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REVIEW

Therapeutic Nanozymes in Rheumatoid Arthritis Treatment Through Disease Stage-Oriented Strategies

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Abstract: Rheumatoid arthritis (RA) progresses through distinct pathophysiological states, transitioning from acute inflammatory phases with largely reversible tissue damage to chronic destructive stages characterized by irreversible structural alterations. Current therapeutic approaches largely employ uniform interventions without accounting for this disease heterogeneity, potentially compromising treatment efficacy. Dysregulated reactive oxygen species metabolism represents a mechanistic thread connecting RA stages. Acute inflammation is characterized by intense oxidative bursts, whereas chronic RA exhibits persistent oxidative stress, establishing a stage-dependent rationale for enzyme-based intervention. However, natural antioxidant enzymes are rapidly inactivated within the harsh inflammatory microenvironment, which is defined by acidic conditions and elevated proteolytic activity. Nanozymes are nanomaterials with enzyme-like catalytic activities, which overcome these limitations through enhanced environmental stability, tunable catalytic activity, and multifunctional integration. In contrast to prior nanozyme reviews that primarily organized discussions by material types or catalytic mechanisms, this review adopts a stage-oriented framework that aligns therapeutic strategies with the temporal evolution of RA pathophysiology. During acute inflammatory phases, nanozyme platforms integrate catalytic performance optimization, targeted delivery mechanisms, and synergistic anti-inflammatory interventions to rapidly neutralize oxidative stress and disrupt inflammatory cascades before irreversible damage occurs. In chronic destructive phases, therapeutic approaches combine sustained catalytic activity, precision targeting of established pathological structures, and multifunctional integration to concurrently suppress residual inflammation and promote tissue regeneration. This review compares nanozyme therapeutics with established RA treatments, including disease-modifying antirheumatic drugs and biological agents, to clarify their potential clinical positioning. Key challenges for clinical translation include long-term safety characterization; pharmacokinetic evaluation, particularly for intra-articular delivery; regulatory pathway development; and manufacturing scalability. Overall, this review establishes a stage-oriented nanozyme therapeutic framework aligned with RA progression patterns and provides translational guidance for developing nanozyme therapeutics tailored to individual pathological characteristics in RA management.

Keywords: Rheumatoid arthritis, nanozymes, reactive oxygen species, catalytic nanomaterials, precision medicine

Introduction

Rheumatoid arthritis (RA) affects 0.25–1% of the global population and imposes substantial disability burden and economic costs through direct medical expenses and lost productivity.[1,2] Current therapeutic strategies, including disease-modifying antirheumatic drugs (DMARDs), biological agents targeting specific cytokines, and Janus kinase (JAK) inhibitors, have improved outcomes for many RA patients.[3,4] However, these approaches largely employ uniform

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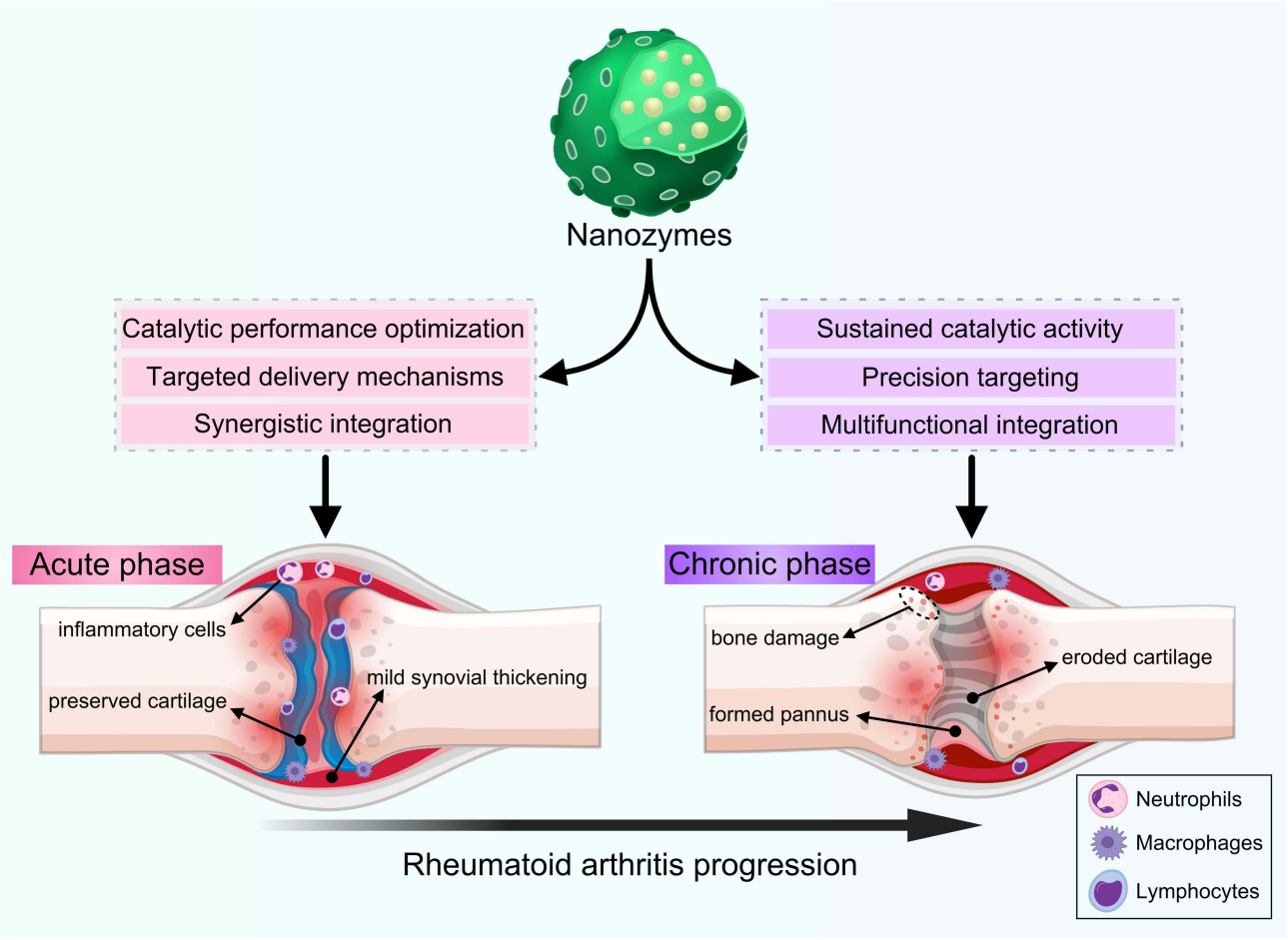
Graphical Abstract



interventions across heterogeneous patient populations without accounting for the distinct pathophysiological states through which RA progresses. The disease evolves from early inflammatory phases characterized by immune hyperactivation and reversible tissue damage to chronic destructive stages marked by irreversible structural alterations, including pannus formation, cartilage erosion, and bone destruction.[5,6] This pathophysiological heterogeneity suggests that therapeutic strategies optimized for one disease stage may prove suboptimal when applied to different stages; yet, clinical practice has traditionally overlooked these temporal variations in favor of standardized treatment protocols. The disconnect between uniform therapeutic approaches and stage-dependent pathological mechanisms may partially explain why substantial proportions of RA patients experience inadequate disease control despite access to advanced medications.[7]

