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REVIEW

Nanozyme-Mediated Joint Homeostasis Restoration: Emerging Strategies for Arthritis Therapy

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Abstract: Severe oxidative stress and inflammatory cascades drive the pathological progression of rheumatoid arthritis (RA), osteoarthritis (OA), and gouty arthritis (GA). Conventional pharmacotherapies and natural enzyme interventions are frequently constrained by factors such as systemic toxicity and poor intra-articular bioavailability. In contrast, nanozymes have garnered researcher's attention by virtue of their superior physicochemical stability, cost-effectiveness, and tunable reactive oxygen species (ROS) scavenging capacities. They exhibit unique advantages in the field of arthritis therapy, featuring single-atom catalysts, efficient multi-enzyme catalytic activities, and significantly prolonged synovial retention half-lives. To bridge critical gaps in the existing review literature, this review focuses on nanozyme-mediated therapeutics for the three most common types of arthritis, systematically summarizing the latest advancements in this domain. First, the review elucidates the pathomechanisms of RA, OA, and GA to establish a therapeutic rationale. Subsequently, the article traces the evolution of nanozyme engineering designs for specific disease applications. Finally, critical barriers to clinical translation are analyzed, including long-term biosafety, pharmacokinetics, and industrial standardization. This review elucidates the therapeutic functions of nanozymes across distinct pathological microenvironments, establishing a clinical demand-driven classification framework. By mapping material-inherent catalytic properties directly to specific clinical requisites, this article provides actionable insights to bridge the translational gap between fundamental biomaterials research and clinical practice.

Keywords: nanozymes, arthritis, oxidative stress, reactive oxygen species, immunomodulation

Introduction

Rapid advancements in nanomedicine have introduced novel strategies to overcome traditional biomedical limitations.[1] Nanozymes—nanomaterials with intrinsic enzyme-like catalytic activity—have emerged as a significant therapeutic focus, integrating nanoscale physicochemical properties with high catalytic efficiency.[2,3] Compared to natural enzymes, nanozymes circumvent conformational instability, high production costs, and complex functionalization, offering superior structural stability, industrial scalability, and tunable catalytic activity.[4] Crucially, by mimicking antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), and glutathione peroxidase (GPx), nanozymes effectively remodel pathological microenvironments via reactive oxygen/nitrogen species (ROS/RNS)[5] scavenging and immune homeostasis regulation.[6,7] This microenvironmental modulation directly addresses the oxidative stress and inflammatory cascades central to the pathogenesis of rheumatoid arthritis (RA), osteoarthritis (OA), and gouty arthritis (GA).[8–10] Consequently, the introduction of nanozyme technology into arthritis therapeutics offers new possibilities for advancing therapeutic approaches.[11,12]

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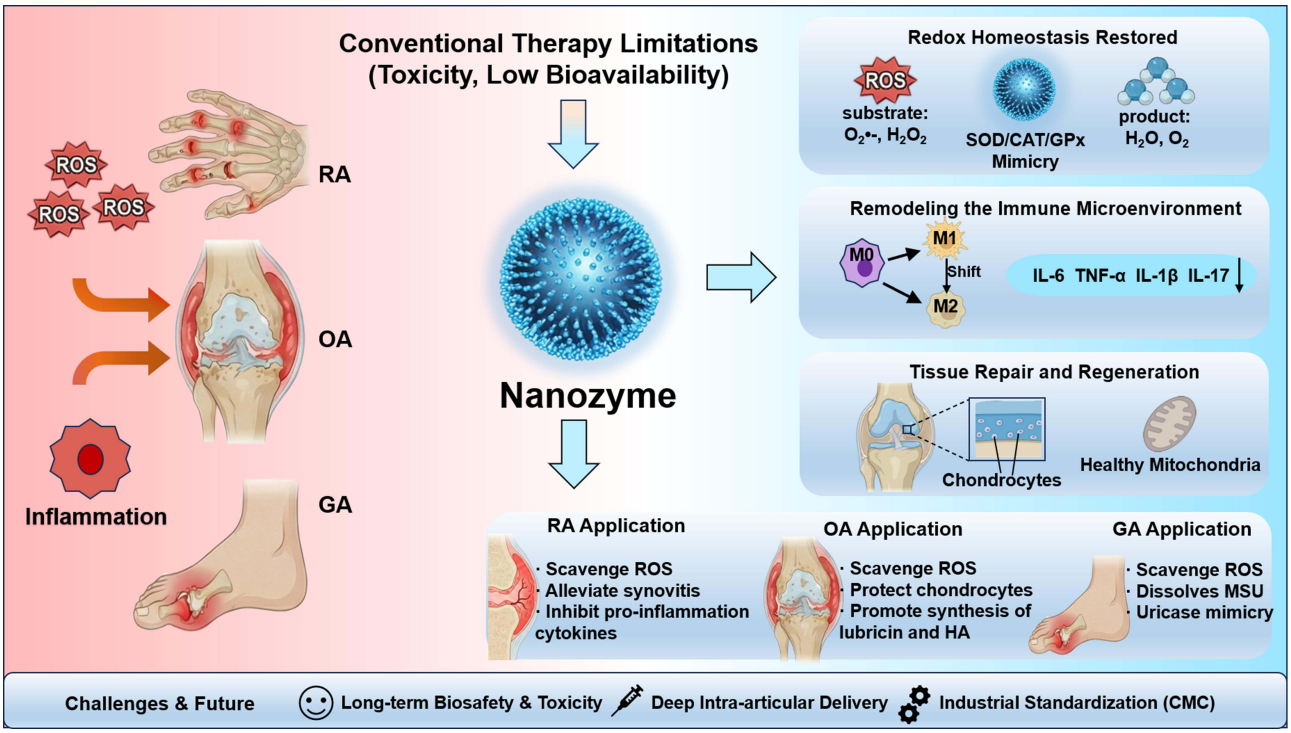
Exacerbated by aging populations and shifting lifestyles, the rising global incidence of RA, OA, and GA constitutes a major public health burden.[13,14] Current clinical management primarily relies on pharmacotherapies, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs), and targeted biologics such as tumor necrosis factor-α (TNF-α) inhibitors.[15,16] These interventions effectively manage symptoms: NSAIDs and GCs rapidly suppress acute inflammation,[17] whereas biologics significantly slow disease progression.[18] However, current clinical treatments still face significant limitations. Long-term systemic NSAID and GC use induces adverse effects, including gastrointestinal ulcers, cardiovascular risks, and osteoporosis.[17] Widespread application of targeted biologics is restricted by high costs, immunogenicity, and secondary infection risks.[18] Furthermore, these therapies primarily provide symptomatic relief or single-pathway blockade rather than reversing the damaged joint microenvironment. Similarly, the complexity of the intra-articular environment is one of the major factors contributing to the poor bioavailability and suboptimal targeting efficacy of conventional small-molecule drugs in clinical applications.[19,20] To address these challenges, nanozymes offer a compelling alternative, providing multi-target microenvironment remodeling, sustained antioxidant catalysis, and programmable targeted delivery.

However, a profound translational gap separates laboratory nanocatalysis from clinical joint disease modification, whereas existing reviews predominantly adopt a chemistry-oriented classification based on material synthesis methodologies, focusing on aspects such as catalytic mechanisms, activity regulation, and fields of development and application.[4,6] In contrast, this review advocates for a return to a function-first paradigm in nanozyme development. We systematically summarize and discuss the various strategies for alleviating the pathological microenvironment of arthritis over the past five years (Scheme 1). By correlating atomic-level active site engineering of nanozymes with the distinct pathophysiological features of RA, OA and GA, we propose a framework with a unique perspective from translational medicine. Following this, We detail nanozyme design strategies, focusing on therapeutic applications and mechanisms for joint microenvironment remodeling. Finally, we assess translational obstacles, with a particular focus on long-term biosafety and in vivo metabolism, and outline future research directions. We hope this review serves as a robust theoretical



Scheme 1 Nanozyme-base strategies for arthritis treatment.

framework, inspiring innovative approaches for the design of safer, smarter, and more efficient nanomedicines for arthritis management.

Pathological Characteristics and Conventional Therapy

Core Pathological Mechanisms

Joint inflammation results from multifactorial disruptions to tissue homeostasis, driving progressive degeneration. Despite differing etiologies, RA, OA, and GA share five pathological hallmarks: oxidative stress, cytokine dysregulation, immune cell imbalance, synovial hyperplasia, and cartilage degeneration (Figure 1).

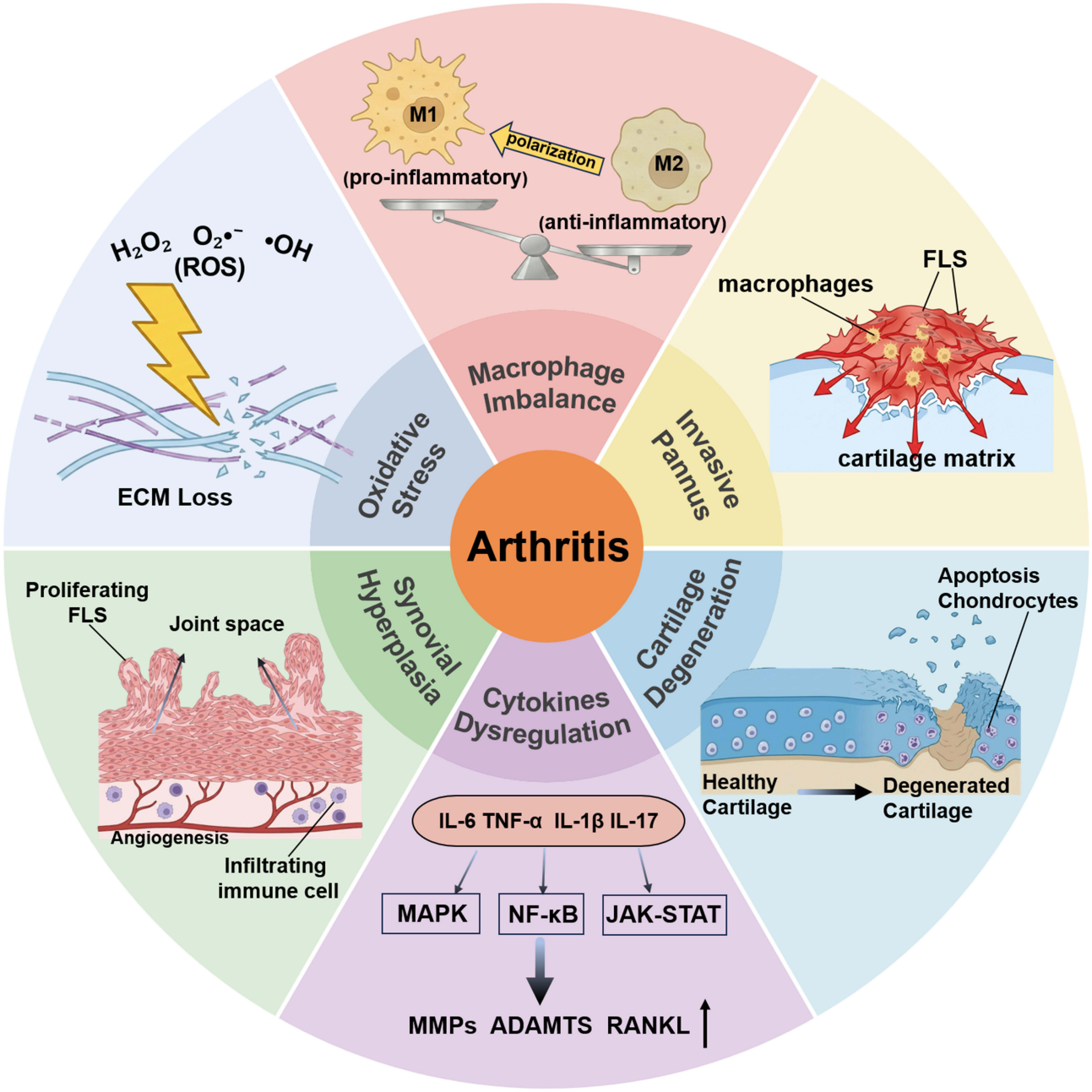


Figure 1 Common pathological features of arthritis.

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Oxidative Stress and ROS Accumulation

While physiological ROS are essential signaling molecules for cellular homeostasis, the articular microenvironment disrupts this balance via a vicious hypoxia-inflammation cycle. Hypoxia-induced ROS generation and hypoxia-inducible factor 1 subunit α (HIF-1α) upregulation overwhelm endogenous antioxidants (eg, SOD, CAT), precipitating profound oxidative stress.[21] Consequently, excessive ROS inflict direct macromolecular oxidative damage and act as second messengers to activate the nuclear factor-κB (NF-κB) pathway, driving a pro-inflammatory/pro-oxidative feedback loop.[22] Despite varying origins, ROS-mediated pathological consequences converge across arthritis subtypes. In RA, immune cell respiratory bursts and sustained ROS release by fibroblast-like synoviocytes (FLS) synergistically amplify TNF-α expression.[23,24] Mechanical overload and aging induce mitochondrial ROS accumulation, activating the HIF-α/Matrix Metalloproteinase(MMP) 13 axis to drive chondrocyte catabolism and joint degradation.[25,26] Furthermore, in GA, ROS generated during immune cell phagocytosis of urate crystals serve as the essential trigger for NLRP3 inflammasome activation, fundamentally driving crystal-induced acute joint inflammation.[27,28]

Uncontrolled Release of Pro-Inflammatory Cytokines

In arthritis, dysregulated pro-inflammatory cytokines orchestrate molecular networks driving progressive joint destruction.[29] Elevated synovial expression of TNF-α, IL-1β, IL-6, and IL-17 synergistically promotes immune infiltration, angiogenesis, and extensive matrix degradation, fundamentally destabilizing the articular environment.[30,31] Distinct cytokine profiles dictate disease-specific manifestations: RA features a TNF-α and IL-6-dominated "cytokine storm" directly driving pannus formation;[32] OA presents as DAMP-induced low-grade chronic inflammation, suppressing cartilage synthesis and sensitizing pain pathways; whereas GA relies on an IL-1β-centric cascade to trigger acute inflammation.[33,34] Despite these divergent modalities, all arthritic forms ultimately perpetuate irreversible joint destruction by establishing self-sustaining inflammatory microenvironments that chronically elevate pro-inflammatory signaling and abrogate tissue repair mechanisms.[35]

Macrophage Polarization Imbalance

Macrophage phenotypic plasticity fundamentally regulates joint inflammation, and the polarization disequilibrium between M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes underpins arthritis chronicity and tissue repair failure.[36] Driven by the sustained activation of pathways such as Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Toll-like receptor 4 (TLR4)/Myeloid differentiation factor (MyD88)/NF-κB, M1 macrophages release copious pro-inflammatory mediators and propagate bone destruction,[37] whereas the reparative functions of the M2 phenotype are concurrently suppressed.[38] Targeting these signaling cascades is thus necessary to reverse pathogenic macrophage polarization. While M1-driven inflammation consistently fuels joint pathology, specific manifestations vary: in RA, M1 macrophages primarily drive persistent bone erosion;[39] in OA, M1-secreted factors induce osteophyte formation;[40] and in GA, "frustrated phagocytosis" of urate crystals forms chronic granulomas (tophi).[41] Therefore, targeted macrophage repolarization represents a pivotal strategy for chronic arthritis management.

Synovial Hyperplasia and Pannus Formation

Synovial hyperplasia and invasive pannus formation link articular inflammation to structural destruction. Chronic inflammation confers tumor-like anti-apoptotic and invasive phenotypes upon FLS. Alongside hypoxia-induced neovascularization, these transformed cells form a protease-rich "synovium-vascular" axis that actively degrades cartilage and bone.[42,43] While driven by this common axis, disease-specific manifestations vary: RA is characterized by highly invasive pannus; OA presents with synovitis and fibrosis secondary to cartilage loss; and chronic GA features granulomatous synovitis surrounding tophi, causing distinct "punched-out" bone defects.[44,45]

Chondrocyte Apoptosis and ECM Degradation

Chondrocyte apoptosis and extracellular matrix (ECM) degradation constitute the terminal pathway of irreversible joint dysfunction.[26] Driven by the pro-inflammatory microenvironment, significantly upregulated proteases, specifically MMP-1/13 and ADAMTS-4/5, catalyze the irreversible hydrolysis of type II collagen and aggrecan, making their

inhibition critical for preserving articular structural integrity.[29,46] While distinct pathologies trigger chondrocyte death via unique mechanisms: mitochondrial-mediated senescence and apoptosis in OA;[47,48] Fas/FasL death receptor activation in RA;[49,50] and MSU crystal-induced, NLRP3/IL-1β-driven MMP release in GA,[51] they universally converge on these destructive ECM-degrading programs. Targeting this shared convergence point consequently offers profound broad-spectrum therapeutic potential. Because pro-inflammatory cytokine-driven chondrocyte death and ECM degradation remain the universal drivers of structural damage, specifically inhibiting terminal enzymes like MMP-13 and ADAMTS-5 can effectively arrest progressive joint destruction across arthritic conditions.

