Res*. 2022;13(2):689–701. doi:10.1007/s13346-022-01235-1
136. Alivernini S, MacDonald L, Elmesmari A, et al. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. *Nat Med*. 2020;26(8):1295–1306. doi:10.1038/s41591-020-0939-8
137. Li X, Shen Z, Zhang S, Chen Y, Lu X, Hu X. Nanomaterials in the diagnosis and therapy of osteoarthritis: current research advances and future clinical prospects. *Front Bioeng Biotechnol*. 2025;13:1664799. doi:10.3389/fbioe.2025.1664799
138. Kong H, He Q, Han J, Zhang XA. Nanomaterial-based drug delivery systems targeting functional cells for osteoarthritis treatment: mechanisms, challenges and future prospects. *Int J Nanomed*. 2025;20:5291–5320. doi:10.2147/IJN.S518935
139. Qin Z, Li X, Wang P, et al. Ultrasmall prussian blue nanozyme attenuates osteoarthritis by scavenging reactive oxygen species and regulating macrophage phenotype. *Nano Lett*. 2024;24(37):11697–11705. doi:10.1021/acs.nanolett.4c03314
140. Cho C, Oh H, Lee JS, et al. Prussian blue nanozymes coated with Pluronic attenuate inflammatory osteoarthritis by blocking c-Jun N-terminal kinase phosphorylation. *Biomaterials*. 2023;297:122131. doi:10.1016/j.biomaterials.2023.122131
141. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA*. 2021;325(6):568–578. doi:10.1001/jama.2020.22171
142. Delgado-Sanchez I, Fernandez-Pozo N, Duran I. Standardizing single-cell approaches to osteoarthritis: toward a comprehensive cellular atlas. *Osteoarthritis Cartilage*. 2025;34(3):380–383. doi:10.1016/j.joca.2025.08.016
143. Duan JL, Zhang XL, Zhao LQ, et al. Macrophage membrane-camouflaged nanoparticles for targeted drug delivery. *Chin Chem Lett*. 2025:111610. doi:10.1016/j.cclet.2025.111610
144. Liu Y, Xu Z, Qiao M, Cai H, Zhu Z. Metal-based nano-delivery platform for treating bone disease and regeneration. *Front Chem*. 2022;10:955993. doi:10.3389/fchem.2022.955993
145. Yuan S, He DW, Zhou XJ, Jiao HT, Gao Y, Li C. Greening bone healing: the emerging role of plant-derived exosome-like nanoparticles in osteoporosis and osteoarthritis therapy. *Int J Nanomed*. 2026;21:569552. doi:10.2147/IJN.S569552

146. Li L, Xu Z, Gao F, Xu J. Current status and future prospects of nanocarrier-mediated miRNA delivery for osteoarthritis therapy. *Front Med*. 2026;12:1728944. doi:10.3389/fmed.2025.1728944
147. Klyucherev TO, Peshkova MA, Yurkanova MD, et al. Advances in regenerative therapies for inflammatory arthritis: exploring the potential of mesenchymal stem cells and extracellular vesicles. *Int J Mol Sci*. 2025;26(12):5766. doi:10.3390/ijms26125766
148. Morici L, Jordan O, Allémann E, Rodríguez-Nogales C. Recent advances in nanocrystals for arthritis drug delivery. *Expert Opin Drug Deliv*. 2025;22(7):1031–1042. doi:10.1080/17425247.2025.2505758
149. Meng T, He D, Han Z, et al. Nanomaterial-based repurposing of macrophage metabolism and its applications. *Nanomicro Lett*. 2024;16:246. doi:10.1007/s40820-024-01455-9
150. Li JM, Li X, Chan LWC, et al. Lipotoxicity-polarised macrophage-derived exosomes regulate mitochondrial fitness through Miro1-mediated mitophagy inhibition and contribute to type 2 diabetes development in mice. *Diabetologia*. 2023;66(12):2368–2386. doi:10.1007/s00125-023-05992-7
151. Wu Y, Wan S, Yang S, et al. Macrophage cell membrane-based nanoparticles: a new promising biomimetic platform for targeted delivery and treatment. *J Nanobiotechnology*. 2022;20:542. doi:10.1186/s12951-022-01746-6
152. Chen X, Liu Y, Wen Y, et al. A photothermal-triggered nitric oxide nanogenerator combined with siRNA for precise therapy of osteoarthritis by suppressing macrophage inflammation. *Nanoscale*. 2019;11(14):6693–6709. doi:10.1039/C8NR10013F
153. Song Y, Huang Y, Zhou F, Ding J, Zhou W. Macrophage-targeted nanomedicine for chronic diseases immunotherapy. *Chin Chem Lett*. 2022;33(2):597–612. doi:10.1016/j.cclet.2021.08.090
154. Vizoso FJ, Eiro N, Costa L, et al. Mesenchymal stem cells in homeostasis and systemic diseases: hypothesis, evidences, and therapeutic opportunities. *Int J Mol Sci*. 2019;20(15):3738. doi:10.3390/ijms20153738
155. Kim IK, Kim SH, Choi SM, Youn BS, Kim HS. Extracellular vesicles as drug delivery vehicles for rheumatoid arthritis. *Curr Stem Cell Res Ther*. 2016;11(4):329–342. doi:10.2174/1574888x11666151203223251
156. Liao J, Gu Q, Liu Z, et al. Edge advances in nanodrug therapies for osteoarthritis treatment. *Front Pharmacol*. 2024;15:1402825. doi:10.3389/fphar.2024.1402825
157. Henrotin Y, Sanchez C, Bay-Jensen AC, Mobasheri A. Osteoarthritis biomarkers derived from cartilage extracellular matrix: current status and future perspectives. *Ann Phys Rehabil Med*. 2016;59(3):145–148. doi:10.1016/j.rehab.2016.03.004
158. Hua S, de Matos MBC, Metselaar JM, Storm G. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. *Front Pharmacol*. 2018;9:790. doi:10.3389/fphar.2018.00790
159. Li S, Xiong Y, Zhu H, Ma T, Sun X, Xiao J. Microenvironment-responsive nanosystems for osteoarthritis therapy. *Eng Regen*. 2024;5(1):92–110. doi:10.1016/j.engreg.2023.12.002

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