Dysregulated reactive oxygen species (ROS) metabolism represents a mechanistic thread connecting acute and chronic RA pathology, though manifesting through qualitatively distinct patterns at different disease stages.[8,9] During acute inflammatory flares, activated immune cells generate excessive ROS that overwhelm endogenous antioxidant defenses, which creates oxidative bursts that propagate inflammatory cascades and cause direct cellular damage. In chronic RA, persistent oxidative stress continues over extended periods, gradually depleting antioxidant capacity while simultaneously driving inflammatory signaling and matrix degradation. This stage-dependent ROS dysregulation establishes the rationale for enzyme-based therapeutic intervention. Antioxidant enzymes, including superoxide dismutase

(SOD), catalase (CAT), and glutathione peroxidase (GPx), possess the catalytic capacity to restore redox balance by eliminating pathological ROS concentrations.[10]

Natural antioxidant enzymes demonstrate exceptional catalytic efficiency; yet, the harsh inflammatory microenvironment of affected joints in RA presents conditions that rapidly inactivate these protein-based catalysts.[11,12] The synovial fluid of inflamed joints maintains acidic conditions. Elevated proteolytic enzymes, including matrix metalloproteinases (MMPs) and cathepsins, reach concentrations far exceeding those in healthy tissue.[13,14] Studies demonstrate that recombinant antioxidant enzymes exhibit substantially reduced activity when maintained in simulated RA synovial fluid.[15] These stability limitations would necessitate frequent intra-articular injections to maintain therapeutic concentrations, raising concerns about injection-related joint damage, patient compliance, and immunogenicity.[16,17] The discovery that iron oxide nanoparticles possess intrinsic peroxidase-like catalytic activity proved transformative. The catalytic function arose from robust crystal structure rather than precise protein folding.[18] This finding established that inorganic nanomaterials could exhibit enzyme-like functions while maintaining stability under conditions that rapidly denature natural enzymes. Following this discovery, the nanozyme field expanded across multiple material classes, including cerium oxide (CeO_2), platinum nanoparticles, carbon-based nanomaterials, and metal–organic frameworks (MOFs).[19–22] The distinctive properties of nanozymes create opportunities for stage-oriented therapeutic strategies that rationally match platform characteristics to evolving pathophysiological demands in RA.

The growing body of nanozyme research for RA has made valuable contributions to understanding material properties, catalytic mechanisms, and anti-inflammatory applications. Previous reviews have comprehensively cataloged nanozyme material types and elucidated fundamental catalytic principles relevant to inflammatory diseases. However, these discussions have generally organized therapeutic strategies around material classifications or catalytic mechanisms rather than disease progression patterns. Given that RA evolves through distinct pathophysiological states with fundamentally different therapeutic requirements, this review adopts a complementary organizational approach for nanozyme therapeutic strategies around the temporal evolution of RA pathophysiology, recognizing that optimal nanozyme design varies with disease stage and enables rational matching of platform characteristics to evolving pathological demands. We first establish distinct pathological signatures characterizing acute inflammatory and chronic destructive phases while providing criteria for stage identification. Subsequently, we present representative nanozyme platforms designed for acute inflammatory phase intervention and those addressing chronic destructive phase challenges, demonstrating how material properties, delivery mechanisms, and therapeutic integration strategies adapt to stage-dependent pathological demands. Finally, we discuss key challenges confronting clinical translation and future research directions that could accelerate progression toward clinical implementation. These platforms potentially offer RA patients more effective treatment options matched to their individual disease characteristics.

Disease Staging and Characterization of RA

RA progresses through distinct pathophysiological states that necessitate different therapeutic approaches. Traditional clinical staging systems, such as the American College of Rheumatology functional classification, provide prognostic information but present limitations for guiding mechanism-based interventions.[23] These classifications primarily reflect cumulative structural damage and symptom severity but do not capture the underlying biological processes actively driving RA at specific timepoints. For therapeutics targeting pathological mechanisms, including oxidative stress, hypoxia, and matrix degradation, a framework oriented toward disease mechanisms offers greater therapeutic relevance than duration-based or symptom-based classifications.[24] The distinction between acute inflammatory and chronic destructive phases in RA rests primarily on reversibility potential rather than disease duration.[25] Acute phase damage results predominantly from inflammatory mediators whose direct effects can substantially resolve once inflammation subsides. In contrast, chronic phase damage stems from established structural alterations, including formed pannus, eroded cartilage, and destroyed bone, that persist despite inflammatory control.[26,27] This qualitative difference in pathological mechanisms establishes the foundation for stage-oriented therapeutic strategies. Clinical implementation

faces challenges in accurately identifying disease stage in individual RA patients, where multiple joints may simultaneously exist in different pathological states.

Acute Inflammatory Phase Pathology

The acute inflammatory phase represents immune system hyperactivation characterized by explosive cellular and molecular responses.[28] Loss of self-tolerance triggers abnormal T cell recognition of modified self-antigens, particularly citrullinated proteins generated through posttranslational modification. Activated T cells stimulate B cell proliferation, driving the production of rheumatoid factor and anticitrullinated protein antibodies that form immune complexes depositing in synovial tissue and activating complement cascades.[29] Proinflammatory cytokine concentrations in synovial fluid increase markedly compared with serum levels within days of onset, followed by massive inflammatory cell infiltration, with neutrophils and M1 macrophages comprising the majority of infiltrating populations. Synovial fluid leukocyte counts rise substantially during peak inflammation, with neutrophils accounting for the predominant cellular component.[30]