Developments and Challenges of Current Therapies

Current clinical paradigms for RA, OA, and GA primarily rely on the stepwise administration of GCs, NSAIDs, DMARDs, and biological agents.[52] However, the necessity for high-dose systemic administration to overcome low intra-articular bioavailability inevitably precipitates systemic toxicity while failing to effectively neutralize the localized reactive oxygen species sustaining chronic inflammation. Prolonged glucocorticoid exposure induces metabolic disturbances and accelerates cartilage degradation, whereas NSAIDs carry concurrent gastrointestinal and cardiovascular risks alongside disruptions to chondrocyte metabolism.[53,54] The therapeutic efficacy of conventional DMARDs is frequently constrained by hepatotoxicity and gastrointestinal intolerance.[55] Despite biologics improving RA outcomes, nearly 40% of patients develop secondary resistance due to anti-drug antibodies, and the clinical utility of convenient oral JAK inhibitors (eg, tofacitinib, baricitinib, upadacitinib) remains restricted by elevated risks of thrombosis and malignancy.[56,57] Disease-specific challenges further undermine therapeutic efficacy beyond systemic toxicity: standard regimens for refractory RA struggle to address central sensitization and synovial fibrosis;[58] OA treatment is relegated to palliative management or joint replacement absent approved disease-modifying agents;[59] and gout management is complicated by poor patient adherence to urate-lowering therapies alongside allergic reactions triggered by highly immunogenic drugs.[60,61] Collectively, existing standard therapies prove inadequate in dismantling the central hypoxia-ROS-inflammation axis within the articular microenvironment, rendering them incapable of arresting the vicious cycle of joint destruction.

Multidimensional explorations at the research frontier attempt to circumvent these clinical bottlenecks, although such emerging strategies present distinct translational barriers. At the molecular intervention level, small-molecule antioxidants and natural polyphenols, including resveratrol, curcumin and quercetin, function by scavenging free radicals or activating the Nrf2 pathway. Specifically, resveratrol upregulates SOD to suppress NF-κB activation, while quercetin mitigates chondrocyte endoplasmic reticulum stress via the SIRT1/AMPK axis.[62] However, poor aqueous solubility, weak chemical stability, and marginal intra-articular bioavailability severely compromise their in vivo therapeutic efficacy relative to in vitro performance.[63] Exogenous natural antioxidant enzymes (SOD, CAT, GPx), theoretically represent highly efficient and specific interventions, yet they remain susceptible to rapid lymphatic clearance and proteolytic inactivation driven by the mildly acidic microenvironment and elevated MMP concentrations within the inflamed joint cavity.[64] While specific biologics and small-molecule inhibitors achieve precise blockade of inflammatory signaling but frequently elicit resistance through compensatory pathway activation, concurrently increasing the risk of systemic immunosuppression during long-term administration.[65] Advanced genetic tools like CRISPR-Cas9 gene editing offers precise transcriptional silencing of pro-inflammatory genes. Nevertheless, off-target effects and Cas9 protein immunogenicity remain primary obstacles to clinical translation.[66,67] Within biologics and regenerative medicine, mesenchymal stem cells (MSCs) and their exosomes exhibit unique advantages in inducing M2 macrophage polarization and promoting cartilage regeneration, yet localized oxidative stress and acidic conditions drastically restrict the survival and functional durability of transplanted cells.[68] Similarly, recently highlighted 15-hydroxyprostaglandin dehydrogenase (15-PGDH) inhibitors, which promote endogenous cartilage regeneration by protecting PGE2, demonstrate encouraging outcomes in animal models. But their human safety profiles, articular targeting efficiency, and impact on systemic immunity require robust clinical validation.[69] Beyond joint disorders, nanomaterial platforms have been actively investigated in related musculoskeletal conditions, such as lubricious nanofibers for tendon adhesion prevention and gradient scaffolds for tendon-bone interface regeneration.[70,71] Finally, advanced tissue engineering and delivery technologies, including 3D-printed bioscaffolds, long-acting microparticle release systems, and in situ cross-linked

hydrogels, prolong intra-articular drug retention and modulate release kinetics, yet these approaches necessitate deeper evaluation regarding their adaptability to individual anatomical variations, the long-term biocompatibility of degradation products, and scalable manufacturing.[72]

However, despite continuous advances in therapeutic modalities, the multi-layered barrier system arising from the inherent physiological and biomechanical architecture of the intra-articular microenvironment fundamentally limits the efficacy of these interventions.[73] Locally administered small molecules and biologics exhibit transient intra-articular half-lives, driven by rapid lymphatic drainage and clearance through the highly vascularized synovium.[74] In weight-bearing joints such as the knee, physiological biomechanical loading accelerates this clearance via a hydrodynamic pumping mechanism. Alterations in the non-Newtonian viscosity of synovial fluid exacerbate this therapeutic loss, while the high viscosity of healthy fluid naturally limits drug diffusion, arthritic inflammation triggers the enzymatic degradation of hyaluronic acid.[75,76] This depolymerization converts the fluid into a low-viscosity state, dismantling its physical buffering capacity and accelerating convective wash-out. Systemic administration offers little recourse, as the restrictive blood-joint barrier necessitates supra-therapeutic dosing that frequently induces systemic toxicity. Retaining a therapeutic agent within the joint space does not guarantee efficacy, given that the dense, avascular, and negatively charged extracellular matrix of articular cartilage presents significant steric and electrostatic resistance to deep chondrocyte penetration.[77] This structural barrier is compounded by a hostile inflammatory microenvironment characterized by severe hypoxia, localized acidosis, and robust reactive oxygen species generation, which rapidly denature unshielded molecules. These limitations are further modified by anatomical scale. Small extremity joints present strict volumetric constraints that trigger acute intra-articular pressure spikes upon injection, whereas the lower temperature of the first metatarsophalangeal joint accelerates monosodium urate crystallization, forming physical obstructions to drug delivery.[73]

Consequently, overcoming these multifaceted barriers necessitates a shift from conventional unshielded monotherapies toward advanced, microenvironment-responsive delivery systems. Multifunctional nanozymes represent a pivotal innovation. By integrating multi-enzyme catalytic homeostasis restoration with targeted cargo delivery, they effectively circumvent physiological barriers to achieve sustained, disease-modifying outcomes.

Engineering Design of Nanozymes in Arthritis Therapy

Nanozymes: From Inorganic Nanoparticles to Single-Atom Catalysts

The development of nanozymes originated from the seminal discovery of intrinsic peroxidase-like activity in ferromagnetic nanoparticles.[78] These materials were later formally defined by Wei and Wang as nanomaterials that strictly adhere to Michaelis-Menten kinetics.[79] However, the clinical application of first-generation inorganic nanozymes, such as CeO_2, was often limited by catalytic heterogeneity and low atomic utilization (Figure 2a).[80] To overcome these constraints, researchers began focusing on structural diversification to enhance both biocompatibility and multifunctionality. Second-generation nanozymes employ diverse structural designs to meet the complex requirements of the articular environment.[81] For instance, carbon-based nanomaterials like carbon dots utilize π-conjugated electronic systems to enable integrated photothermal theranostics (Figure 2b).[82] Simultaneously, Metal-Organic Frameworks (MOFzymes) provide high porosity to optimize substrate diffusion within viscous synovial fluid (Figure 2c).[52] These MOFs function as "molecular cages" that facilitate synergistic drug delivery for arthritis management. Single-Atom Nanozymes (SAzymes) represent the current peak of catalytic efficiency in this field. This superior performance arises from the dispersion of catalytic metal centers to the atomic limit, which achieves nearly 100% atom economy.[83] Furthermore, SAzymes are engineered with precise M-Nx coordination environments, such as Fe-N_4 centers, to mimic the structures of natural metalloenzymes (Figure 2d–f).[84–86] By replicating the geometric and electronic features of heme, these materials offer highly specific catalytic activity. Recent advancements in dual-atom engineering have further optimized the catalytic potential of these platforms. For example, Cu-Mn synergy is used to modulate the d-band center of active sites, which significantly lowers the activation energy for ROS scavenging.[87] This evolutionary trajectory reflects a fundamental paradigm shift from discovering catalytic activity to customizing it for specific needs. Recognized by IUPAC as a top emerging technology, these rationally designed atomic sites now provide a robust material foundation for precision arthritis therapy.

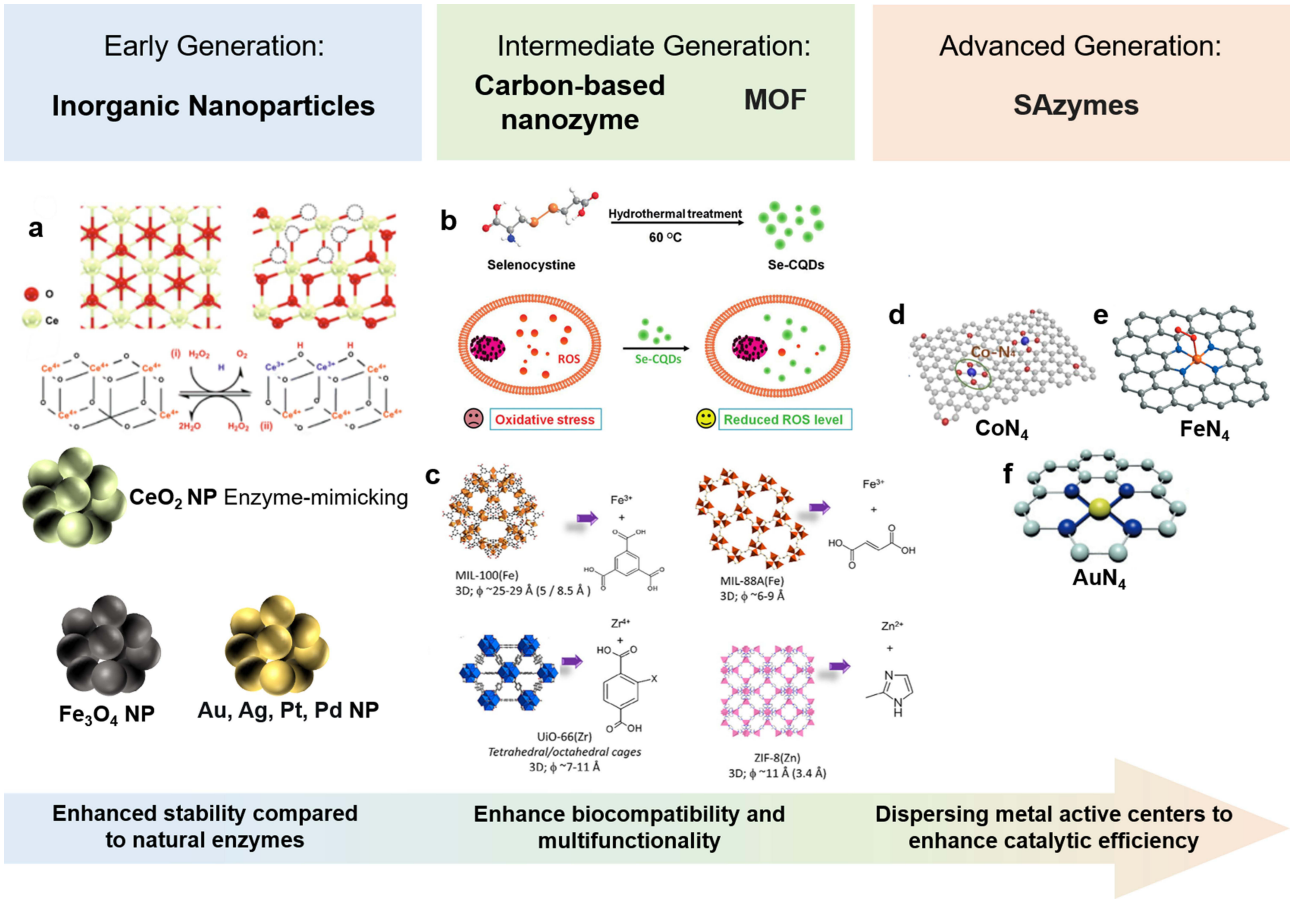

Figure 2 (**a**) Top view (left) and side view (right) of the CeO_2 structural model. Atomistic-level catalytic mechanisms for the CAT-mimicking reactions of nanoceria. Adapted with permission.[80] Copyright 2019, Royal Society of Chemistry (**b**) Synthesis of Se-CQDs with green fluorescence by the hydrothermal treatment of selenocystine. Adapted with permission.[82] Copyright 2017, John Wiley and Sons (**c**) Typical biosafe MOFs include MIL-100(Fe)-NH2, MIL-101(Fe), ZIF-8(Zn) and UiO-66(Zr). Fe, Zr and Zn polyhedra are in Orange or red, blue, and pink, respectively. Adapted with permission.[52] Copyright 2025, John Wiley and Sons (**d**) CoN_4. Adapted with permission.[84] Copyright 2018, Elsevier; (**e**) Structure of different SACs: FeN4.[85] Adapted with permission. Copyright 2017, Wiley-VCH; (**f**) AuN4. Adapted with permission.[86] Copyright 2019, Wiley-VCH.

Enzyme-Mimetic Catalytic Mechanisms

Nanozyme therapeutic efficacy arises from recapitulating endogenous antioxidant defenses through precise material engineering.(Figure 3).[5] SOD-mimics utilize reversible metal redox cycles, such as Ce^{3+}/Ce^{4+} valence switching in ceria nanoparticles, to catalyze the dismutation of superoxide anion radical ($O_2^{\bullet-}$).[88] At the atomic scale, electronic modulation determines this efficiency. Specifically, Fe-Cu dual-atom configurations enhance activity by upshifting the d-band center, thereby optimizing $O_2^{\bullet-}$ adsorption kinetics. Consequently, these electronic adjustments lower protonation energy barriers and facilitate the efficient removal of reactive species.[89]

SOD activity constitutes the primary antioxidant defense, yet exclusive reliance on it triggers hydrogen peroxide (H_2O_2) accumulation. Excess H_2O_2 risks conversion into cytotoxic •OH via the Fenton reaction.[90] Incorporating CAT-like activity is therefore essential for a comprehensive therapeutic strategy.[6] Nanozymes like MnO_2 or Prussian Blue decompose H_2O_2 while evolving O_2 to alleviate synovial hypoxia. The POD-like activity exerts a synergistic effect by utilizing endogenous reducing substrates present in the microenvironment, such as glutathione (GSH), ascorbic acid, and even thiol groups of certain proteins, to catalyze the decomposition of H_2O_2 into water and oxidized substrates. This in situ reoxygenation downregulates the HIF-1α pathway and suppresses metabolic inflammation.[91] Se-based GPx mimics further mitigate oxidative damage by detoxifying organic peroxides. Surface selenium centers undergo reversible redox cycling between selenol (-SeH) and selenenic acid (-SeOH). Using endogenous GSH as an electron donor, these

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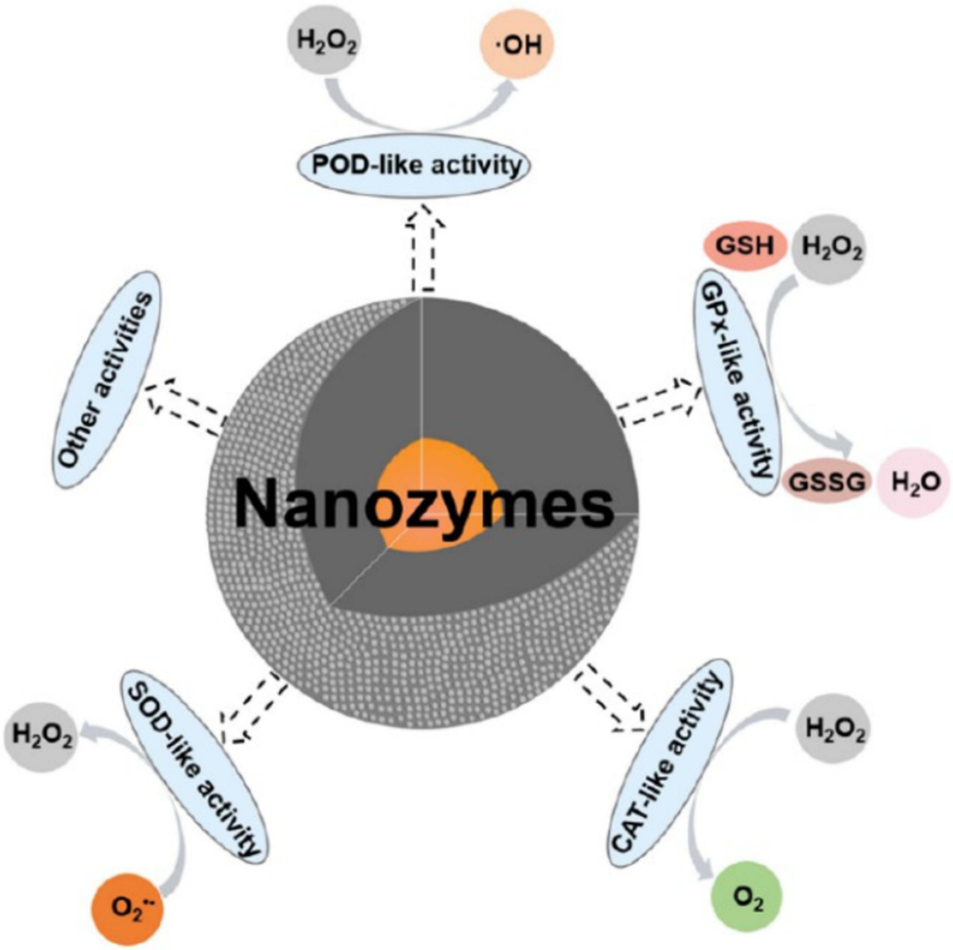

Figure 3 Schematic representation of the main enzyme-like activities of nanozymes. Reproduced with permission.[5] Copyright 2025, American Chemical Society.

mimics reduce toxic peroxides to benign alcohols. Consequently, this catalytic process arrests lipid peroxidation and prevents chondrocyte ferroptosis.[92]