Activated neutrophils undergo respiratory burst and produce superoxide anion ($O_2\bullet^-$) through nicotinamide adenine dinucleotide phosphate oxidase at rates exceeding normal tissue antioxidant capacity.[31] This superoxide rapidly dismutates to hydrogen peroxide (H_2O_2), which can be further converted to highly reactive hydroxyl radicals (•OH) through Fenton chemistry. Vascular responses amplify this oxidative stress through endothelial cell upregulation of adhesion molecules, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Vascular permeability increases through vascular endothelial cadherin (VE-cadherin) disruption and tight junction disassembly, facilitating continued immune cell infiltration.[32] The synovial lining layer exhibits mild-to-moderate hyperplasia while maintaining relatively regular cellular arrangement. Fibroblast-like synoviocytes (FLSs) and macrophage-like synoviocytes proliferate in response to growth factors and cytokines and establish vascular networks that differ qualitatively from the dense, disorganized neovascular networks characteristic of chronic pannus tissue.[33]

Cartilage and bone structural integrity remains largely preserved during this phase, which creates the therapeutic window that distinguishes acute from chronic RA.[34] Cartilage surfaces may exhibit mild edema and superficial proteoglycan depletion; however, chondrocyte arrangement remains undisturbed. Stratification persists intact, and the tidemark separating calcified from uncalcified cartilage remains visible. Subchondral bone plates maintain continuity. Trabecular architecture remains organized. Osteoclast activity, while potentially elevated, does not produce visible erosions.[35] This preservation of structural integrity means that effective suppression of acute inflammation before irreversible tissue destruction occurs can potentially prevent progression to chronic destructive RA. The precise timing of this therapeutic window varies considerably among RA patients and even among different joints within individual patients, which complicates clinical decision-making regarding intervention intensity and timing. In commonly used RA animal models, acute inflammation manifests within defined temporal windows that vary with model type: collagen-induced arthritis typically demonstrates acute inflammation during days 21–28; adjuvant-induced arthritis shows acute inflammation during days 7–14; and K/BxN serum transfer models exhibit acute inflammation during days 3–7. These compressed timescales may not accurately reflect the more prolonged and variable acute phases observed in human RA. These model-specific temporal patterns provide experimental frameworks for evaluating acute-phase therapeutics but require careful interpretation when extrapolating to human RA.[36] Such fundamental differences between RA animal models and human RA progression underscore the importance of understanding stage-specific pathophysiology when translating preclinical findings to clinical applications.

Chronic Destructive Phase Pathology

The chronic destructive phase emerges when persistent inflammation drives irreversible tissue destruction through mechanisms qualitatively distinct from acute injury. Pannus formation represents the pathological hallmark of this transition.[37] This invasive tissue comprises hyperplastic FLS exhibiting characteristics including autonomous proliferation independent of external growth signals, apoptosis resistance through upregulated antiapoptotic proteins, and tissue invasion capacity through matrix-degrading enzyme production. The synovial lining layer thickens substantially and

exhibits dense, irregular arrangement with loss of normal tissue architecture. Dense networks of pathological neovessels permeate the tissue, sustained by persistent vascular endothelial growth factor (VEGF) expression and displaying thin walls, irregular caliber, and chaotic spatial arrangement characteristic of pathological angiogenesis.[38] When histological sections clearly demonstrate proliferative synovium contacting cartilage edges with visible surface irregularity or erosion at contact zones, chronic destructive phase establishment becomes unambiguous; however, the precise moment of transition from reversible to irreversible pathology remains difficult to define clinically. Early pannus formation may be detectable by advanced imaging modalities before becoming apparent through conventional assessment methods. Cartilage destruction proceeds through coordinated degradative pathways involving multiple enzyme systems. Matrix metalloproteinases, particularly MMP-3 and MMP-13, cleave type II collagen triple helical structures. Aggrecanases, including a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4) and ADAMTS-5, cleave aggrecan core protein, releasing glycosaminoglycan-rich fragments and depleting the cartilage of its load-bearing macromolecule.[39,40] Histologically, cartilage transitions from smooth intact surfaces to irregular topography and develops progressive fibrillation, vertical fissures extending from superficial to deep zones, and focal areas of complete loss exposing underlying bone. Safranin O staining intensity diminishes as proteoglycan content decreases. Chondrocytes undergo phenotypic transformation from anabolic states maintaining matrix homeostasis to catabolic states expressing elevated matrix-degrading enzymes. Chondrocyte spatial organization becomes disrupted with loss of normal zonal architecture; cell clusters appear, representing clonal proliferation; and empty lacunae increase in frequency, indicating cell death.[41,42] Once cartilage degradation reaches this advanced state, reversal becomes impossible given the limited regenerative capacity of adult articular cartilage. The exact threshold beyond which regeneration fails remains incompletely defined and may vary based on patient age, genetic factors, and metabolic status.

Bone erosion provides definitive evidence of chronic destructive phase establishment and represents another critical destructive process determining disability outcomes in RA.[43] Imbalanced receptor activator of nuclear factor kappa B ligand (RANKL) to osteoprotegerin (OPG) ratios, driven by inflammatory cytokines and T cell-derived factors, lead to excessive osteoclast differentiation and activation.[44] Mature osteoclasts attach to bone surfaces through integrin-mediated adhesion and form sealed compartments beneath ruffled borders where they secrete hydrochloric acid, dissolving mineral, and cathepsin K, degrading organic matrix. Bone erosion initiates at bare areas at cartilage–bone junctions. Initial focal defects gradually expand and coalesce as osteoclastic activity continues. After subchondral plate integrity breaches, inflammation extends into underlying bone marrow, which causes trabecular resorption and local bone density decrease.[45] Subchondral bone plates display focal discontinuities or larger defects, and originally dense compact bone becomes porous and irregular. Bone surfaces exhibit characteristic resorption lacunae appearing as scalloped concavities, frequently with multinucleated osteoclasts visible within these depressions.[46] The progression from initial marginal erosions to extensive bone destruction follows variable time courses among RA patients and is influenced by factors such as autoantibody profiles, genetic susceptibility markers, and concurrent metabolic bone disease. This variability complicates prognostic prediction based solely on disease duration. In RA animal models, the chronic destructive phase typically emerges beyond these acute windows: collagen-induced arthritis progresses to chronic destruction beyond day 28; adjuvant-induced arthritis enters chronic phases beyond day 21; and K/BxN serum transfer models develop chronic features beyond day 10. These timelines provide experimental benchmarks but exhibit less variability than the heterogeneous progression patterns observed in human RA, which emphasizes the importance of individualized stage assessment rather than relying solely on temporal criteria for therapeutic decision-making.

Stage-Specific Pathological Signatures and Identification Criteria

The pathological differences between acute inflammatory and chronic destructive phases in RA manifest across multiple diagnostic dimensions that collectively enable stage identification, although no single criterion provides absolute discrimination. Histopathological examination provides the most definitive assessment. Acute-phase tissue displays massive inflammatory cell infiltration with neutrophil predominance, mild-to-moderate synovial hyperplasia maintaining regular architecture, preserved cartilage stratification with an intact tidemark, and continuous subchondral bone without erosions. Chronic-phase tissue exhibits marked synovial hyperplasia with irregular cellular arrangement, pannus formation contacting cartilage surfaces, cartilage fibrillation with proteoglycan depletion, and bone erosions characterized by

osteoclast-lined resorption lacunae. The presence of pannus contacting cartilage with visible surface irregularity serves as a definitive marker of chronic-phase establishment. However, obtaining tissue for histological examination requires invasive procedures that may not be clinically feasible in all RA patients.

Imaging modalities offer complementary information with varying sensitivity for early pathological changes in RA. In the acute phase, radiography typically reveals only soft-tissue swelling without bone alterations, whereas in the chronic phase, it demonstrates cortical discontinuities and joint space narrowing. Micro-computed tomography (micro-CT) detects quantifiable erosion volumes and reduced bone volume fraction during chronic destruction while preserving sensitivity to bone microarchitecture during acute inflammation. Magnetic resonance imaging (MRI) detects synovial enhancement without formed pannus in acute RA. Chronic RA displays cartilage defects and enhancing pannus tissue invading the cartilage. Interpretation of imaging findings requires consideration that inflammatory synovitis and early pannus formation exist on a continuum rather than as discrete states, potentially creating diagnostic ambiguity during transitional periods. This continuous nature of RA progression necessitates integration of multiple imaging modalities with clinical and laboratory parameters for accurate stage determination.

Molecular biomarker profiles further distinguish RA disease phases, although considerable overlap exists between stages. Acute inflammation features elevated concentrations of tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6); increased myeloperoxidase and neutrophil elastase, reflecting neutrophil activation; and increased acute-phase reactants, including C-reactive protein (CRP) and serum amyloid A. The chronic phase exhibits sustained but moderate cytokine levels, markedly elevated MMP-3 and MMP-13 indicating active matrix degradation, an increased RANKL-to-OPG ratio reflecting osteoclast activation, persistently elevated VEGF supporting pathological angiogenesis, and elevated vimentin and alpha-smooth muscle actin (α-SMA) marking fibroblast transformation. The distinguishing features across pathological dimensions are synthesized in Table 1, which presents comparative characteristics relevant for stage identification and their implications for therapeutic objectives. This comprehensive characterization framework enables clinicians and researchers to assess RA disease stage through integration of

Table 1 Comparative Features of Acute Inflammatory and Chronic Destructive Phases in RA

Dimension	Acute Inflammatory Phase	Chronic Destructive Phase
Dominant Pathological Process	Reversible immune hyperactivation with neutrophil respiratory burst and cytokine storm	Irreversible structural destruction with autonomous pannus invasion and osteoclast-driven bone erosion
Histopathological Features	Massive inflammatory infiltrate with neutrophil predominance; synovial hyperplasia with regular arrangement; preserved cartilage; continuous bone	Marked synovial hyperplasia with irregular arrangement; pannus contacting cartilage; cartilage fibrillation; bone erosions with osteoclast-lined lacunae
Imaging Features	Radiography shows soft tissue swelling only; micro-CT reveals preserved bone structure; MRI demonstrates synovial enhancement without formed pannus	Radiography shows cortical discontinuities and narrowed joint space; micro-CT reveals reduced bone volume with erosions; MRI demonstrates cartilage defects and enhancing pannus
Molecular Biomarker Profile	Elevated TNF-α, IL-1β, and IL-6; high myeloperoxidase and neutrophil elastase; elevated acute phase reactants	Sustained moderate cytokines; markedly elevated MMP-3 and MMP-13; increased RANKL/OPG ratio; persistently elevated VEGF
ROS Generation Pattern	Explosive burst from neutrophil respiratory activity exceeding endogenous capacity	Sustained moderate elevation from activated macrophages and transformed fibroblasts
Structural Reversibility	Tissue damage potentially reversible with effective inflammatory suppression	Structural alterations including formed pannus and eroded tissue are irreversible

(*Continued*)

Table 1 (Continued).

Dimension	Acute Inflammatory Phase	Chronic Destructive Phase
Typical Temporal Windows in Animal Models	Collagen-induced arthritis: days 21–28; Adjuvant-induced arthritis: days 7–14; K/BxN serum transfer: days 3–7	Collagen-induced arthritis: beyond day 28; Adjuvant-induced arthritis: beyond day 21; K/BxN serum transfer: beyond day 10
Therapeutic Objectives	Rapid suppression of inflammatory amplification to prevent transition to irreversible destruction	Protection of remaining tissue from ongoing degradation; creation of microenvironments permitting limited repair

histopathological, imaging, and molecular parameters, thereby facilitating implementation of stage-oriented therapeutic strategies.

The fundamental distinction between these phases in RA rests on reversibility potential rather than temporal progression alone. Acute-phase pathology results from inflammatory mediators whose effects can substantially resolve once inflammation is controlled, creating opportunities for tissue recovery if intervention occurs before structural damage accumulates. Chronic-phase pathology stems from established architectural alterations that persist independent of ongoing inflammation intensity, necessitating therapeutic approaches focused on halting progression rather than reversing established damage. This qualitative difference establishes the foundation for stage-oriented therapeutic strategies. Clinical application must account for the reality that RA disease stage exists on a continuum rather than as discrete categories, and individual RA patients may exhibit mixed features that complicate straightforward classification. Understanding this continuum is essential for developing flexible therapeutic algorithms that can adapt to the heterogeneous presentations encountered in clinical practice. This multidimensional characterization framework provides a theoretical foundation for patient stratification when nanozyme platforms advance to clinical evaluation. Integration of histopathological, imaging, and molecular biomarker information could guide matching of stage-appropriate therapeutic strategies to individual disease characteristics. However, specific diagnostic thresholds and clinical decision algorithms require prospective validation, as the current framework derives primarily from animal model observations and pathophysiological reasoning.

Evolution and Therapeutic Potential of Nanozymes

Dysregulated ROS metabolism pervades the RA disease continuum, manifesting as explosive oxidative bursts during acute inflammation and persistent low-grade oxidative stress in chronic disease.[47] This stage-dependent ROS dysregulation establishes the rationale for enzyme-based therapeutic intervention, as antioxidant enzymes possess the catalytic capacity to restore redox balance.[48] However, the harsh inflammatory microenvironment of affected joints, characterized by acidic pH and high concentrations of proteolytic enzymes, rapidly inactivates natural protein enzymes. The evolution from natural enzymes through artificial mimics to nanomaterials with enzyme-like catalytic activities represents progressive attempts to preserve catalytic function while eliminating stability limitations, with each generation addressing specific shortcomings of its predecessors.[49–52] This evolutionary trajectory has culminated in nanozyme platforms that combine catalytic efficiency approaching that of natural enzymes with the environmental stability necessary for therapeutic applications in inflammatory diseases.