Advanced "cascade defense systems" address multifaceted oxidative stress through two strategic approaches. First, heterostructures or all-in-one atomic frameworks integrate multi-enzyme activities to ensure the instantaneous conversion of intermediates into H_2O and O_2. Second, metabolic cascades, such as NIR-responsive SAzymes, modulate mitochondrial respiratory chain complexes. This dual strategy scavenges existing ROS while effectively inhibiting de novo generation.[93]

Design for Joint Environments

Engineering Strategies for Articular Nanozyme Delivery

The superior physicochemical stability of nanozymes provides the fundamental basis for their therapeutic efficacy within the intra-articular cavity. Unlike natural enzymes that are susceptible to proteolytic degradation, nanozymes maintain catalytic integrity even amidst local biochemical stressors.[94] To maximize intra-articular retention, researchers have exploited size-exclusion effects and bioadhesive interactions to achieve passive targeting. For instance, hydrogel encapsulation serves as a robust depot system that enables sustained release of nanozymes while concurrently imposing physical barriers against lymphatic drainage.[95] Similarly, micron-sized aggregation or microsphere encapsulation leverages the size-dependent clearance threshold of synovial tissue. Particles exceeding approximately 500 nm exhibit significantly prolonged retention compared to smaller counterparts, owing to reduced lymphatic uptake.[96]

Beyond passive strategies, active recognition and targeting emerge when nanozyme surfaces are functionalized with ligands designed to specifically bind overexpressed receptors or characteristic components within the inflamed joint. Hyaluronic acid modification confers CD44-targeting capabilities to nanozymes, facilitating preferential accumulation in activated synovial fibroblasts and macrophages.[97,98] Folic acid functionalization exploits the elevated expression of folate receptor β (FRβ) on activated macrophages in RA and OA.[99,100] RGD peptide modifications directly target the upregulated integrin αvβ3 on angiogenic endothelium and synovial fibroblasts.[101] Meanwhile, advances in cell membrane coating technology endow nanozymes with both active targeting capability and innate immune evasion as well as proteolytic protection. PEGylation and biomimetic coatings (eg, macrophage or platelet membranes) construct a protective barrier around the catalytic core, thereby maximizing circulation persistence and intra-articular retention.[35,102–104]

The dense synovial lining and the avascular, negatively charged cartilaginous matrix present formidable biological barriers to deep nanozyme penetration. To address these challenges, researchers have explored size-reduction strategies (eg, sub-50 nm nanozymes) to facilitate traversal through synovial fenestrations,[105,106] while employing cationic surface modifications to enhance electrostatic binding to the negatively charged cartilage extracellular matrix.[107] In addition, conjugating cartilage-targeting peptides like WYRGRL to the nanozyme surface endows these therapeutics with a specific affinity for structural cartilage components.[108] This targeted approach enables enhanced accumulation within avascular cartilaginous zones that remain difficult to access via conventional drug delivery modalities.

Intelligent Stimulus-Responsive Design

The acidic nature of the arthritic microenvironment is characterized by synovial pH values of approximately 6.5 and intralysosomal pH below 5.2.[109] Utilizing this acidic gradient, pH-sensitive nanozymes can be constructed to achieve site-specific drug release and catalytic activity activation at the lesion site, enabling precise remodeling of the articular microenvironment. A representative example is the Ce-MOF@$CaCO_3$ (Ce-Ca) platform, which orchestrates a pH-responsive cascade: the $CaCO_3$ shell dissolves at pH 5.5, simultaneously neutralizing local acidity and releasing Ca^{2+} ions to promote subchondral bone repair; subsequently, the exposed Ce-MOF core exerts SOD/CAT-mimetic activities, eliminates extracellular ATP to inhibit M1 macrophage pyroptosis, and generates adenosine to drive M2 repolarization.[110] Complementing this design, the Se/LDH@PEG-M system exploits joint acidosis to trigger degradation and release Mg^{2+}, Se, and Mito-TEMPO, thereby restoring mitochondrial respiratory activity and correcting glycolytic reprogramming through GPx-mimetic catalysis.[111] Taking multi-stage response kinetics a step further, the PCM@MnO_2 system employs pH-dependent dissociation of its polydopamine (PDA) shell at pH 6.5 to enable targeted cellular binding, whereas subsequent lysosomal core degradation at pH 5.2 triggers both methotrexate burst release and MnO_2-catalyzed in situ oxygenation, collectively reversing the pro-inflammatory macrophage phenotype (Figure 4).[109]

Beyond pH responsiveness, pathologically elevated ROS levels serve as equally sensitive switches for on-demand drug release.[112] The thioacetal-linked CP-GA-PKP nanosystem undergoes ROS-specific cleavage, shedding its polyethylene glycol (PEG) shield to expose an adhesive PDA core for enhanced intra-articular retention. Concurrently, the released gallic acid synergizes with the exposed Ce-MOF-Pt dual catalytic centers to execute SOD- and CAT-like activities, effectively scavenging superoxide radicals and hydrogen peroxide.[113] In acute GA, macrophage membrane-coated HMPB-Pt@MM nanozymes achieve homologous targeting to inflamed joints, scavenging ROS/•OH and mimicking urate oxidase to convert insoluble uric acid into allantoin, thereby eliminating crystals and alleviating hypoxia.[114]

Hypoxia represents a critical pathological hallmark of both RA and OA.[115] Synovial hyperplasia, coupled with inflammatory cell infiltration, drives a precipitous decline in intra-articular oxygen tension (to as low as 2–4%), which in turn stabilizes HIF-1α and upregulates VEGF, thereby promoting pannus formation and cartilage erosion.[116] The Au@CeO_2 Nano heterojunction leverages the Localized Surface Plasmon Resonance (LSPR) effect of its gold core under NIR irradiation to generate local hyperthermia, accelerating CAT-mimetic O_2 evolution from its ceria shell and suppressing HIF-1α/VEGF.[117] Similarly, Macrophage microvesicle-modified amorphous MnO_2 (MMV-MnO_2@DSP) targets deep inflammatory cartilage and synoviocytes, converting H_2O_2 to dissolved O_2 to reverse glycolytic reprogramming and modulate subchondral bone.[109]

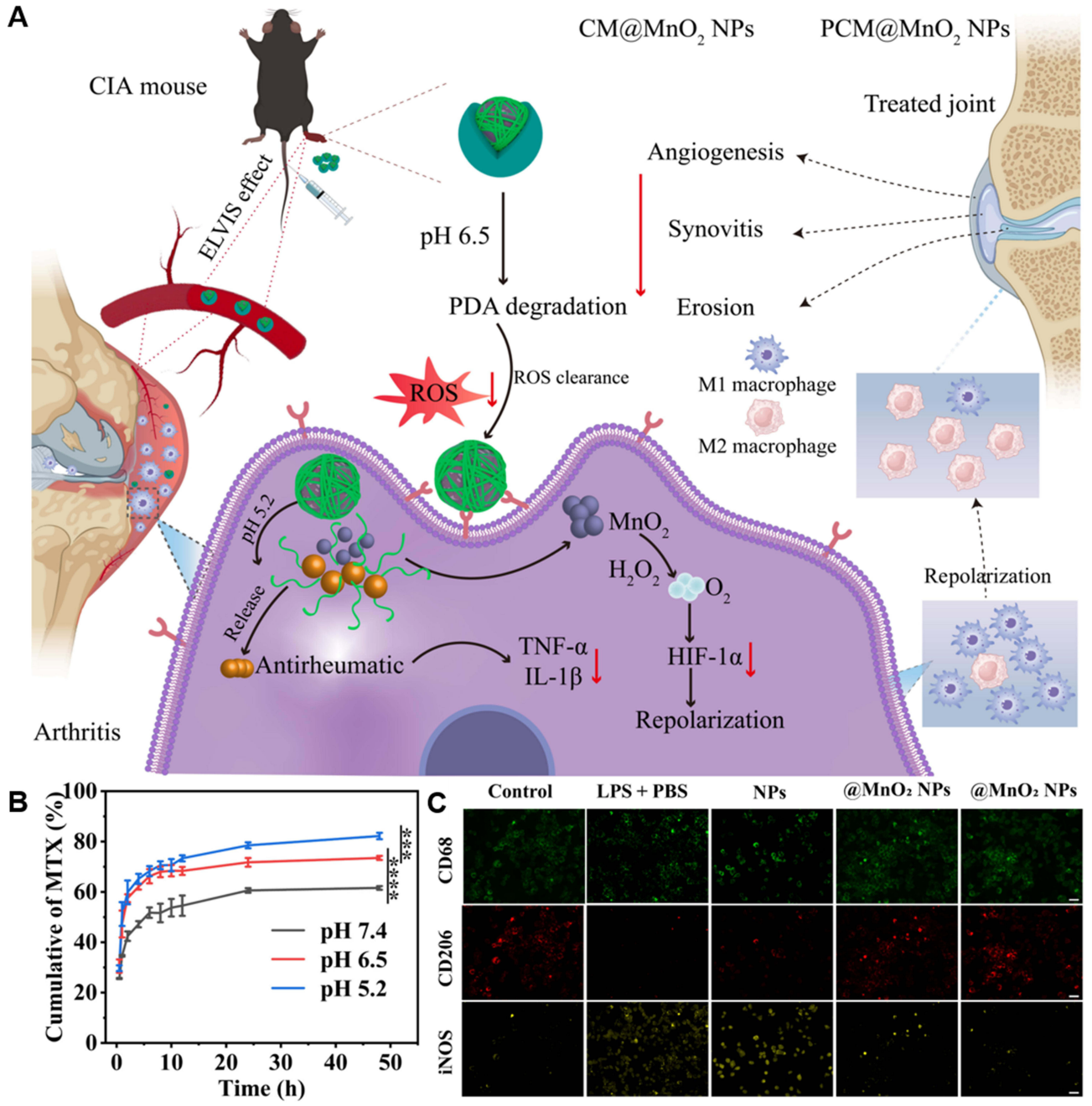

Figure 4 Schematic Diagram of the pH-Responsive PCM@MnO_2 System. (**A**): Application of PCM@MnO_2 NPs in RA treatment and related mechanisms. Under RA acidic conditions, PDA was degraded from PCM@MnO_2 NPs to scavenge reactive oxygen species (ROS). CM@MnO_2 NPs were internalized by macrophages through interaction between CS and CD44. Under intracellular conditions of low pH, CM@MnO_2 NPs disintegrated to release MnO_2 and MTX, which could produce O_2 and inhibit inflammatory factors, respectively. PCM@MnO_2 NPs effectively treated RA by improving the oxidative stress microenvironment. (**B**): In vitro release of MTX from PCM@MnO_2 NPs at different pHs. (**C**): PCM@MnO_2 NPs induced M1-to-M2 polarization (iNOS (yellow)↓; CD206 (red)↑).[109] Copyright 2025, Springer Nature.

Beyond pH and ROS, overexpressed MMPs serve as specific enzymatic switches: TGMS-modified lipid nanomicelles enable instantaneous drug burst release exclusively during high-MMP disease flares while remaining stable during remission to prevent systemic leakage.[118,119] Consequently, Intelligent, stimuli-responsive designs further enhance the precision of nanozyme therapy, which is particularly advantageous for reducing systemic side effects and improving in vivo biosafety.

Nonetheless, current research on smart responsive nanozymes for arthritis remains constrained by significant limitations. Contemporary designs indiscriminately apply "ROS scavenging" strategy. Physiological ROS, serving as

essential second messengers for intracellular signaling and redox homeostasis, cannot be exhaustively depleted without risking microenvironmental disruption. Nevertheless, systematic quantification of in vivo catalytic thresholds remains largely absent. Furthermore, the M1/M2 macrophage repolarization observed in cell cultures or rodent models may prove overly reductionist when extrapolated to the highly heterogeneous and temporally dynamic human arthritic joint. These models inadequately address the multidimensionality of the synovial immune microenvironment, the continuum of macrophage activation states, and the complex pathological feedback circuits that sustain chronic inflammation.

Applications of Nanozymes in Arthritis Therapy

Rheumatoid Arthritis (RA)

The RA microenvironment is characterized by a self-sustaining cascade of persistent inflammatory infiltration, hypoxia, and excessive reactive oxygen species (ROS) accumulation that drives bone and cartilage destruction.[120] Traditional anti-rheumatic therapies have proven effective in clinical practice, yet they rarely disrupt this vicious feedback loop. Nanozymes, with their superior stability and responsive multi-enzyme mimetic activities, enables targeted microenvironmental remodeling and precision joint theranostics. In the context of RA, they primarily serve as immunomodulators and hypoxia relievers, counteracting autoimmune-driven synovial hyperplasia and T-cell dysregulation through ROS scavenging, HIF-1α suppression, and NETs degradation. This section systematically reviews recent advances in nanozyme-mediated RA therapy across four dimensions: redox homeostasis restoration, immunomodulation, tissue repair, and multifunctional synergistic treatment (Table 1).

Remodeling the Oxidative Microenvironment

Targeting the core pathological hallmarks of rheumatoid arthritis, the design strategy for nanozymes has evolved into a synergistic system that integrates both ROS scavenging and in situ oxygen generation. By mimicking the catalytic cascade reactions of natural antioxidant enzymes, these nanozymes achieve systematic depletion of excessive ROS, thereby effectively suppressing the cascade activation of key inflammatory signaling pathways—such as NF-κB, MAPK, NLRP3/caspase-1, cGAS-STING, and JAK/STAT—and ultimately reshaping the homeostasis of the articular immune microenvironment. Specifically, Kim et al developed MFC-MSNs utilizing manganese ferrite to decompose H_2O_2 via the Fenton reaction within H_2O_2-rich environments, generating O_2 to alleviate tissue hypoxia while incorporating ceria to scavenge hydroxyl radicals (•OH), thereby achieving synergistic ROS elimination and oxygenation (Figure 5).[121] This strategy was subsequently extended to hydrogel scaffolds like MnCoO and MXene to effectively alleviate hypoxia.[125,144] These materials significantly enhance the survival and differentiation of bone marrow mesenchymal stem cells (BMSCs). Furthermore, integrating Mn_3O_4 with polydopamine (PDA) or thermosensitive liposomes enables a synergy of photothermal therapy (PTT), chemotherapy, and ROS scavenging.[143] Consequently, these multi-modal platforms provide comprehensive microenvironmental regulation.[22,145]

Cerium-based nanozymes serve as classical antioxidants, exhibiting dual SOD- and CAT-like activities via the Ce^{3+}/Ce^{4+} redox couple. For example, Zhou et al[98] integrated cerium oxide with ROS-responsive micelles to facilitate gated drug release and inhibit inflammatory signaling, specifically by suppressing IκB degradation and p65 nuclear translocation, thereby blocking the NF-κB pathway. To accommodate the specific intestinal environment, Wang et al[139] modulated the valence state of Au/CeOX via gold deposition to design a nanozyme with an "OXD-SOD-POD" cascade that selectively suppresses CAT activity, thereby scavenging ROS while avoiding oxygen generation to preserve anaerobic intestinal conditions.