Evolutionary Trajectory from Natural Enzymes to Nanozymes

Natural antioxidant enzymes, including SOD, CAT, and GPx, possess exceptional catalytic efficiency. SOD catalyzes $O_2^{\bullet-}$ disproportionation at near diffusion-limited rates, while CAT decomposes H_2O_2 with remarkable efficiency approaching one million turnovers per second; however, the protein nature of these enzymes imposes fundamental barriers to therapeutic application in inflammatory environments. The synovial fluid of inflamed joints maintains acidic conditions compared with physiological pH, while proteolytic enzymes, including MMPs, neutrophil elastase, and cathepsins, reach concentrations far exceeding those in healthy tissue. Studies reveal that recombinant human SOD activity declines

substantially when maintained in simulated RA synovial fluid, while natural CAT shows similarly rapid inactivation upon deviation from its optimal pH.[53] These stability limitations would necessitate frequent intra-articular injections to maintain therapeutic concentrations, raising concerns regarding injection-related joint damage, patient compliance, and immunogenicity associated with repeated protein exposure. The short functional half-life of natural enzymes in inflammatory environments fundamentally limits their clinical applicability, regardless of their intrinsic catalytic superiority.

Recognition of these challenges drove efforts to create catalysts that mimic enzyme function without relying on protein structure. Early artificial enzyme research from the 1960s through the 1990s sought to recreate enzymatic catalysis using synthetic molecular scaffolds, including cyclodextrin inclusion complexes, molecularly imprinted polymers, and catalytic antibodies.[54] The discovery of catalytic RNA in 1982 challenged the assumption that enzymatic activity required protein structure, introducing ribozymes capable of catalyzing phosphodiester bond reactions. These artificial enzymes achieved important conceptual advances by demonstrating that catalytic function does not inherently require precise three-dimensional protein structures. However, their practical utility for therapeutic applications remained limited because cyclodextrins, molecularly imprinted polymers, and nucleic acid catalysts still relied primarily on organic macromolecules subject to chemical degradation under harsh conditions. While potentially more stable than proteins in some environments, these materials could not withstand the combination of acidic pH, high proteolytic enzyme concentrations, and oxidative stress characteristic of RA inflammation.[55] Production costs remained high, requiring sophisticated synthesis procedures, and these artificial enzymes offered no fundamental solution to the environmental stability problem that precluded natural enzyme use. The limitations of both natural enzymes and early artificial mimics highlighted the need for catalytic materials with fundamentally different structural bases that could maintain activity under pathological conditions while retaining sufficient catalytic efficiency for therapeutic applications.[56]

The emergence of nanomaterial catalysis represented a qualitative advance beyond previous approaches by demonstrating that inorganic materials with no structural similarity to proteins could exhibit enzyme-like catalytic activities. The 2007 report that iron oxide nanoparticles possess intrinsic peroxidase-like catalytic activity proved transformative, as it required no surface modification or catalytic group conjugation to achieve enzyme activity.[18] The catalytic activity arose from surface iron atoms in multiple oxidation states capable of facilitating electron transfer, a mechanism entirely distinct from the precisely positioned amino acid residues comprising natural enzyme active sites.[57] This mechanistic distinction from protein enzymes conferred significant advantages for therapeutic applications in harsh environments. Catalytic activity did not depend on maintaining precise three-dimensional protein folding stabilized by weak noncovalent interactions but instead arose from the robust crystal structure of the iron oxide lattice and surface chemistry determined by inorganic bonding.[58] Iron oxide nanoparticles maintained peroxidase-like activity for extended periods under conditions simulating RA synovial fluid, whereas natural horseradish peroxidase lost activity within hours under identical conditions.[59] The inorganic nature of these materials rendered them immune to proteolytic degradation, as proteases evolved to cleave peptide bonds cannot attack metal–oxygen bonds in the iron oxide lattice.[60] This fundamental stability advantage, combined with retained catalytic function, established nanomaterials as viable alternatives to natural enzymes for applications in harsh biological environments where protein-based catalysts rapidly lose function.

Following this discovery, nanozyme research expanded across multiple material classes and catalytic activities, as illustrated in Figure 1. Cerium oxide nanoparticles demonstrated both SOD-like and CAT-like activities through reversible cycling between Ce^{3+} and Ce^{4+} oxidation states, with the ratio of these oxidation states tunable through synthesis conditions to optimize specific catalytic profiles.[61] Platinum nanoparticles exhibited efficient CAT-like activity, decomposing H_2O_2 through surface-mediated reactions with turnover rates approaching those of natural CAT.[62] Carbon-based nanomaterials, including graphene derivatives and carbon nanotubes, joined the expanding nanozyme family, with catalytic activities often enhanced through heteroatom doping that introduces nitrogen, sulfur, or phosphorus into the carbon framework.[63,64] MOFs and Prussian blue analogs demonstrated multiple enzyme-like activities arising from their ordered metal node structures, with the periodic arrangement of catalytic sites mimicking the active-site architecture of natural metalloproteases.[65,66] This nanomaterial diversity created opportunities for rational matching of material properties to disease-specific requirements, addressing the stability challenges that prevented natural enzyme application while offering tunable catalytic properties and multifunctional integration capabilities unavailable with protein-based systems.

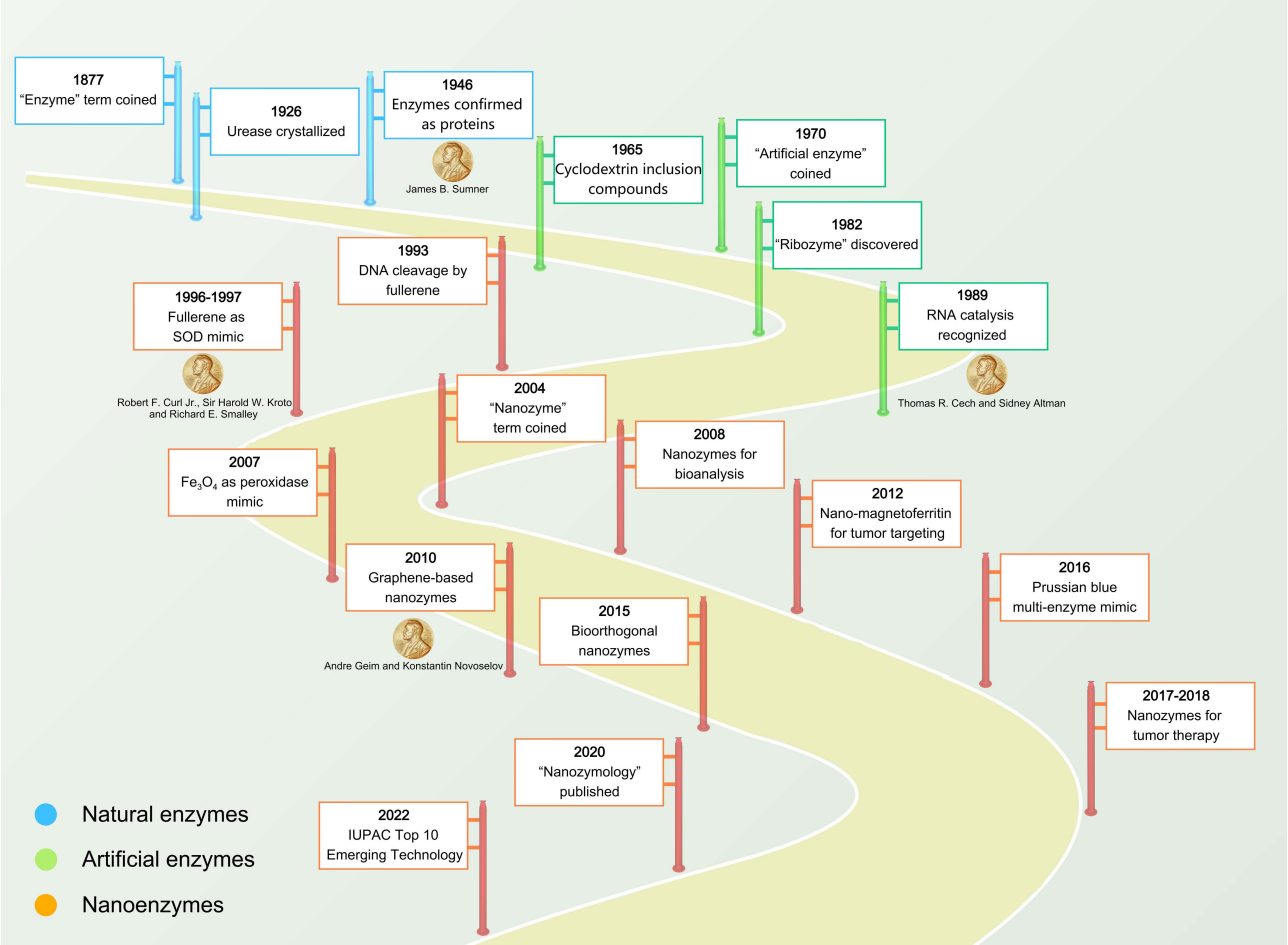


Figure 1 Evolutionary timeline of enzyme development from natural enzymes to nanozymes. This figure was created using MedPeer (medpeer.cn).

The expanding repertoire of nanozyme materials has provided researchers with a rich toolkit for designing therapeutic platforms tailored to the specific pathophysiological demands of different disease stages in RA.

Therapeutic Advantages of Nanozymes for Stage-Oriented RA Treatment

The distinctive properties of nanozymes address critical challenges posed by RA pathophysiology in ways that natural enzymes or conventional pharmaceuticals cannot match.[67] Nanozyme stability enables substantially reduced dosing frequency compared with natural enzymes, with single administrations potentially providing therapeutic coverage for extended periods depending on clearance kinetics and disease severity.[68] For chronic-phase applications requiring sustained long-term ROS management, this stability advantage is particularly valuable, as infrequent dosing is far more feasible than the repeated injections necessary to maintain effective concentrations of rapidly degrading natural enzymes in the inflammatory joint environment.[69]

The tunability of nanozyme properties through materials engineering enables optimization for stage-specific therapeutic requirements.[70] Size control represents a powerful parameter with direct implications for matching catalytic profiles to disease-phase demands. Modulation of cerium oxide particle size produces variation in the SOD-to-CAT activity ratio spanning substantial ranges. Smaller particles exhibit SOD activity exceeding CAT activity due to higher surface Ce^{3+} ratios characteristic of ultrasmall particles with high surface-to-volume ratios, whereas intermediate-sized particles show balanced SOD and CAT activities.[71] This size-dependent catalytic profile modulation enables rational design suited to the distinct ROS profiles characterizing acute versus chronic RA phases. Heteroatom doping of carbon-based nanozymes provides another dimension of tunability. Nitrogen-doped graphene quantum dots with varying

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nitrogen content achieve modulation of peroxidase-like activity across wide ranges, with low-doping formulations exhibiting modest activity and high-doping formulations providing enhanced catalytic activity.[72] This tunability enables formulation optimization that balances therapeutic efficacy against potential perturbation of physiological ROS involved in normal cellular signaling. Surface modification strategies further expand the design space, allowing incorporation of targeting ligands, stealth coatings, or pH-responsive elements that modulate activity based on local microenvironmental conditions.[73] The ability to rationally adjust catalytic profiles through synthetic parameter modification represents a capability unattainable with fixed natural enzyme structures, enabling matching of nanozyme properties to the fundamentally different requirements of acute inflammatory suppression versus chronic tissue protection in RA treatment.

Nanozyme platforms accommodate multifunctional integration, addressing the reality that RA pathology extends beyond oxidative stress alone to encompass metabolic dysregulation, pathological angiogenesis, and structural tissue damage.[74] Single-target pharmaceuticals typically address only one aspect of this complex pathophysiology, necessitating combination therapies to achieve disease control. The intrinsic properties of certain nanozymes provide built-in multifunctionality without requiring additional components.[75] Iron oxide nanozymes combine peroxidase-like catalytic activity with superparamagnetism, enabling MRI contrast and magnetic field–guided targeting.[76] Gold nanozymes exhibit surface plasmon resonance properties alongside oxidase- and peroxidase-like activities, enabling the integration of photothermal capabilities with catalytic therapy.[77] Beyond intrinsic multifunctionality, nanozyme platforms accommodate loading or conjugation of pharmaceutical agents through surface modification with polymers or lipids to create drug-encapsulating shells or through incorporation within porous structures such as MOFs, where release kinetics become controllable through framework composition and pore architecture.[78] Integration of nanozymes into tissue engineering scaffolds enables combination of sustained antioxidant protection with structural support for residual cartilage and creation of microenvironments conducive to limited repair in damaged regions.[79]

The advantages of nanozymes for RA treatment emerge clearly when considering the specific challenges posed by stage-dependent pathophysiology: stability in inflammatory environments addresses the fundamental barrier preventing natural enzyme application in diseased joints; tunability through materials engineering enables optimization for stage-specific demands, with high-efficiency catalysts suited to acute intervention requirements and sustained-activity platforms appropriate for chronic management needs; and capacity for multifunctional integration permits the construction of therapeutic systems that address the complex pathology of RA beyond ROS elimination alone. The diverse material options available provide opportunities for matching nanozyme properties to application requirements across disease stages, establishing the foundation for the stage-oriented therapeutic strategies examined in the following section.