Beyond cerium, noble metal nanozymes offer superior broad-spectrum antioxidant performance. For instance, PtTe heterostructures (HPT)[97] and CeO_2-Pt Janus nanoplatforms[129] utilize high-density Pt active sites for enhanced ROS scavenging. Furthermore, integrating multiple noble metal, such as the PtPdCo trimetallic nanozyme developed by Zhang et al, can simultaneously achieve SOD, CAT, POD, and AAO activities, thus significantly broadening the catalytic spectrum.[142]

To maximize this catalytic efficiency, recent studies have transitioned toward single-atom catalysis. Incorporating atomically dispersed active sites, such as in copper single-atom-loaded graphene quantum dots or Pd single-atom-

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Table 1 Nanozyme Therapy for Rheumatoid Arthritis (RA)

Nanozyme	Combination	Material	Formulation	RA Model	Enzyme-Like	Key Findings
MFC-MSNs[121]	MTX	$MnFe_2O_4$; CeO_2; MSN;	Intra-articular injection	AIA rat	SOD, CAT	Synergistic O_2 generation and ROS scavenging reversed macrophage polarization (M1 to M2), reduced Fenton reaction cytotoxicity and enhanced MTX efficacy.
Rh/SPX-HSA[122]	SPX	Rh; HSA	Intravenous injection	CIA mouse	POD, CAT	The synergistic interplay between nanozyme-driven oxygen generation and the sonosensitizer SPX elevated SDT, which effectively suppressed inflammation and bone erosion via HSA-mediated active targeting.
HIF-CaP-rHDL[123]	HIF-1α siRNA	CaP; apoE3-rHDL	Intravenous injection	CIA mouse	-	Targeted delivery of HIF-1α siRNA and CaP inhibited multiple inflammatory pathways (HIF-1α, NF-κB, MAPK), relieving bone erosion and osteoclastogenesis.
HA@M@PB@SIN NPs[35]	SIN	PB, Macrophage/RBC hybrid membrane, HA	Intravenous injection	AIA rat	CAT, SOD, POD	Biomimetic nanozyme targeted inflammatory cells, scavenged ROS, and delivered SIN to synergistically suppress joint inflammation and bone destruction.
VQ-CuS@MnO2/MET[124]	MET	CuS, MnO_2, VQ,	Intravenous injection	CIA/AIA rat	SOD, CAT	Nanozyme-modified MSCs maintained viability under oxidative stress and enhanced chondrogenesis and anti-inflammatory effects in RA.
uPB-Exo[105]	-	uPB, Neutrophil Exosomes	Intravenous injection	CIA mouse	SOD, CAT	Exosome-coated PBNPs targeted synovitis, scavenged ROS, and regulated Th17/Treg balance to attenuate joint injury and inflammation.
ε-PLE@MnCoO/Gel[125]	BMSCs	MnCoO, ε-polylysine, HA hydrogel	Injectable hydrogel	AIA rabbit	CAT	Hydrogel acted as an H_2O_2-driven oxygenerator, scavenging ROS and supplying O_2 to protect encapsulated BMSCs and improve osseointegration.
NBOP NPs[126]	Notopterol	BR, oPDA, PEG	Intravenous injection	CIA rat	CAT, NO scavenging	Dual-responsive nanoparticles scavenged ROS/NO and released notopterol to inhibit JAK-STAT pathway, regulating inflammatory microenvironment.
MMV-MnO2@DSP[127]	DSP	Hollow-MnO_2, Macrophage microvesicles	Intravenous injection	CIA rat	SOD, CAT	Messenger nanozyme accumulated in macrophages, restored O_2^-/H_2O_2 metabolism, and blocked TNF-α/IL-1β feedback loops to treat RA.
Ce-MSCNVs[128]	-	CeO_2 nanoparticles, MSC nanovesicles	Intra-articular injection	CIA mouse	SOD, CAT	Hybrid system scavenged ROS, induced M2 polarization, and promoted Treg generation, restoring immune tolerance and treating RA.
HPT[97]	-	Pt, Te, HA	Intravenous injection	CIA mouse	SOD, CAT	HA-modified PtTe nanorods scavenged ROS and enhanced PTT efficacy, effectively alleviating inflammation in RA.
Janus-CPS-MI[129]	MCL, ICG	CeO_2-Pt, PMO	Intravenous injection	CIA mouse	CAT, SOD	Janus nanoplatform enabled simultaneous diagnosis and therapy, enhancing ROS scavenging and delivering MCL to synergistically treat RA.
Fh-PVP[106]	-	Fh, PVP	Intravenous injection	AIA mouse	CAT	Fh nanoparticles acted as catalase mimics, converting H_2O_2 into O_2 to simultaneously alleviate oxidative stress and hypoxia in RA.
HA@RH-CeO_X[98]	RH	CeO_X, HA	Intra-articular injection	CIA rat	SOD, CAT	ROS-responsive micelles delivered Rhein and ceria nanozymes to reprogram M1 macrophages via redox homeostasis regulation, treating RA.
MPM@Lipo[22]	MTX	PDA, MnO_2, Liposome	Intravenous injection	AIA rat	POD, CAT	Multifunctional liposomes combined chemotherapy, PTT, and oxygen enrichment to clear inflammatory cells and improve hypoxic microenvironment.
MΦ-CNPs[104]	-	PLGA Copolymer, Macrophage membrane	-	In vitro study	Cytokine scavenging	Macrophage-mimicking nanoparticles effectively scavenged multiple proinflammatory cytokines in serum and synovial fluid from RA patients.

MFO/PDA Coating[130]	-	$MnFe_2O_4$, PDA	Implant coating	AIA rat	SOD, CAT	Nanozyme coating reprogrammed macrophage mitochondrial metabolism by scavenging ROS, promoting immunomodulatory osseointegration in RA.
Pd@MSe-TPP[131]	-	Pd, MSe, TPP	Intravenous injection	CIA mouse	CAT, GPx	Dual-driven Janus nanomotors autonomously regulated mitochondrial O_2 and ROS imbalance, effectively treating RA.
FeCu@CDs[132]	-	Fe, Cu, Carbon Dots	-	Human samples	POD	Bimetallic doped carbon dots with enhanced peroxidase activity enabled dual-mode (colorimetric/fluorometric) detection of the rheumatoid arthritis drug D-penicillamine in tablets and urine.
DAGQD@Cu@KGN-SO3-/DA-HA[133]	KGN	Cu, Graphene Quantum Dots, Dopamine/ Sulfonated HA	Injectable hydrogel	CIA rat/OIA rabbit	SOD, CAT, •OH scavenging	Injectable bioadhesive hydrogel containing Cu single-atom nanozymes and KGN scavenged ROS, reduced friction, and promoted cartilage repair in rheumatoid arthritis rats.
Ce@CS/DNase nanoge[134] I	DNase I	Ce, Chitosan	Injectable nanogel	CIA mouse	SOD, CAT, •OH scavenging	Bioinspired nanogels with intrinsic SOD/CAT activity and conjugated DNase I targeted inflammatory cascades, degrading NETs and scavenging ROS to suppress rheumatoid arthritis progression.
n(CDs)[135]	No	Fe-doped Carbon Dots, Phosphate-group gel	Intravenous injection	CIA rat	SOD, CAT, •OH scavenging	Bone-targeting carbon dot nanogels (n(CDs)) scavenged ROS and activated the Nrf2 signaling pathway to restore redox balance and alleviate inflammation in CIA rats.
MM@PCNSs/IGU[103]	IGU	Porous Carbon Nanospheres, Macrophage Membrane	Intravenous injection	CIA mouse	SOD, CAT	Macrophage membrane-coated carbon nanozymes loaded with IGU achieved inflammation targeting, NIR-triggered drug release, and ROS scavenging for synergistic rheumatoid arthritis therapy.
Rapa-FMn@PMS[136]	Rapa	MnO_2, Mesoporous Silica, PDA, Folic Acid	Intra-articular injection	AIA mouse	SOD, CAT, •OH scavenging	Folic acid-modified, rapamycin-loaded MnO_2 nanomotors targeted M1 macrophages, scavenged H_2O_2 to drive motion, and repolarized macrophages to treat rheumatoid arthritis.
Co-COF@MOF[137]	-	Co-COF, MOF, c-MWCNTs	-	Rat serum	POD	Core-shell Co-COF@MOF nanozymes with dual-catalytic activity enabled ultrasensitive electrochemical detection of anti-mutated citrullinated vimentin (Anti-MCV) for early rheumatoid arthritis diagnosis.
DN-Mito[138]	Mitochondria	PB nanozyme, Polymer, DNA hydrogel	Injectable hydrogel	CIA mouse	SOD, CAT, POD	Polymer-modified DNA hydrogels codelivering living mitochondria and nanozymes scavenged ROS and restored mitochondrial function to effectively alleviate inflammation in rheumatoid arthritis.
Au/CeOX(0.93) @SA[139]	-	Au, CeO_2, Sodium Alginate	Oral administration	CIA rat	OXD, SOD, POD	Oral administration of valence-engineered Au/CeOx nanozymes scavenged intestinal ROS via self-cascade catalysis, modulating the microbiota-gut-joint axis to alleviate systemic inflammation in RA.
Metal-SCNPs[140]	No	Polypeptide, Metal clusters (Fe, Mn, Co, Cu, Zn)	Intravenous injection	AIA mouse	SOD, POD	Polypeptide single-chain nanoparticles coordinated with metal ions mimicked natural enzyme folding and activity, providing a scalable route to artificial enzymes (potential for future therapy).
PSC@IGU[141]	IGU	SOD, CAT (Natural), PCL	Transdermal drug delivery	CIA mouse	SOD, CAT	PSC@IGU microneedles scavenged ROS, generated O_2 via cascade catalysis, and delivered IGU to synergistically modulate macrophages and suppress inflammation/ bone damage in RA mice.

(*Continued*)

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Table 1 (Continued).

Nanozyme	Combination	Material	Formulation	RA Model	Enzyme-Like	Key Findings
HPPCQ[142]	CQ	Pt, Pd, Co, HA	IV injection	CIA mouse	SOD, CAT, POD	HA-modified trimetallic nanozymes exhibited triple enzyme activities to scavenge ROS, regulating macrophage polarization and autophagy levels to effectively treat rheumatoid arthritis.
MTX-Mn3O4 @PDA[143]	MTX	Mn_3O_4, PDA	Intra-articular injection	CIA mouse	SOD, CAT	NIR-responsive nanoplatform combined photothermal therapy and ROS scavenging to kill inflammatory cells, inhibit fibroblasts, and release MTX for synergistic RA treatment.
MXenzyme/ Gel@V2C[144]	SMT	V_2CTx MXene, HA/CS hydrogel	Injectable hydrogel	AIA rabbit	SOD, CAT, GPx	MXenzyme hydrogel scavenged ROS/RNS and supplied O_2, creating a favorable microenvironment for encapsulated BMSCs to survive and promote osteochondral regeneration in RA.

Abbreviations: AIA, Adjuvant-induced arthritis; CIA, Collagen-induced arthritis; CAT, Catalase; SOD, Superoxide dismutase; POD, Peroxidase; OXD, Oxidase; GPx, Glutathione peroxidase; MTX, Methotrexate; SPX, Sparfloxacin; SIN, Sinomenine hydrochloride; MET, Metformin; MSN, Mesoporous silica; ROS, Reactive oxygen species; Rh, Rhodium; HAS, Human Serum Albumin; SDT, Sonodynamic therapy; PB, Prussian Blue; HA, Hyaluronic acid; CaP, Calcium phosphate; apoE3-rHDL, Apolipoprotein E3- reconstituted high density lipoprotein; VQ, MSC-targeting peptide; uPB, Ultra-small Prussian Blue; MnCoO, Manganese cobalt oxide; BR, Bilirubin; oPDA, o-phenylenediamine; PEG, Polyethylene glycol; DSP, Dexamethasone Sodium Phosphate; Pt, Platinum, Te, Tellurium; PTT, Photothermal therapy; MCL, Micheliolide; ICG, Indocyanine green; PMO, Periodic Mesoporous Organosilica; PVP, Polyvinylpyrrolidone; Fh, Ferrihydrite; RH, Rhein; PDA, Polydopamine; PLGA, Polylactic acid - glycolic acid; Pd, Palladium; MSe, Mesoporous Selenium; TPP, Triphenylphosphine; KGN, Kartogenin; OIA, Ovalbumin induced arthritis; IGU, Iguratimod; Rapa, Rapamycin; c-MWCNTs, Carboxylated multi-walled carbon nanotubes; COF, Covalent Organic Framework; MOF, Metal-Organic Framework; PCL, Polycaprolactone; CQ, Chloroquine; CS, Chondroitin sulfate; SMT, S-methylisothiourea.

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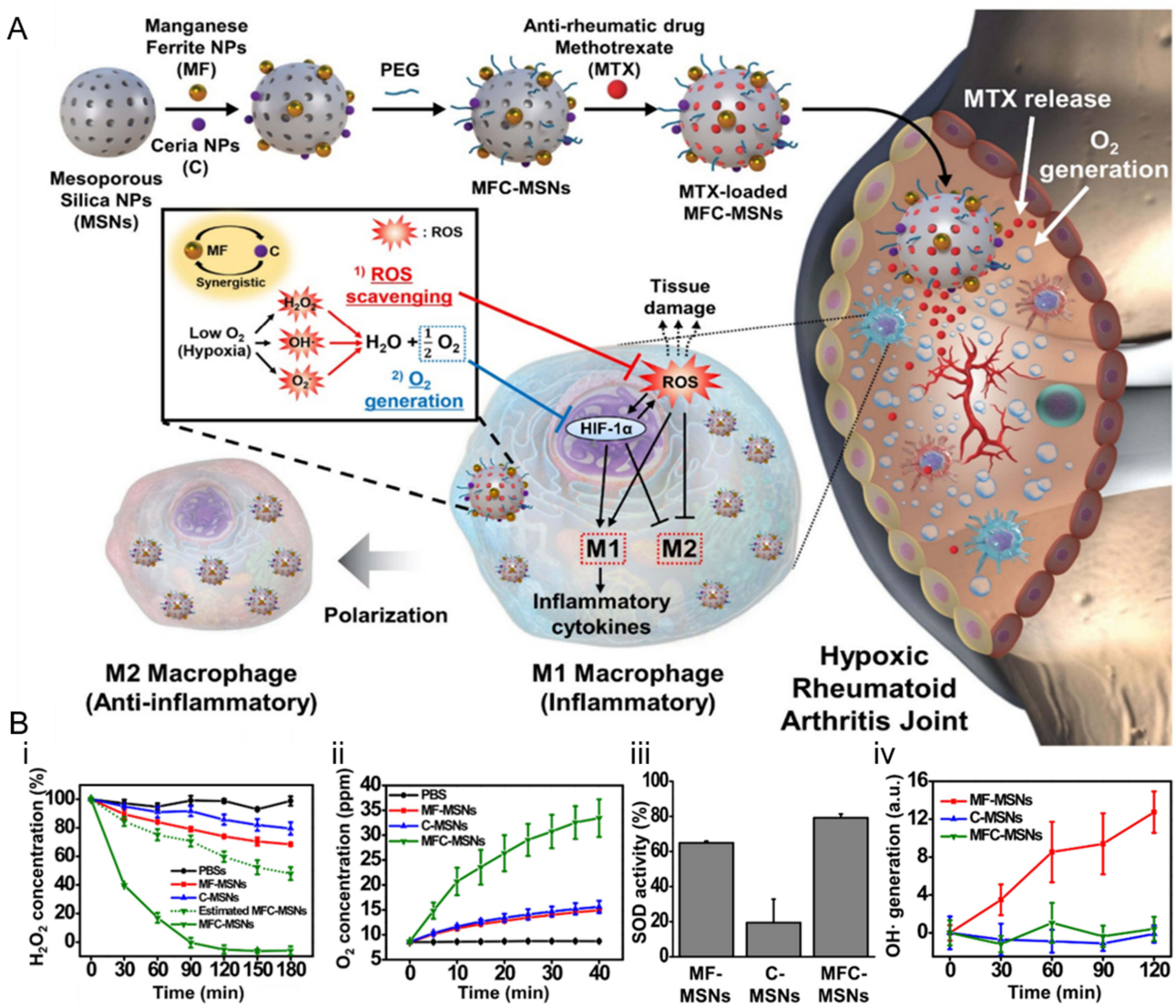

Figure 5 (**A**): Therapeutic mechanisms of MFC-MSNs in RA treatment. MFC-MSNs synergistically scavenge ROS and generate O_2; Promotes macrophage repolarization; Capable of loading methotrexate. (**B**): Synergistic ROS scavenging and O_2 generation by MFC-MSNs compared with MFMSNs and C-MSNs. (i) H_2O_2 degradation curves in the presence of MF-MSNs, C-MSNs, and MFC-MSNs at pH 7.4 (n = 3). Estimated H_2O_2 degradation of MFC-MSNs was obtained by adding the degraded H_2O_2 concentrations of MF-MSNs and C-MSNs. (ii) O_2 generation curves in 1 M H_2O_2 solution in the presence of NPs under physiological conditions (n = 3). (iii) SOD activity of MF-MSNs, C-MSNs, and MFC-MSNs (n = 3). (iv) Time-dependent hydroxyl radical generation of MF-MSNs, C-MSNs, and MFC-MSNs in the presence of H_2O_2 (n = 3). Reproduced with permission.[121] Copyright 2026, ACS Nano.

modified selenium nanomotors, significantly lowers reaction energy barriers and accelerates electron transfer.[131,133] Consequently, single-atom engineering provides a robust strategy for drastically improving nanozyme performance.

Similarly, iron-based materials like ferrihydrite nanoparticles have been optimized for targeted ROS conversion.[106] While traditional iron nanozymes rely on basic nanocatalytic mechanisms, recent advancements focus on elevating biosafety alongside efficiency. By mimicking natural protein folding, Yang et al designed a biomimetic peptide single-chain artificial enzyme. Ultimately, this structural innovation achieves high SOD/POD-like activity while maintaining extremely low iron loading (<5%).[140]

Remodeling the Immune Microenvironment

Restoring synovial immune homeostasis, primarily by repolarizing macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, is a central therapeutic objective in RA management. Nanozymes facilitate this phenotypic reprogramming through ROS scavenging, metabolic modulation, and synergistic pharmacological

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interactions. By mitigating oxidative stress and hypoxia, nanozymes effectively inhibit pro-inflammatory signaling pathways—including NF-κB, MAPK, and JAK-STAT—thereby fostering M2 polarization.[103,121,126,127,142]

To advance this immune reprogramming, researchers have developed multifunctional nanoplatforms that target both innate and adaptive immunity. For example, the ceria-mesenchymal stem cell nanovesicle hybrid system (Ce-MSCNVs) engineered by Koo et al promoted M2 polarization and induced regulatory T cell (Treg) differentiation to restore immune equilibrium.[128] Similarly, ROS-responsive micelles developed by Zhou et al[98] synergistically suppressed TLR4 signaling by co-delivering rhein and cerium ions, which concurrently inhibited p65 phosphorylation and IκBα degradation to block NF-κB activation, downregulate IL-1β and TNF-α transcription, and subsequently suppress JAK2/STAT1 phosphorylation. To ensure long-term efficacy, Zhang et al[142] incorporated chloroquine into their system to inhibit ferroptosis in M2 macrophages during transition, effectively preserving the stability of the anti-inflammatory phenotype.

Beyond phenotypic modulation, directly scavenging or sequestering pathogenic factors within the microenvironment serves as a crucial complementary strategy. For instance, Jin et al[134] designed a biomimetic nanogel integrating ceria nanozymes with DNase I to simultaneously scavenge ROS and degrade Neutrophil Extracellular Traps (NETs). Moreover, macrophage membrane-coated nanoparticles have proven highly effective as broad-spectrum "decoys" to neutralize pro-inflammatory cytokines and mediators.[103,104] To further guide these interventions, Niu et al[137] developed electrochemical sensors for the high-sensitivity detection of autoantibodies (eg, Anti-MCV), enabling crucial early-stage therapeutic timing. Ultimately, coupling early immune detection with targeted environmental neutralization comprehensively arrests the inflammatory cascade.