Stage-Oriented Nanozyme Therapeutics for RA

Translating the stage-oriented framework into therapeutic implementation requires matching nanozyme platform characteristics to evolving pathological demands across RA progression. Acute inflammatory and chronic destructive phases present fundamentally different therapeutic requirements, necessitating distinct design strategies. We first examine acute inflammatory phase therapeutics through three complementary approaches. Catalytic performance optimization enables rapid neutralization of burst oxidative stress. Targeted delivery mechanisms ensure therapeutically relevant concentrations at inflammatory foci. Synergistic integration with anti-inflammatory interventions addresses multifaceted pathology beyond oxidative stress alone. We subsequently present chronic destructive phase platforms featuring sustained catalytic activity for long-term protection, precision targeting of established pathological structures including formed pannus and eroded bone, and multifunctional integration combining catalytic therapy with physical ablation and promotion of tissue regeneration. Representative platforms within each category demonstrate how material properties, delivery mechanisms, and therapeutic integration strategies adapt to stage-dependent pathological demands in RA.

Nanozyme Therapeutics in the Acute Inflammatory Phase

Acute inflammatory phase RA generates burst production of ROS that function as critical signaling molecules, amplifying pathological cascades beyond their direct tissue-damaging effects. $O_2\bullet^-$ and H_2O_2 activate nuclear factor kappa B (NF-κB) through oxidation of inhibitory proteins, triggering transcription of proinflammatory cytokine genes including

TNF-α, IL-1β, and IL-6. These ROS simultaneously activate mitogen-activated protein kinase cascades and JAK–STAT pathways that further amplify inflammatory gene expression and perpetuate immune cell recruitment. Oxidative modification of lipids and proteins generates damage-associated molecular patterns that activate pattern recognition receptors, establishing self-sustaining inflammatory loops. Catalytic elimination of ROS at this stage interrupts these signaling cascades before irreversible tissue destruction is established, providing a mechanistic rationale for rapid nanozyme intervention during acute phases.

Catalytic Performance Optimization for Burst ROS Elimination

Acute inflammatory phase RA generates rapid ROS production through neutrophil respiratory burst and macrophage activation. Oxidative stress overwhelms endogenous antioxidant defenses within hours of onset. Nanozyme strategies address this challenge through three approaches of ascending complexity. Single enzymatic activity platforms provide focused catalytic intervention. External energy-activated systems enable spatiotemporal control. Multienzymatic architectures achieve comprehensive ROS network neutralization.

Single enzymatic activity platforms establish foundational catalytic intervention through materials mimicking a single natural antioxidant enzyme. Cerium-based nanozymes exploit reversible Ce^{3+}/Ce^{4+} redox cycling to confer regenerative antioxidant properties. Ce^{3+} oxidation scavenges $O_2\bullet^-$ radicals, while subsequent Ce^{4+} reduction decomposes H_2O_2. This dual reactivity enables continuous ROS elimination without catalyst depletion. By maintaining both oxidation states, cerium-based platforms prevent ROS from reaching concentrations sufficient to activate inflammatory signaling pathways.[80] Cerium-modified gold nanoclusters demonstrated superior ROS-scavenging capacity in preclinical studies. Therapeutic efficacy surpassed methotrexate in downregulating proinflammatory cytokine release. Evaluation in adjuvant-induced arthritis models revealed anti-inflammatory effects mediated through STAT3–IL-6 signaling pathway modulation. Radiographic confirmation showed joint protection.[81,82] These single-enzyme platforms establish the catalytic foundation for ROS elimination.

External energy activation amplifies catalytic efficiency through stimulus-responsive mechanisms that leverage nanomaterial energy-susceptible properties. Near-infrared photothermal activation of $Au@CeO_2$ core-shell structures accelerates hydrogen peroxide decomposition kinetics. Photoacoustic imaging confirms enhanced oxygen production alleviating hypoxic conditions, concurrent with selective thermal ablation of hyperproliferative inflammatory cells.[83] Microwave activation offers superior deep-tissue penetration advantages. MOF nanocomposites containing UiO-66-NH_2 and Mn_3O_4 exploit microwave-susceptible properties to generate therapeutic hyperthermia, triggering CAT-like activity enhancement and pH-sensitive coordination complex dissociation for synergistic antioxidant release (Figure 2a). Dual mechanisms achieve substantial improvements in body weight recovery and ankle thickness reduction through oxygen production relieving joint hypoxia concurrent with thermal catalytic enhancement.[84] Refinements incorporating CeO_2 and celastrol demonstrate that microwave irradiation enhances both SOD-like and CAT-like activities, with nonthermal effects synergistically promoting M1-to-M2 macrophage repolarization, achieving reduced inflammatory infiltration and improved cartilage preservation.[85]

Multienzymatic architectures enable comprehensive ROS network neutralization, addressing the chemical diversity of pathological oxidants including $O_2\bullet^-$ radicals, H_2O_2, •OH, and peroxynitrite.[72] Triple-enzyme systems based on PtPdCo-CQ nanocatalysts achieve hierarchical scavenging through coordinated SOD, CAT, and peroxidase mimetic activities, enabling sequential catalytic processing with minimized diffusion limitations (Figure 2b). Controlled chloroquine release further inhibits autophagy-dependent ferroptosis in M2 macrophages, providing sustained anti-inflammatory effects. Validation in collagen-induced arthritis models reveals substantial clinical score reductions and prevention of cartilage destruction exceeding those of single-enzyme counterparts.[86] Dual-component combinations provide alternative synergy pathways. Manganese ferrite– and ceria–co-decorated mesoporous silica achieves functional complementarity, wherein manganese ferrite generates oxygen through Fenton-like reactions while ceria scavenges intermediate •OH, effectively downregulating hypoxia-inducible factor-1α and facilitating macrophage phenotype transition.[87] This cooperative mechanism enables efficient hydrogen peroxide decomposition while minimizing accumulation of toxic •OH intermediates, thereby addressing a critical limitation of single-component oxygen-generating nanozymes and demonstrating superior therapeutic outcomes in preclinical arthritis models.