Tissue Repair and Regeneration

To address the irreversible osteochondral destruction in RA, nanozyme applications have expanded into regenerative tissue engineering. Functionalized hydrogel scaffolds, for example, are now engineered to recapitulate specific articular anatomies. Hu et al developed a $LiMn_2O_4$ nanozyme-loaded bilayer hydrogel that biomimetically simulates the cartilage and subchondral layers, thereby promoting the synergistic regeneration of both tissues.[146] Integrating functional mitochondria with Prussian blue nanozymes within a DNA hydrogel facilitates efficient tissue repair by restoring cellular energy metabolism.[138] Furthermore, a copper single-atom nanozyme hydrogel combines anti-inflammatory effects with a specialized lubricating network. This design effectively mitigates friction-induced mechanical damage and ensures robust long-term adhesion (Figure 6).[133]

Parallel to hydrogel development, advances in implant surface engineering and cell-based therapies have further enhanced osteochondral regeneration. For instance, applying a $MnFe_2O_4$ coating to titanium substrates successfully induces immunomodulatory osseointegration.[130] This process is driven by the reprogramming of macrophage mitochondrial metabolism from glycolysis to oxidative phosphorylation. Additionally, augmenting mesenchymal stem cells (MSCs) with nanozymes provides crucial antioxidant protection.[124] This intracellular modification enhances MSC survival, fosters M2 polarization, and accelerates subsequent cartilage repair. Beyond localized joint interventions, current research also explores systemic modulation via the "microbiota-gut-joint axis." Adopting this macroscopic perspective, researchers have developed orally administered, valence-tunable Au/CeO_2 nanozymes.[139] These unique agents scavenge intestinal ROS while actively suppressing oxygen generation to preserve strict anaerobic homeostasis. By subsequently modulating short-chain fatty acid metabolism, this mechanism achieves remote, systemic therapeutic efficacy against RA.

Multi-Functional Platform

Nanozymes are increasingly serving as pivotal hubs for integrating physical modalities, pharmacotherapy, and diagnostic imaging. In physical field-assisted therapies, for example, coupling PTT with nanozymes effectively mitigates heat-induced oxidative stress. Materials such as Pt-Te, Pd, carbon-based nanostructures, and Mn_3O_4 leverage their photothermal conversion capabilities to generate localized hyperthermia under near-infrared (NIR) irradiation. This process thermally ablates inflammatory macrophages while synergistically accelerating enzymatic ROS scavenging.[22,97,103,143] Similarly, combining sonodynamic therapy (SDT) with sonosensitizer-conjugated rhodium nanozymes couples ultrasound-triggered ROS generation with self-oxygenation, utilizing human serum albumin for active targeting.[122] Therefore,

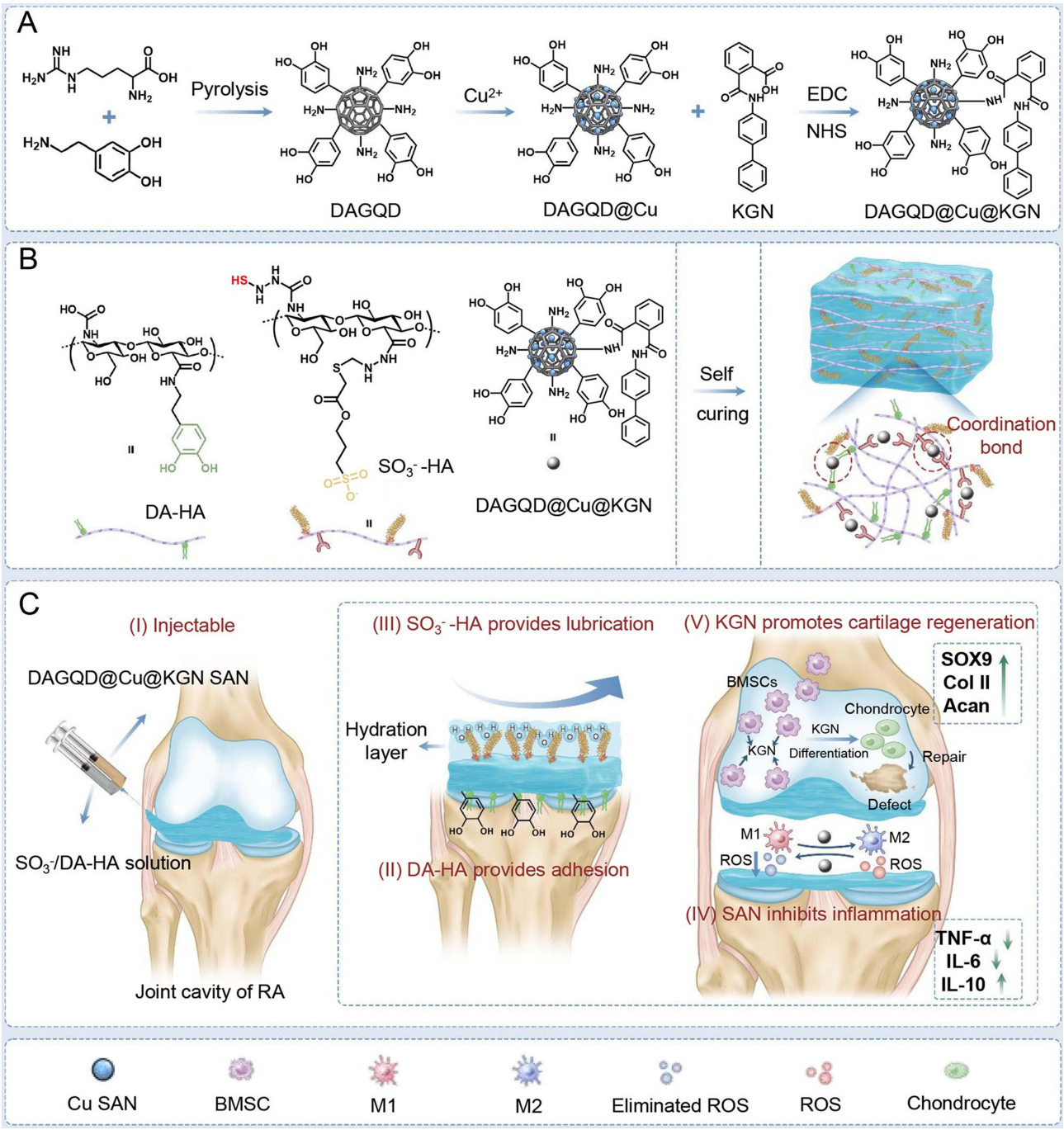

Figure 6 (**A**) Synthesis of DAGQD@Cu SAN and DAGQD@Cu@KGN SAN. (**B**) Synthesis of DAGQD@Cu@KGN-SO_3−/DA-HA hydrogel. (**C**) DAGQD@Cu@KGN-SO_3−/DA-HA hydrogel for RA therapy. (I) Hydrogel self-cures in situ within the joint cavity; (II, III) DAGQD@Cu@KGN-SO_3−/DA-HA hydrogel displays lubrication and adhesion properties; (IV) Regulation of inflammatory microenvironment facilitated by SAN with remarkable ROS-scavenging capabilities; (V) KGN released from the hydrogel promotes the recruitment of BMSCs and induces their differentiation into chondrocytes, facilitating the repair of cartilage damaged by RA. Reproduced with permission.[133] Copyright 2025, Springer Nature.

integrating external physical stimuli with intrinsic nanozyme catalysis achieves mutually reinforcing therapeutic outcomes.

To complement these physical therapies, nanozymes also facilitate the seamless convergence of chemotherapy and catalytic therapy. This versatility is largely due to their intrinsic porous or hollow architectures, which render them superior drug delivery vehicles. Therapeutic agents, such as methotrexate,[22,121,143] dexamethasone,[127] rapamycin[136] and

iguratimod,[103,141] are frequently encapsulated and released via engineered pH- or ROS-responsive mechanisms. Beyond traditional small molecules, these carriers also enable combined gene-chemotherapy; for instance, complexing HIF-1α siRNA with calcium phosphate transcriptionally blocks hypoxia signaling.[123] Nanozymes provide highly adaptable platforms for precise, stimulus-triggered multimodal treatments.

Beyond therapeutic delivery, integrating diagnostic and imaging capabilities enables the real-time monitoring of treatment efficacy. Theranostic nanozyme platforms routinely incorporate advanced techniques such as NIR-II fluorescence,[129] magnetic resonance imaging (MRI),[105] and photoacoustic imaging.[121] Moreover, nanozyme-based sensors allow for the ultrasensitive detection of RA biomarkers like anti-MCV[137] and therapeutics such as D-penicillamine[132] aiding in both early diagnosis and therapeutic monitoring.

Osteoarthritis (OA)

The pathophysiology of OA is multifaceted. It is characterized by an intricate interplay of oxidative stress, chronic inflammation, chondrocyte metabolic dysregulation, and ECM degradation. While natural antioxidant enzymes (eg, SOD, CAT) offer theoretical regulatory potential, their clinical utility is frequently compromised by inherent instability within the harsh pathological microenvironment. Conversely, nanozymes possess stability and tunable multi-enzyme mimetic capabilities, encompassing SOD-, CAT-, and GPx-like activities. For OA, these properties frame nanozymes as chondroprotective agents that focus on mitochondrial quality control, Nrf2 activation, and cartilage matrix preservation to counteract the degenerative and senescence-associated pathology. Therefore, nanozymes have transcended the role of passive ROS. They have evolved into active disease-modifying agents capable of precisely remodeling organelle function and the immune microenvironment (Table 2).

Redox Homeostasis Remodeling

Excessive ROS accumulation drives chondrocyte senescence, apoptosis, and ECM degradation in OA. Consequently, engineering nanozymes that mimic natural antioxidants constitutes a primary therapeutic strategy. Metal oxide nanozymes, such as Mn_3O_4, exhibit robust, broad-spectrum catalytic properties, specifically dual SOD- and CAT-like activities, that significantly attenuate intracellular ROS. Thus, these metal-based systems effectively preserve cartilage integrity.[152,156,172] To mitigate the inherent cytotoxicity of bare metal oxides, surface coatings have been employed to minimize cytotoxicity while retaining high catalytic efficiency, such as PDA coating on Cr2O3 and Mn_3O_4.[171,172] Structural design serves as a crucial strategy to further amplify the catalytic efficiency of nanozymes. Defect-rich hollow RuO_2 nanospheres (d-RuO_2) leverage their amorphous and hollow architecture to maximize active site exposure, surpassing crystalline equivalents.[174] Beyond macroscopic architectures, engineering at the atomic level provides additional enhancements. Specifically, synergistic dual-atom Fe-Fe sites directly amplify ROS clearance capacity (Figure 7).[179] Similarly, cobalt single-atom-doped platinum nanozymes (Pt/Co-SA-NSG) exhibit augmented SOD/CAT-mimetic activities.[154]

Due to their structural tunability, metal-organic frameworks (MOFs) have emerged as prominent scaffolds for antioxidant nanozymes. Copper-based MOFs, for example, have been engineered as safe nanozymes offering comprehensive antioxidant protection (SOD/CAT/•OH scavenging) devoid of pro-oxidant side effects.[165] Prussian blue (PB) analogues constitute another major class, with both ultrasmall (3.5 nm) PB nanozymes[161] and hollow manganese-PB variants[149] exhibiting exceptional ROS scavenging and hypoxia-mitigating capabilities. Furthermore, integrating PB into self-hydrogen-releasing platforms achieves synergistic oxidative stress alleviation via concurrent H2 therapy and enzymatic catalysis.[176] To further enhance biocompatibility and targeting specificity, diverse surface modification strategies have been adopted. For instance, lubricin-inspired PAF nanozymes (PAMPS-grafted amino-fullerene)[158] and Pluronic F127-coated Prussian blue[150] have successfully improved material stability and cellular uptake. Moreover, stimuli-responsive systems have also been developed, such as a ceria-based "mitochondria inspector" that enables the on-demand, ROS-triggered release of SOD/CAT-mimetic CeNPs for precise oxidative stress intervention.[167]

Table 2 Nanozyme Therapy for Osteoarthritis (OA)

Nanozyme	Combination	Material	Formulation	OA Model	Enzyme-Like	Key Findings
HPBzyme[147]	-	PVP, $K_3[Fe(CN)_6]$, $Bi(NO_3)_3$	Intra-articular injection	Rat medial meniscectomy model	SOD, CAT, OH scavenging	Remodeled OA microenvironment; Scavenged ROS and inhibited inflammation via TLR4/NF-κB pathway regulation; Protected chondrocytes from apoptosis and delayed OA progression in rat model.
MnO_2/HA/PRP[148]	PRP	BSA-MnO_2, HA	Injectable Hydrogel	Rat (MIA-induced)	SOD, CAT, POD	Hydrogel provided lubrication; Combined ROS scavenging (MnO_2) with tissue repair (PRP growth factors); Alleviated oxidative stress, promoted chondrocyte proliferation, and ameliorated OA in vivo.
HMPBzyme[149]	-	Mn -doped PB	Intra-articular injection	Rat (MIA-induced)	SOD, CAT	Biodegradable nanozyme; Modulated macrophage polarization (M1 to M2) and relieved hypoxia; Scavenged ROS, suppressed HIF-1α, and promoted cartilage matrix anabolism in OA rats.
PPBzymes[150]	-	Pluronic F127-coated PB	Intra-articular injection	Mouse DMM model	CAT, OH scavenging	Blocked c-Jun N-terminal kinase (JNK) phosphorylation to inhibit inflammation; Effectively scavenged ROS, reduced cartilage degradation, and relieved pain in OA mice.
Mil-88a[151]	-	Fe-MOF	Intra-articular injection	OA Mouse	POD, SOD	Promoted anabolic gene expression (Col2) and inhibited catabolic genes (MMP13); High biocompatibility and improved OARSI scores in OA mouse model.
Mn_3O_4@CS[152]	-	Mn_3O_4, CS Hydrogel	Injectable Hydrogel	Mouse DMM model	SOD, CAT	Reprogrammed chondrocyte metabolism and suppressed inflammation via ROS scavenging; Long-term retention (7 days) and effective cartilage protection in early-stage OA mice.
TP-Au@PCN[153]	Tea Polyphenol	Au, Zirconium-based porphyrin MOF	Intra-articular injection	Rat ACLT model	CAT, OH scavenging	NIR-triggered photocatalytic ROS scavenging and photothermal Tea Polyphenol release repaired mitochondria, enhanced autophagy, and killed bacteria.
Pt/Co-SA-NSG[154]	-	Pt, Co, N/S-doped Graphene	Intra-articular injection	Rat ACLT model	SOD, CAT	Synergistic dual active centers (Co-N_4 and Pt) enhanced SOD/CAT activity; Superior ROS scavenging and anti-inflammatory effects compared to Pt NPs alone; Protected mitochondria under NIR-II irradiation.
MPMP[155]	-	MoS_2, Mg-doped PDA, Polysulfobetaine	Intra-articular injection	Mouse (MIA-induced)	SOD, CAT, HAS	Zwitterionic Dual-Bionic Photothermal Nanozyme; Mimicked antioxidases (ROS scavenging) and hyaluronan synthase (HA production); Photothermal effect enhanced lubrication and upregulated HSP70 to promote chondrogenesis.
Mn_3O_4/UIO-TPP[156]	-	Mn_3O_4, UIO-66 MOF, Triphenylphosphine	Intra-articular injection	Rat ACLT model	SOD, CAT, OH scavenging	Targeted mitochondria to scavenge ROS and restore mitochondrial function (membrane potential, ATP); Sequential catalysis (SOD/CAT-like) inhibited inflammation and apoptosis in OA.
Pt@PCN222-Mn[157]	-	Pt, Manganese-based MOF	Intra-articular injection	Rat TMJ-OA (UAC) model	SOD, CAT	Inhibited ROS-NF-κB and MAPK signaling pathways; Remodeled inflammatory microenvironment, reducing chondrocyte apoptosis and cartilage degradation.

(*Continued*)

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Table 2 (Continued).

Nanozyme	Combination	Material	Formulation	OA Model	Enzyme-Like	Key Findings
PAF[158]	-	PAMPS-grafted Amino Fullerene	Intra-articular injection	Rat medial meniscectomy model	SOD, OH scavenging	Lubricin-Inspired Nanozymes with "In-Out" Strategy; "Out": Restored lubrication to reduce friction; "In": Mitigated oxidative stress and improved mitochondrial function; Reconstructed cartilage lubrication system and delayed OA progression.
LiMn2O4 bilayer hydrogel scaffold[146]	-	LiMn2O4, GelMA/HAMA Hydrogel, Sodium alginate	Implantation	Rat osteochondral defect model	SOD, CAT, GPx	By simulating the osteochondral anatomical structure, clearing ROS, upregulating antioxidant proteins, modulating macrophage polarization, and activating the AMPK pathway, it effectively promoted the synergistic regeneration of cartilage and subchondral bone.
Pt@SF/oxPL[159]	-	Pt, Silk Fibroin, Pullula	Injectable Hydrogel	Rat ACLT model	SOD, CAT	Scavenged ROS via CAT/SOD-like activity and suppressed chondrocyte ferroptosis; Intra-articular injection provided sustained release and cartilage protection.
KGN@HMZC@HA[160]	KGN	Zn-doped Hollow Mesoporous CeOx, HA	Intra-articular injection	Rat (MIA-induced)	SOD, CAT	Chemically programmed nanozyme; Remodeled microenvironment by scavenging ROS, producing O_2, and repolarizing macrophages (M1 to M2); Controlled release of KGN promoted cartilage regeneration.
USPBNPs[161]	-	Ultrasmall PB, PVP	Intra-articular injection	Rat (MIA-induced)	CAT	Exhibited superior ROS scavenging and CAT-like activity due to sub-5 nm size; Repolarized macrophages and achieved therapeutic efficacy comparable to hydrocortisone in vivo.
ε-PLE/MnCoO@Gel[162]	-	MnCoO, ε-Polylysine, HA Hydrogel	Injectable Hydrogel	Rat joint instability model	CAT	Continuously eliminated ROS and modulated immune microenvironment (M1 to M2); Downregulated inflammatory factors (MMP-13, TNF-α) and enhanced cartilage repair genes (COL-2, SOX-9).
miR/IrO_2@ZIF-8[163]	AntagomiR-181a	IrO_2, ZIF-8 MOF	Intra-articular injection	Mouse DMM model	SOD, CAT	Enhanced stability and delivery of antisense oligonucleotides (ASO); Synergistic therapy combining ROS scavenging with gene silencing for effective OA treatment.
PdZn/CoSA-NC[164]	-	PdZn intermetallic NPs, Co Single Atom, N-doped Carbon	Intra-articular injection	Rat ACLT model	SOD, CAT, GPx	Dual active sites provided highly efficient SOD/CAT/GPx activities; Restored mitochondrial function and regulated purine metabolism to inhibit inflammation (IL-1β).
Cu MOF[165]	-	Copper, 4,4′-bipyridine	Intra-articular injection	Mouse (collagenase-induced)	SOD, CAT, OH scavenging	Potent SOD/CAT/·OH scavenging with negligible pro-oxidant side effects; Relieved hypoxia and modulated macrophage polarization for safe and efficient OA therapy.
MnCoO@HA[166]	-	MnCoO, ε-Polylysine, HA Hydrogel	Injectable Hydrogel	Rat TMJ-OA (MIA) model	CAT	Mesoporous MnCoO nanozymes in HA hydrogel depleted ROS durably; Alleviated oxidative stress and upregulated chondrogenic gene expression.
RHM@PMNP[167]	Metformin	CeO_2, ROS-responsive hydrogel	Injectable Hydrogel	Rat DMM model	SOD, CAT	Combined CeO_2 and Metformin to enhance mitochondrial quality control via autophagy; Scavenged damaged mitochondria and ROS, preserving chondrocyte homeostasis and reducing OA progression.

GGM@CM@HPBPT[168]	-	Hollow PB, TPP, Chondrocyte Membrane	Injectable Hydrogel	Mouse ACLT model	CAT	Membrane Biomimetic Nanozyme in Glycyrrhizic Acid Hydrogel; Achieved precise mitochondrial ROS scavenging by overcoming immune barriers; Inhibited STING pathway to suppress inflammation and promote cartilage repair in OA.
Se/PRP-OGel[169]	PRP	Se, Oxidized Chondroitin Sulfate	Injectable Hydrogel	Rat MIA model	SOD, CAT, ·OH scavenging	"Outside-in" (SeNPs scavenged ROS) and "Inside-out" (PRP promotes regeneration) dual strategy effectively repaired cartilage.
CeO_2/RH Gels[170]	-	CeO_2, Rhein (Self-assembled)	Injectable Hydrogel	Rat OA model (Modified Hulth)	SOD, ROS/RNS scavenging	CeO_2 triggered Rhein self-assembly; combined antioxidant enzyme activity with drug effects; Reprogrammed macrophages (M1 to M2) and alleviated chondrocyte inflammation via RONS scavenging.
PDA-Cr_2O_3[171]	-	Cr_2O_3, PDA	Intra-articular injection	Rat ACLT model	SOD, CAT	PDA coating improved biocompatibility of Cr_2O_3 nanozyme, enabling efficient ROS scavenging and inflammation inhibition.
Mn_3O_4@PDA[172]	-	Mn_3O_4, PDA	Intra-articular injection	Rat ACLT model	SOD, CAT	Mimicked Manganese Superoxide Dismutase (Mn-SOD) with high efficiency; Reduced oxidative stress and inflammation in chondrocytes, alleviating OA progression with good biocompatibility.
Mitocelle[173]	-	Potassium ferricyanide, Iron chloride tetrahydrate, Povidone	Intra-articular injection	Mouse DMM model	ROS scavenging	Targeted dysfunctional mitochondria and inhibited the NOX4-p22phox axis; Recovered mitochondrial function to treat cellular organelle disorders and osteoarthritis.
d-RuO_2[174]	-	Defective Hollow RuO_2 Nanospheres	Intra-articular injection	Mouse DMM model	SOD, CAT, OH scavenging	Amorphous structure provided superior antioxidant activity compared to crystalline forms; Attenuated OA by suppressing the ROS/NLRP3/Caspase-1 signaling pathway and relieving pain.
HTM-N@Gel[175]	Nicotinamide Mononucleotide	MnO_2 nanozyme, NMN, Hydrogel	Injectable Hydrogel	Rat OA model	SOD, CAT	Co-delivered NAD^+ and generated O_2 via MnO_2 nanozymes; Reactivated mitochondrial respiratory chain and alleviated chondrocyte senescence to treat OA.
Se-HMPB @AB@COS[176]	Ammonia Borane	Hollow Mesoporous PB, Se, Ammonia Borane	Intra-articular injection	Mouse ACLT model	SOD, GSH-Px like	Released hydrogen gas (H_2) to penetrate mitochondria and reduce oxidative stress; Reversed mitochondrial dysfunction and exerted anti-inflammatory effects in OA therapy.
Zn-LB NPs[177]	Loureirin B	Zinc ions	Intra-articular injection	Mouse MIA model	ABTS, DPPH, PTIO scavenging	Integrated antioxidant and immunomodulatory functions by coordinating Zn with Loureirin B; Restored mitochondrial function in chondrocytes and reprogrammed macrophages (M1 to M2) to treat OA.
MHTCK[178]	KAFAK peptide	CeO_2, TPP, Fused Cell Membrane, HA	Intra-articular injection	Rat (Tear of the ACL and medial meniscus)	SOD, CAT	Fused macrophage-synoviocyte membrane coated CeO_2 nanozymes and anti-inflammatory peptide (KAFAK); Targeted mitochondria to scavenge ROS, preserved bioenergetics, and prolonged joint retention.

(*Continued*)

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Table 2 (Continued).

Nanozyme	Combination	Material	Formulation	OA Model	Enzyme-Like	Key Findings
Fe_2-NCs[179]	-	Fe-Fe dual-atom, N-doped Carbon	Intra-articular injection	Mouse ACLT model	SOD, CAT, GPx	Fe-Fe dimers on N-doped carbon mimicked antioxidant enzymes with enhanced ROS scavenging; Inhibited NOX4, restored ATP, and suppressed NF-κB signaling to mitigate oxidative stress and cartilage degeneration.
HAD/PtCu/PRP[180]	PRP	PtCu, HA-Dopamine	Injectable Adhesive	Rat MIA model	SOD, CAT, OXD Oxidase	PtCu nanozymes catalyzed dopamine-modified HA crosslinking without external oxidants; Combined ROS scavenging with PRP's regenerative effects to relieve pain and improve the OA microenvironment.

Abbreviations: PB, Prussian Blue; MAPK, Mitogen-Activated Protein Kinase; ROS, Reactive Oxygen Species; NF-κB, Nuclear Factor kappa B; KGN, Kartogenin; ASO, Antisense oligonucleotides; DMM, Destabilization of the medial meniscus; ACLT, Anterior cruciate ligament transection; PDA, Polydopamine; PAMPS, Poly-2-acrylamide-2methylpropanesulfonic acid sodium salt; PRP, Platelet-Rich Plasma; PVP, Polyvinylpyrrolidone; PRP, Platelet-Rich Plasma; HA, hyaluronic acid; MIA, Monosodium iodoacetate; MOF, Metal-Organic Framework; CS, Chondroitin Sulfate; CAT, Catalase; SOD, Superoxide dismutase; POD, Peroxidase; OXD, Oxidase; HAS, Hyaluronan Synthase; TPP, Triphenylphosphonium; TMJ, Temporomandibular joint; UAC, Unilateral anterior crossbite.

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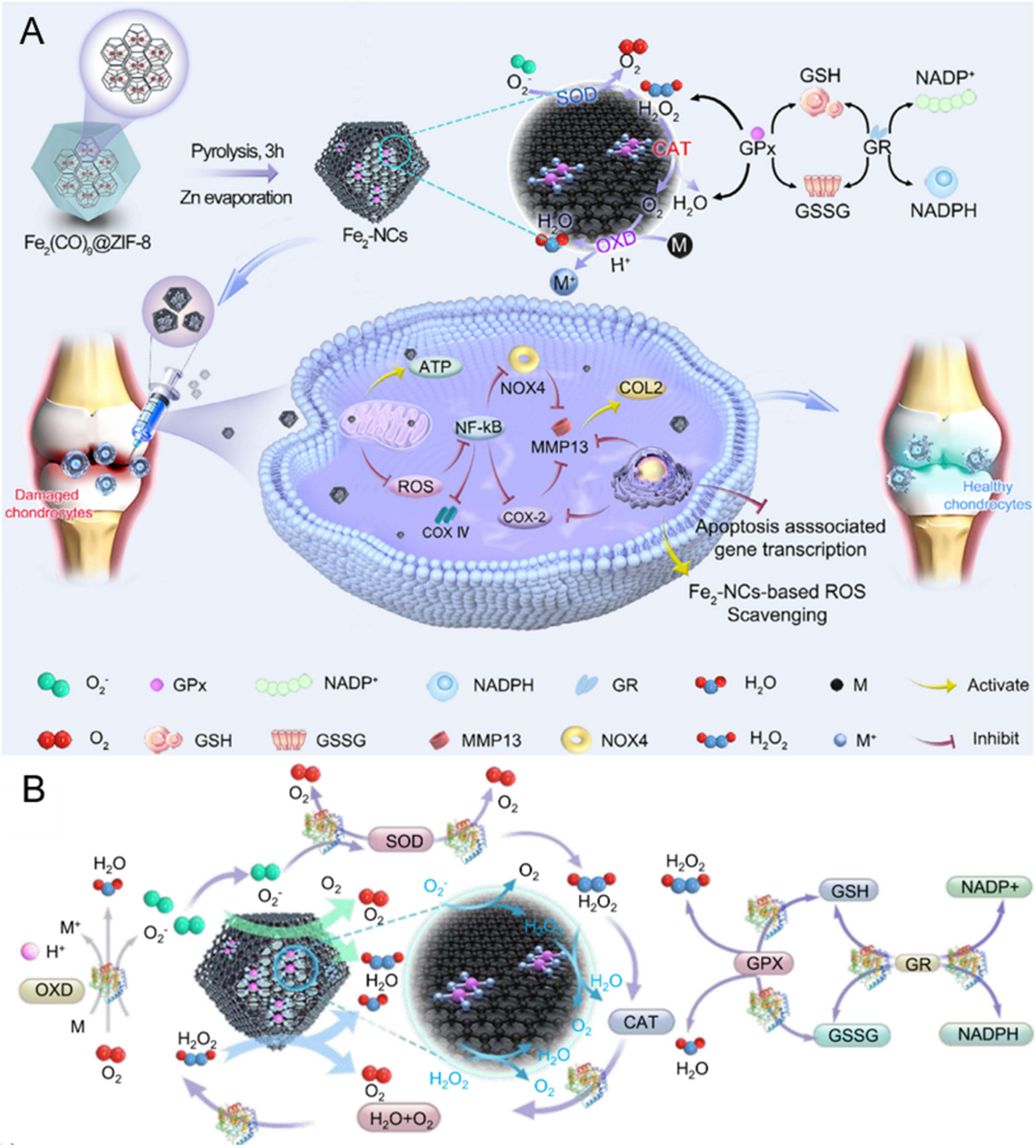

Figure 7 (**A**): Schematic synthesis and mechanism illustration of Fe_2-NCs, which perform as SOD, CAT, and GSH-Px to sequentially scavenge ROS and GSH for mitigating OA. (**B**): Bioinspired catalytic defense mechanism: Nanozyme-mediated sequential ROS scavenging mimicking SOD, CAT, OXD, and GPx enzymatic cascades. Reproduced with permission.[179] Copyright 2025, Wiley-VCH GmbH.

Immune Microenvironment Remodeling

OA is increasingly recognized not merely as a degenerative wear disorder but as a complex inflammatory pathology. Within this context, nanozymes remodel the joint immune microenvironment primarily by directing macrophage polarization, shifting the phenotype from pro-inflammatory M1 to anti-inflammatory M2 states. Extensive evidence corroborates that nanozymes modulate this plasticity via ROS scavenging, which subsequently suppresses key

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inflammatory cascades including NF-κB, MAPK, and JNK. For example, ultrasmall Prussian blue nanozymes,[161] hollow Prussian blue analogs,[149] and PdZn/CoSA-NC nanozymes[164] effectively induce this transition, decreasing pro-inflammatory markers (eg, iNOS, TNF-α) while elevating anti-inflammatory mediators (eg, Arg-1, IL-10). Mechanistically, PdZn/CoSA-NC nanozymes also inhibit M1 activation through purine metabolism modulation.[164]

Integrating nanozymes with bioactive molecules establishes a dual-action paradigm that couples antioxidative capacity with targeted immunomodulation. For instance, CeO_2 nanozyme-mediated self-assembly of rhein hydrogels synergistically suppresses the IL-6/JAK2/STAT1 axis.[170] Similarly, Xu et al[177] developed a Zinc–Loureirin B (Zn-LB) coordination nanozyme enhanced both drug bioavailability and immunomodulatory efficacy. Additionally, Yang et al[178] engineered a biomimetic nanoplatform incorporating anti-inflammatory peptide (KAFAK) and macrophage-synoviocyte hybrid membrane coating, achieving dual-targeted therapy against synovitis and cartilage degradation.

At the molecular level, rationally designed nanozymes exert anti-inflammatory efficacy by intercepting specific signaling cascades. Key examples include the targeted blockade of JNK phosphorylation and NF-κB signaling,[150] alongside the dual inhibition of the ROS-NF-κB and MAPK pathways.[157] Additionally, hollow Prussian blue nanozymes mitigate inflammation and apoptosis via Rac1/NF-κB axis suppression.[147] Ultimately, these precise molecular interventions profoundly ameliorate the osteoarthritic inflammatory microenvironment.

From Mitochondrial Repair to Tissue Repair

Recent advances in OA pathophysiology highlight subcellular targeting as the next frontier in nanozyme therapeutics. Because mitochondrial dysfunction initiates chondrocyte senescence and apoptosis, conjugating targeting moieties, such as triphenylphosphine (TPP), enables precise organelle localization. For example, Mn_3O_4/UIO-TPP nanozymes effectively scavenge mitochondrial ROS. This targeted intervention restores membrane potential and preserves mitochondrial DNA (mtDNA) integrity.[156] Intervening in pathological mitochondrial cascades represents a vital homeostatic strategy. To combat respiratory chain impairment, the HTM-N@Gel NAD+/O_2 co-delivery system restores mitochondrial bioenergetics by synchronously replenishing electron donors and acceptors (Figure 8).[175] Furthermore, active intervention in pathological mitochondrial pathways represents an emerging trend. Notably, the "Mitocelle" Prussian blue nanozyme developed by Lim et al[173] mitigates ROS generation at its source by competitively inhibiting the NOX4-p22phox interaction.

The elimination of dysfunctional mitochondria via mitophagy is critical for maintaining chondrocyte homeostasis. Microsphere system assembling ceria nanozymes with metformin has been shown to activate autophagy for this purpose.[167] Similarly, NIR-triggered MOF nanozymes[153] and hydrogen-releasing nanozymes[176] have demonstrated efficacy in preserving mitochondrial function, promoting mitophagy, and retarding chondrocyte senescence. Beyond senescence mitigation, nanozymes are employed to inhibit other cell death modalities. For example, a platinum nanozyme-loaded silk fibroin/oxidized pullulan hydrogel (Pt@SF/oxPL) effectively suppressed chondrocyte ferroptosis by scavenging ROS and lipid peroxides.[159] Additionally, a biomimetic membrane-camouflaged nanozyme (CM@HPBPT) was found to attenuate inflammation-induced chondrocyte injury by intercepting the cGAS-STING pathway mediated by cytosolic mtDNA leakage.[168]

Multifunctional Synergistic Therapy

To overcome the intrinsic limitations of monotherapies, researchers have developed synergistic platforms integrating nanozymes with modalities like PTT, gene interference, and drug delivery, which markedly amplifies targeted therapeutic outcomes. NIR-responsive nanozymes facilitate the synergistic coupling of PTT with enzymatic catalysis. For instance, a NIR-triggered, tea polyphenol (TP)- modified metal-organic framework (TP-Au@PCN) facilitates concurrent photocatalytic ROS scavenging and photothermally controlled drug release.[153] Similarly, Pt/Co single-atom nanozymes exhibit augmented enzymatic activity and photothermal conversion under NIR-II irradiation.[154] Additionally, zwitterionic nanozymes mimicking both antioxidant enzymes and hyaluronan synthase (HAS) utilize mild photothermal stimulation to upregulate heat shock protein 70 (HSP70), thereby fostering cartilage regeneration.[155]

Nanozymes frequently function as versatile vehicles for therapeutic cargo. Combining MOF-encapsulated iridium oxide (IrO_2) nanozymes with antisense oligonucleotides (ASO) enables simultaneous ROS scavenging and miR-181a

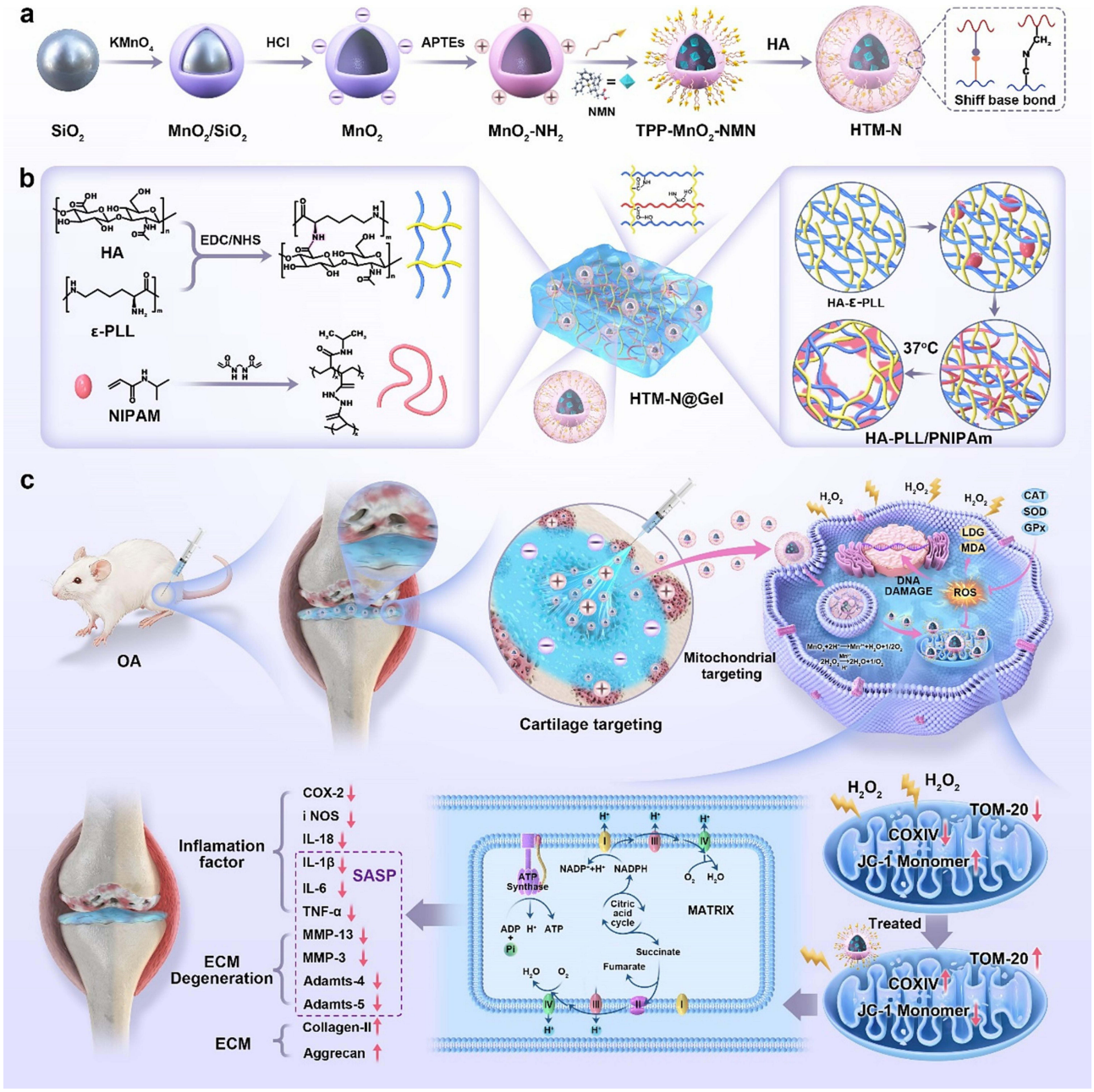

Figure 8 Design of the cartilage-mitochondria cascade-targeting composite hydrogel and its therapeutic mechanism for OA. (**a**) Synthesis of mitochondrialtargeting functionalized MnO_2-based nanozymes. (**b**) Fabrication of cartilage-targeting interpenetrating network hydrogel microcarriers. (**c**) Minimally invasive intra-articular injection of the composite hydrogel, where the positively charged hydrogel surface facilitates cartilage adhesion, followed by the in situ release of mitochondrial-targeting functionalized MnO_2-based nanozymes. This process mitigates oxidative stress-induced chondrocyte senescence, thereby inhibiting OA progression. Reproduced with permission.[175] Copyright 2025, Elsevier.

silencing to actively modulate chondrocyte metabolism.[163] Parallelly, Kartogenin-loaded nanozymes utilize precise pH-responsive release kinetics to drive the chondrogenic differentiation of mesenchymal stem cells.[160] Moreover, hydrogel systems incorporating platelet-rich plasma (PRP) leverage the synergy between PRP-derived growth factors and the antioxidative capacity of selenium nanozymes to achieve comprehensive "inside-out" and "outside-in" tissue repair.[70,148,169]

Achieving prolonged intra-articular retention and on-demand drug release necessitates the development of intelligent hydrogel matrices. These materials are characterized by injectability, self-healing properties, and environmental responsiveness such as pH, ROS, or temperature. Prominent examples include Schiff base-crosslinked hyaluronic acid

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hydrogels,[162,166] silk fibroin/oxidized pullulan scaffolds,[159] and mitochondria-targeting NAD+/O_2 co-delivery interpenetrating networks.[175] Furthermore, pH- and ROS-responsive hydrogels developed by Zhou et al[148] and Wang et al[162] respectively, have demonstrated significantly enhanced therapeutic efficacy and sustained retention.

In summary, nanozymes significantly ameliorate OA pathology through multifaceted mechanisms, encompassing ROS scavenging, immune polarization modulation, inflammatory pathway suppression, and the promotion of cartilage matrix synthesis. Preclinical studies consistently evidence improvements in histology, cytokine profiles, and locomotor function, alongside favorable biocompatibility and safety profiles. Looking forward, the integration of organ-on-a-chip models with rigorous clinical translational research positions nanozymes as a promising avenue for developing DMOADs.

Gouty Arthritis (GA)

GA pathogenesis fundamentally originates from MSU crystal deposition and the consequent sterile inflammation. While biological urate oxidase exhibits potent uricolytic activity, its clinical translation is significantly impeded by intrinsic immunogenicity and the oxidative injury provoked by its catalytic byproduct, hydrogen peroxide (H_2O_2).[5] The advent of nanozymes represents a paradigm shift addressing these challenges. For GA, nanozymes are positioned as rapid ROS scavengers and purine metabolic regulators, with particular emphasis on NLRP3 inflammasome inhibition and uric acid metabolism modulation to terminate the MSU crystal-triggered acute inflammatory burst. Current design philosophies have transcended simple mono-enzyme mimicry, evolving into intelligent theranostic systems that orchestrate "self-cascading" catalysis, atomic-level active site engineering, and immune microenvironment reprogramming (Table 3).

Re-Establishing Redox Homeostasis

To circumvent the "ROS dilemma", in which natural uricase generates hydrogen peroxide (H_2O_2) and thereby exacerbating inflammation, researchers have increasingly focused on designing bi- or multi-functional nanozymes. These integrated platforms possess intrinsic urate oxidase (UOX) alongside CAT/SOD activities, enabling simultaneous uric acid clearance and ROS elimination. For example, optimizing a Pt/CeO_2 nanozyme at a 1:5 molar ratio utilizes Pt for UOX mimicry while leveraging CeO_2 oxygen vacancies for potent CAT activity. Consequently, this synergistic design achieves the instantaneous scavenging of degradation-induced H_2O_2.[181]

Furthermore, catalytic efficiency can be amplified through precise nanostructural and morphological engineering. Xi et al synthesized ultrathin PdPt3 and PdIr3 cubic hollow nanocages (HNCs). This distinct topology maximizes active site exposure and optimizes electronic structures via alloying, thereby driving an efficient ROS scavenging cycle (Figure 9).[188] Additionally, Ye et al elucidated the size-dependence of catalytic activity, identifying that 46 nm two-dimensional Pd@Ir nanosheets exhibit the lowest activation energy for uric acid degradation (35.9 kJ/mol). Crucially, these nanosheets facilitate O_2 regeneration via a self-cascading reaction mechanism, effectively mitigating the hypoxic microenvironment.[190]

Dissolution of Monosodium Urate Crystals

Beyond systemic uric acid clearance, directly modulating MSU crystal nucleation serves as a pivotal objective in comprehensive gout management. To this end, Liu et al constructed a biomimetic architecture mirroring natural enzyme pockets.[183] By utilizing arginine-rich peptides (protamine) to direct the growth of rhodium nanoclusters (RhNCs) on reduced graphene oxide (rGO) surfaces. This design endowed the material with exceptional substrate affinity (Km approaching that of natural enzymes) and robust physiological stability, effectively prolonging the induction period for urate crystallization. Earlier investigations by the same group corroborated that arginine peptide-guided Pt nanoclusters (ARP-PtNC) mimic the multi-enzyme cascade functions of peroxisomes, thereby suppressing the formation of needle-like crystals.[183,184]

Advancing to atomic precision, the direct dissolution of mature crystals constitutes a distinct and highly effective physicochemical intervention. Lin et al developed a Mn-N-C single-atom nanozyme (P–Mn–N–C) by precisely modulating the Mn^{4+}/Mn^{2+} redox equilibrium and the nitrogen coordination sphere.[182] This nanomaterial not only exhibits triple enzyme-mimetic activity but also directly adsorbs and erode pre-existing MSU crystals via surface charge interactions.

Table 3 Nanozyme Therapy for Gouty Arthritis(GA)

Nanozyme	Combination	Material	Formulation	GA Model	Enzyme-Like	Key Findings
Pt/CeO_2 (1/5)[181]	-	Pt; CeO_2; PVP	Intra-articular injection	Rat (MSU-induced)	UOD, CAT, SOD	Pt/CeO_2 (1/5) enables self-cascade uric acid degradation and H_2O_2 elimination, effectively relieving pain and edema in acute gout.
P–Mn–N–C[182]	-	Mn; Nitrogen-doped porous carbon matrix; PEG	Intra-articular injection	Mouse (MSU-induced)	UOD, CAT, SOD	P-Mn-N-C exhibits triple-enzyme activity to directly dissolve MSU crystals and scavenge ROS, relieving acute gout pain and inflammation faster than colchicine with excellent biocompatibility.
PRTM-RhNC @rGO[183]	-	RhNC; rGO; PRTM	-	In vitro study	UOD	Biomimetic nanozyme with a 3D pocket-like structure exhibited high uricase selectivity/activity, strong anti-poisoning stability, and significantly inhibited urate crystallization.
ARP-PtNC[184]	-	PtNC; PRTM	-	In vitro study	UOD, CAT, SOD	Single peptide-Pt nanozyme mimics peroxisome with triple activities, efficiently degrading uric acid, scavenging ROS, and significantly inhibiting MSUM crystallization.
FALNZs[185]	-	CeO_2; Folic-acid modified liposomes; BSA-template	Intra-articular injection	Mouse (MSU-induced)	SOD, CAT	FALNZs targeted M1 macrophages via folate receptors, scavenged ROS via SOD/CAT activities, repolarized macrophages to M2 phenotype, and significantly alleviated joint swelling and inflammation.
BIM NPs[186]	Indomethacin	MnO_2; BSA-template	Intra-articular injection	Mouse (MSU-induced)	CAT	BIM NPs effectively scavenged ROS, inhibited neutrophil infiltration/ NETosis, uniquely promoted neutrophil reverse migration, polarized macrophages to M2 phenotype, and alleviated joint swelling.
Pt-CeO2 bionic meniscus[187]	-	Pt; CeO_2; PCL Scaffold	Implant	In vitro study	UOD, CAT, SOD	3D-printed bionic meniscus with gradient structure and Pt-CeO_2 nanozymes efficiently degrades uric acid and scavenges RONS, offering a personalized implantable therapy for gouty arthritis.
HMPB-Pt@MM[114]	-	HMPB; $PtCl_4$; Macrophage Membrane	Intravenous injection	Mouse (MSU-induced)	UOD, CAT, SOD	HMPB-Pt@MM achieves inflammatory targeting and immune evasion through encapsulation with macrophage membranes, scavenges ROS, metabolizes uric acid, reprograms macrophages (M1 to M0), and effectively inhibits gout flares and recurrence.
$PdPt_3$/$PdIr_3$ HNCs[188]	-	Core/Wall: $PdPt_3$ or $PdIr_3$ Coating: PVP	-	In vitro study	UOD, CAT, SOD	Hollow nanocages enable efficient self-cascade uric acid degradation and H_2O_2 elimination; $PdPt_3$ excels as UOD mimic while $PdIr_3$ serves as SOD.
D-N[EM2][189]	Natural UOD; Resveratrol	Pt NP; HA; PDA; Liposomes coated with macrophage-exosome fusion membranes	Intra-articular or Intravenous injection	Rat (MSU-induced)	CAT	Biomimetic nanosystem achieves synergistic enzyme-photothermal-immunotherapy to reprogram macrophages, degrade urate, and relieve gout symptoms effectively.
2D Pd@Ir NSs[190]	-	Pd; Ir; Coating: PVP	Intra-articular injection	Mouse (MSU-induced)	UOD, CAT	46-nm Pd@Ir NSs exhibit size-dependent lowest activation energy ($35.9 kJ/mol) for uric acid degradation and effective self-cascade H_2O_2 elimination, relieving acute gout symptoms.

(*Continued*)

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Table 3 (Continued).

Nanozyme	Combination	Material	Formulation	GA Model	Enzyme-Like	Key Findings
USM[H]L[191]	MTX; Natural UOD	Liposomes coated with M2 macrophage-erythrocyte hybrid membrane; SPIONs	Intra-articular or Intravenous injection	Rat (MSU-induced)	CAT	USM[H]L can target inflammatory cells to achieve synergistic enzyme-thermal-immunotherapy: UOD and nanozyme degrade uric acid and hydrogen peroxide, respectively; bienzymes improve the CAT abilities of each other; nanozyme produce photothermal effects; and methotrexate has immunomodulatory and anti-inflammatory effects.

Abbreviations: Pt, Platinum; Ce, Cerium; PVP, Polyvinylpyrrolidone; UOD, Urate oxidase; CAT, Catalase; SOD, Superoxide dismutase; PEG, Polyethylene glycol; MSU, Monosodium urate; RNS, reactive nitrogen species; RhNC, Rhodium nanoclusters; PRTM, Protamine; rGO, Reduced graphene oxide; PtNC, Pt nanoparticle cluster; MSUM, Monosodium urate monohydrate; BSA, Bovine serum albumin; PCL, Polycaprolactone; RONS, Reactive Oxygen and Nitrogen Species; HMPB, Hollow Prussian Blue; HA, Hyaluronic acid; PDA, Polydopamine; NSs, Nanosheets; Ir, Iridium; MTX, Methotrexate; SPIONs, Superparamagnetic iron oxide nanoparticles.

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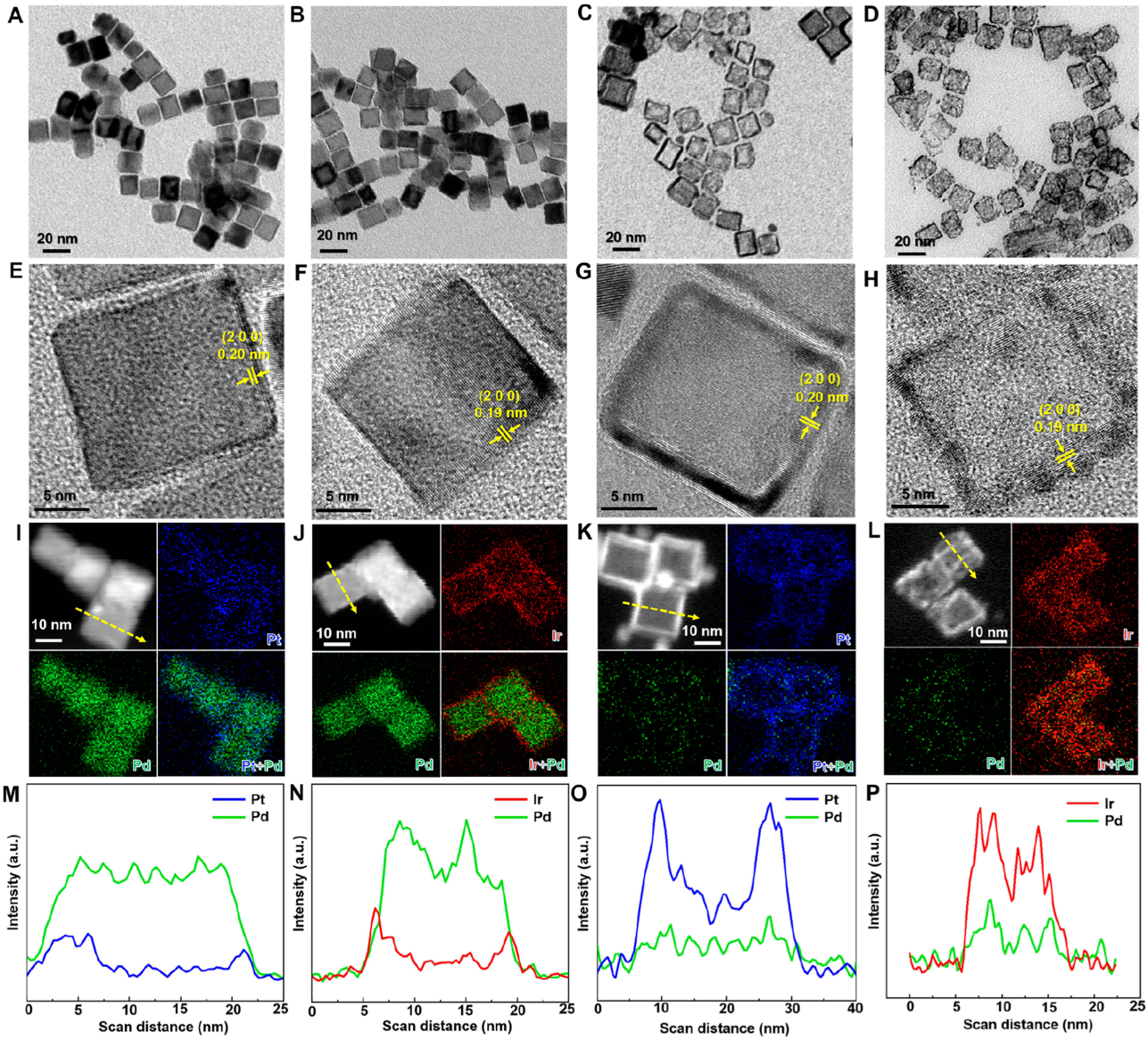

Figure 9 TEM images of (**A**) core/shell Pd/Pt, (**B**) core/shell Pd/Ir nanocubes, and (**C**) $PdPt_3$ and (**D**) $PdIr_3$ HNCs. HR-TEM images of (**E**) Pd/Pt, (**F**) Pd/Ir nanocubes, and (**G**) $PdPt_3$ and (**H**) $PdIr_3$ HNCs. EDS-elemental mappings of (**I**) Pd/Pt, (**J**) Pd/Ir nanocubes, and (**K**) $PdPt_3$ and (**L**) $PdIr_3$ HNCs. EDS-line scans of (**M**) Pd/Pt, (**N**) Pd/Ir nanocubes, and (**O**) $PdPt_3$ and (**P**) $PdIr_3$ HNCs. Reproduced with permission.[188] Copyright 2024, American Chemical Society.

Ultimately, this atomic-level engineering provides a robust therapeutic alternative that fundamentally diverges from conventional pharmacological treatments.

Biomimetic Targeting and Immune Microenvironment Remodeling

As insights into gouty arthritis (GA) pathogenesis deepen, therapeutic paradigms have transitioned from isolated metabolic regulation to holistic immune microenvironment remodeling. To achieve precise lesion targeting while evading immune clearance, biomimetic cell membrane camouflage technologies have been widely adopted.[192] By employing a Trojan horse" strategy, macrophage or erythrocyte membranes endows nanozymes with prolonged circulation half-lives and intrinsic inflammatory tropism. Specifically, macrophage membrane-cloaked Prussian blue/platinum nanozymes (HMPB-Pt@MM) exploit surface receptors (eg, LFA-1) to selectively accumulate inflamed sites.[114] This system suppresses gout recurrence by concurrently metabolizing uric acid and driving M1-to-M2 macrophage repolarization.

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To further elevate functional integration, Chen[191] and Xu[189] developed sophisticated fusion membrane systems such as erythrocyte-macrophage hybrid membranes. These intelligent platforms not only serve as vehicles for uricase and anti-inflammatory agents (eg, methotrexate, resveratrol) but also integrate photothermal agents (SPIONs) or photothermal nanozymes. The resulting synergistic interplay between thermal effects and pharmacotherapy blocks the NF-κB pathway, potently inducing the M1-to-M2 transition. At the molecular level, folate-modified liposomes (FALNZs) selectively target folate receptor β-overexpressing M1 macrophages to arrest inflammatory cascades via intracellular ROS clearance.[185] Parallelly, biomimetic nanoparticles (BIM NPs) utilizing a MnO_2 shell scavenge ROS while releasing indomethacin.[186] These dual-action mechanisms comprehensively resolve inflammation by preventing neutrophil infiltration and promoting reverse migration.

The application of nanozymes in GA therapy is currently transcending traditional formulation limits, extending into implantable biomedical devices. Researchers have integrated Pt-CeO_2 nanozymes into 3D-printed meniscus scaffolds featuring gradient porosity.[187] This biomimetic device provides mechanical support while adaptively regulating catalytic activity in response to local uric acid levels. This innovation marks a critical paradigm shift, transitioning nanozyme therapeutics from acute pharmacological interventions to structure-function integrated tissue engineering for chronic disease management.

Challenges and Future Research

In light of the substantial evidence presented above, it is clear that researchers have accomplished a series of landmark advances in both the design and mechanistic elucidation of nanozymes, substantiating the clinical translational potential of inorganic nanozymes. Across the distinct pathological landscapes of RA, OA, and GA, recent therapeutic breakthroughs share a common paradigm encompassing multi-enzyme cascade catalysis, microenvironmental reprogramming, and hybrid biomaterial integration (Supplementary Table 1).[193] These platforms are engineered with multi-mimetic activities, specifically emulating superoxide SOD, CAT, and urate oxidase, to enable sequential reactive oxygen species (ROS) scavenging and crystal dissolution while suppressing pro-oxidant Fenton side reactions.[194,195] This catalytic relay modulates local immunometabolism, shifts the polarization of M1 macrophages and activated neutrophils toward anti-inflammatory M2 phenotypes, and subsequently dampens the inflammatory cascade.[98] To navigate the physical constraints of dense cartilage extracellular matrices and rapid synovial lymphatic clearance, these inorganic nanocatalysts are incorporated into responsive delivery vectors, such as membrane-camouflaged biomimetic vesicles, ROS-responsive polymeric micelles, and injectable hydrogel scaffolds.[88,114,161] This integration extends intra-articular retention and facilitates chondrocyte targeting, combining localized nanocatalysis with controlled drug release and osteochondral tissue regeneration.[196]

However, translating these laboratory successes into clinical realities is hampered by a dynamic physiological reality: the joint cavity acts as an active biological barrier that counteracts external therapeutic interventions through interconnected oxidative, immune, and proliferative signals. While the inherent multi-enzyme mimetic activity of nanozymes provides a clear biochemical advantage over single-target agents, their systemic or intra-articular deployment raises pressing questions regarding structural integrity, biocompatibility, target specificity, and batch-to-batch consistency. A closer examination of these issues suggests that the current enthusiasm for nanozyme therapy may need to be tempered by a more rigorous assessment of what can realistically be achieved. Consequently, in the following discussion, we shift focus from what has been accomplished to what remains unresolved, offering a critical perspective on the barriers that lie ahead.

Long-Term Biosafety

Biosafety remains the principal impediment to the clinical translation of nanozymes.[197] Unlike conventional small-molecule therapeutics, these platforms frequently incorporate transition metals such as Mn, Pt, Ce, Au, and Pd. Despite this, their long-term in vivo metabolic trajectories and immune interactions remain incompletely elucidated. Surface engineering, specifically PEGylation and biomimetic cell membrane camouflaging, effectively attenuates acute immunogenicity. However, these modifications do not resolve fundamental clearance issues. Evidence indicates that certain metal-based nanozymes (eg, ceria, Prussian blue analogs) may sequester in the liver, spleen, or kidneys for extended

periods.[35,98,105,121,128,151] Compounding this issue, current literature predominantly relies on short-term rodent efficacy models spanning merely 2 to 8 weeks.[35,122,129,134,163,166,173,180] This distinct lack of comprehensive toxicological profiling obscures our understanding of chronic metal burdens. Specifically, it is entirely unknown whether this prolonged retention precipitates organ fibrosis, chronic inflammation, or secondary oxidative injury via Fenton-mediated hydroxyl radical generation.

Beyond systemic risks, localized nanoparticle aggregation within the articular space can paradoxically exacerbate joint pathology. Large aggregates frequently trigger "frustrated phagocytosis," a process where synovial macrophages fail to internalize the material and consequently release pro-inflammatory cytokines. This specific mechanism closely mimics the pathogenicity of monosodium urate crystals in gout.[5] Consequently, the development of biodegradable or ultrasmall, renally clearable nanozymes, coupled with the establishment of a rigorous, full-lifecycle safety evaluation framework, encompassing reproductive and genotoxicity, is a prerequisite for clinical translation.

Catalytic and Delivery Challenges in Joint Nanozyme Therapy

Considerable efforts have been made to address nanozyme catalytic instability in the articular microenvironment, including surface engineering to enhance delivery and stimulus-responsive systems tailored to arthritic pathophysiological cues. Despite these advances, critical deficiencies remain. The formation of a protein corona upon synovial fluid exposure physically occludes active sites and compromises catalytic efficiency, while PEGylation and membrane-camouflaging strategies—though partially effective—often introduce new complexities such as reduced activity or accelerated clearance.[198] Furthermore, the intrinsic pH-dependence of most nanozymes creates a fundamental disconnect: optimal activity frequently occurs in acidic lysosomal compartments (pH 4.0–5.5),[199] yet therapeutic efficacy in OA or RA requires sustained SOD/CAT-mimetic function within the weakly acidic inflammatory milieu (pH 6.5–6.8).[147,159] Compounding these catalytic challenges, intra-articular delivery confronts the paradox of prolonged retention versus deep cartilage penetration. The dense synovial lymphatic network clears free nanoparticles within hours,[200] while bulky hydrogel depots, though improving retention, fail to traverse the negatively charged cartilage ECM, restricting nanozymes to superficial surfaces and limiting efficacy against deep zone degeneration.[125,133,134,138,144,146,148,159,168,169,201–203] Although ultrasmall particles or charge-reversal mechanisms enhance ECM permeability, they simultaneously sacrifice retention time.[204] Overcoming these barriers requires three concurrent efforts: (1) the engineering of pH-insensitive broad-spectrum nanozymes through multi-metal alloying, hetero-junction construction, or defect engineering; (2) the establishment of physiologically relevant activity detection systems that replicate the protein-rich and shear-stress conditions of synovial fluid; and (3) the development of multi-stage delivery systems, such as exosome-based carriers or MMP-responsive particles, that reconcile sustained retention with deep tissue penetration.

Clinical Translation and Production Standardization

Translating nanozyme synthesis from the bench to industrial scales introduces formidable Chemistry, Manufacturing, and Controls (CMC) challenges. Unlike well-defined small molecules or biologics, nanozyme catalytic efficacy depends intrinsically on complex physicochemical properties. These structural determinants encompass crystal lattice integrity, surface defect density, coordination environments, and particle size distribution. During scale-up, even minor deviations in macro-reaction parameters (eg, temperature, agitation rate) can induce profound batch-to-batch variations in catalytic performance.[205] Establishing reproducible, industrial-grade synthetic methodologies is therefore a fundamental prerequisite for guaranteeing therapeutic consistency. Parallel to manufacturing hurdles, a profound standardization and regulatory gap impede clinical progress. The field currently lacks a unified metric or standardized unit for defining nanozymatic activity. Disparate substrates and assay conditions across laboratories confound cross-study comparability and preclude the development of precise clinical dosing regimens. Moreover, existing regulatory frameworks provide no specific guidelines for inorganic, enzyme-mimetic nanomaterials. Defining their regulatory classification demands urgent consensus between regulatory agencies and researchers, whether as drugs, medical devices, or combination products. To successfully cross the threshold into clinical trials, implementing standardized activity assays and rigorous quality control protocols remains strictly imperative.

Future Research Directions

To overcome the translational barriers outlined above, future arthritis-targeted nanozyme research must strategically advance along several interconnected frontiers. First, the vast material parameter space makes traditional trial-and-error development inefficient. Artificial intelligence, particularly machine learning trained on catalytic databases, can establish quantitative structure-activity relationships that link material properties to target enzyme-like activities, enabling rapid and cost-effective predictions of catalytic performance prior to experimental synthesis. Combining density functional theory calculations with machine learning algorithms further enables the prediction of intermediate adsorption energies on various metal oxide surfaces, offering mechanistic insights into catalytic selectivity and turnover rates.

Second, SAzymes, featuring isolated metal atoms atomically dispersed on solid supports, represent a paradigm shift toward precision catalysis, offering maximized atomic utilization and well-defined M-Nx coordination structures that facilitate precise activity regulation. Emerging evidence indicates that tuning the coordination geometry of M-Nx sites can differentially regulate catalytic selectivity, which provides the advantage of mild and controllable ROS regulation, while their atomically dispersed nature concurrently facilitates renal clearance.[89]

Third, the complex, multifactorial pathology of arthritis necessitates multi-enzyme mimetic nanozymes that integrate two or more catalytic activities (eg, SOD + CAT, SOD + GPx, POD + UOD, or the complete quartet) within a single nanoplatform. Core-shell architectures and MOF-based frameworks enable spatial organization of sequential catalysis. Biomimetic camouflage represents another critical developmental direction. By integrating diverse cell membrane coatings, researchers can exploit endogenous receptor-ligand interactions to precisely target the inflamed synovium while concurrently optimizing biocompatibility. Furthermore, the therapeutic paradigm must evolve from isolated antioxidative interventions toward holistic microenvironmental reprogramming by integrating ROS scavenging with targeted delivery of pharmacological or genetic payloads to suppress core inflammatory cascades, notably NF-κB, NLRP3, and JAK-STAT.

Fourth, the heterogeneity of arthritis calls for personalized strategies stratified by synovial fluid cytokine profiles, autoantibody status, and ROS composition. Finally, clinical translation demands a clear roadmap addressing GMP-compliant manufacturing processes, regulatory classification, and the establishment of appropriate clinical trial endpoints. Addressing these unresolved issues will chart the course for future therapeutic applications.

Conclusion

While conventional pharmacotherapies offer rapid symptomatic relief, their capacity to reverse the self-sustaining inflammatory and oxidative microenvironments within arthritic joints remains inherently limited by poor local bioavailability and multifactorial pathogenesis. Nanozymes have demonstrated substantial preclinical efficacy in modulating this pathological niche, driven by their intrinsic enzyme-mimicking activities and programmable physicochemical properties. Their robust capacity to scavenge excessive reactive oxygen and nitrogen species while concurrently remodeling local immunometabolic profiles mechanistically distinguishes them from conventional single-target interventions. Despite these promising preclinical outcomes, current evidence predominantly derives from acute or early-stage animal models that fail to accurately replicate the chronic, multifactorial nature of human arthritis. The long-term intra-articular fate of inorganic nanozymes, encompassing degradation kinetics, metabolic clearance pathways, and potential off-target accumulation, remains inadequately elucidated. Intra-articular injection currently represents the most feasible near-term clinical route, yet issues of joint retention and immunological tolerance to repeated administrations must be addressed. Advancing this field requires focused attention on three critical research priorities. Systematic and prolonged biosafety evaluations in clinically relevant animal models, particularly utilizing immunocompetent, aged, or comorbid subjects, must precede any clinical translation. Mechanistic investigation of synovial clearance and cartilage penetration. And developing active targeting strategies is critical for establishing sufficient therapeutic concentrations within the avascular zones of articular cartilage. Nanozymes offer a conceptually distinct and mechanistically feasible complement to existing arthritis therapeutics, exhibiting the potential to address unmet needs. Realizing this theoretical potential demands rigorous validation through comprehensive in vivo profiling and meticulously designed translational studies. The ultimate

clinical realization of nanozyme strategies hinges not merely on their catalytic efficacy, but fundamentally on their safety, biocompatibility, and deliverability—the primary foci of ongoing and future research endeavors.

Abbreviations

ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; ADAs, Anti-drug antibodies; Anti-MCV, Anti-mutated citrullinated vimentin; ASO, Antisense oligonucleotides; BMSCs, Bone marrow mesenchymal stem cells; CAT, Catalase; CMC, Chemistry, Manufacturing, and Controls; DAMPs, Damage-associated molecular patterns; DMARDs, Disease-modifying anti-rheumatic drugs; DMOADs, Disease-modifying osteoarthritis drugs; ECM, Extracellular matrix; FLS, Fibroblast-like synoviocytes; GA, Gouty arthritis; GCs, Glucocorticoids; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPx, Glutathione peroxidase; GSH, glutathione; HAS, Hyaluronan synthase; HIF-1α, Hypoxia-inducible factor 1 subunit α; H_2O_2, Hydrogen peroxide; IL, Interleukin; IrO_2, Iridium oxide; JAK, Janus Kinase; MMP-13, Matrix metalloproteinase 13; MOFs, Metal-organic frameworks; MSU, Monosodium urate; mtDNA, Mitochondrial DNA; MTX, Methotrexate; MyD88, Myeloid differentiation factor; NETs, Neutrophil extracellular traps; NF-κB, Nuclear factor-Kb; NIR, Near-infrared; NSAIDs, Nonsteroidal anti-inflammatory drugs; OA, Osteoarthritis; OXD, Oxidase; $O_2^{\bullet-}$, Superoxide anion radical; PB, Prussian blue; FRβ, folate receptor β; PDA, Polydopamine; PEG, Polyethylene glycol; LSPR, Localized Surface Plasmon Resonance; POD, Peroxidase; PRP, Platelet-rich plasma; PTT, Photothermal therapy; RA, Rheumatoid arthritis; RhNCs, Rhodium nanoclusters; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SACs, Single-atom catalysts; SAzymes, Single-atom nanozymes; SDT, Sonodynamic therapy; SOD, Superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, Tumor necrosis factor-α; TP, Tea polyphenol; TPP, Triphenylphosphine; •OH, Hydroxyl radicals.

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Disclosure

The authors declare no conflicts of interest in this work.

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