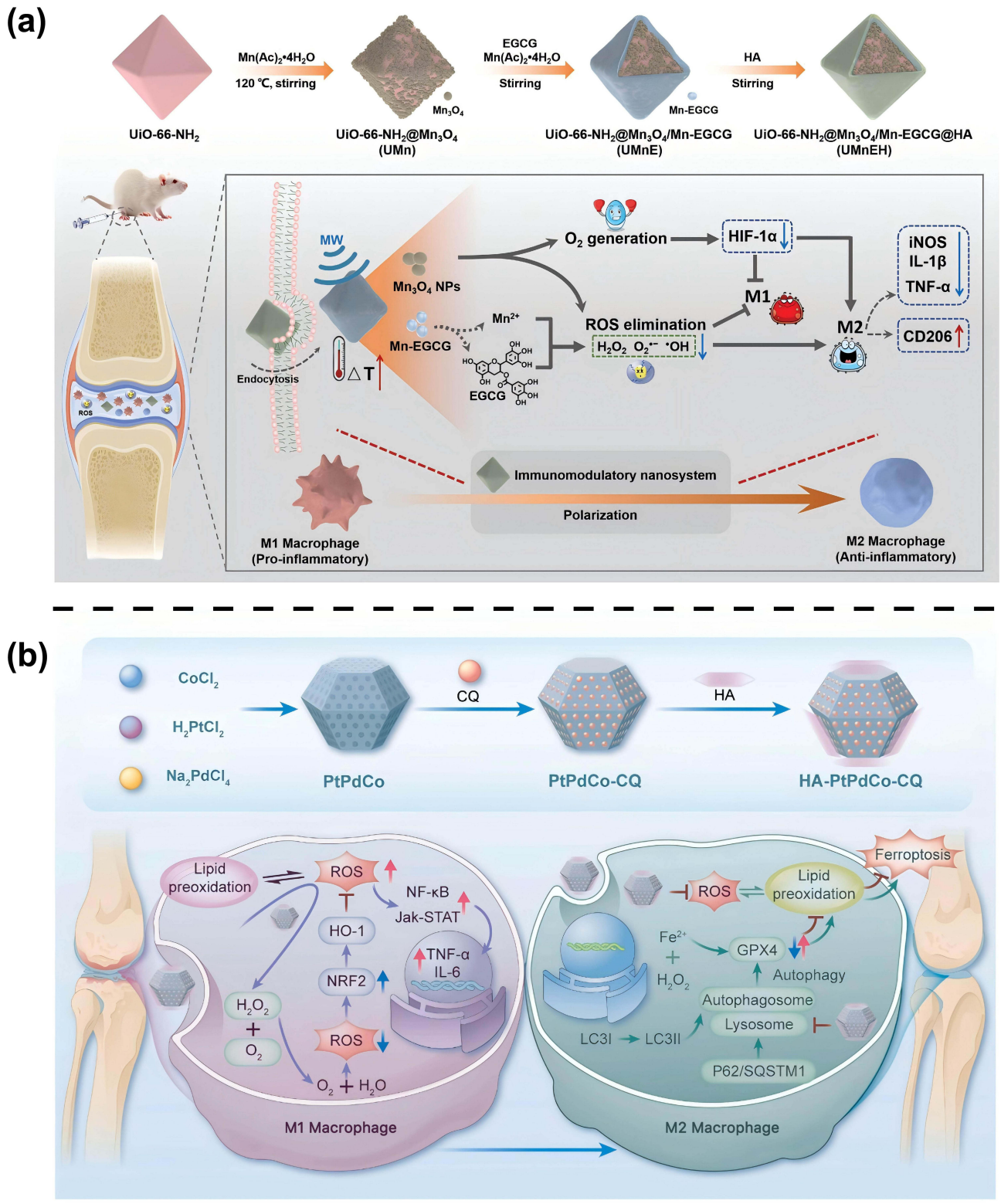

Figure 2 Catalytic performance optimization for burst ROS elimination during the acute inflammatory phase of RA. (**a**) Microwave-activated UiO-66-NH_2/Mn_3O_4/EGCG nanocomposites for enhanced catalytic therapy 84 ↑, upregulation; ↓, downregulation. Copyright 2023, Wiley-VCH. (**b**) Triple-enzyme HA-PtPdCo-CQ nanocatalysts for hierarchical ROS scavenging 86 ↑, upregulation; ↓, downregulation. Copyright 2025, Elsevier.

Mechanistically distinct approaches expand catalytic intervention beyond traditional antioxidant enzyme mimicry. Palladium-based nanozyme platforms function as hydrogen generators under near-infrared activation. Released molecular hydrogen acts as an adaptive immunomodulator, inducing tolerogenic dendritic cells to generate regulatory T cells. This rebalances the dysregulated Th17/Treg ratio characteristic of acute RA.[88] This approach offers long-term immunomodulatory benefits extending beyond immediate ROS neutralization to achieve broader immune regulation. Advanced metal–semiconductor heterostructure platforms integrate photodriven hydrogen evolution with CAT-like activity for synergistic dual-gas delivery. This combination effectively reduces inflammation and oxidative damage in RA models.[89] Collectively, these diverse strategies converge to interrupt oxidative inflammatory cascades before irreversible tissue damage accumulates. Single-enzyme focused intervention provides targeted catalytic activity. Energy-activated spatiotemporal control enables precise therapeutic activation. Multienzymatic comprehensive neutralization achieves broad ROS elimination. Alternative catalytic pathways offer mechanistically distinct therapeutic approaches.

Targeted Delivery to Inflammatory Foci

Therapeutic efficacy in acute RA depends critically on achieving sufficient nanozyme concentrations within inflamed tissues despite physiological barriers. These barriers include synovial membrane impermeability, rapid systemic clearance, and heterogeneous inflammation distribution across multiple joints. Contemporary targeting strategies have evolved from passive accumulation to active recognition of pathological signatures. Surface receptor engagement enables selective cellular uptake. Subcellular localization mechanisms direct nanozymes to specific organelles. Microenvironment-responsive activation triggers therapeutic release at disease sites. Collectively, these approaches address hierarchical delivery barriers from circulation to intracellular therapeutic targets. Surface receptor targeting exploits characteristic membrane protein upregulation on activated inflammatory cells to achieve selective nanozyme accumulation. Folate receptor-α exhibits substantial overexpression on activated M1 macrophages during inflammatory responses. Folic acid–modified systems achieve selective accumulation through receptor-mediated endocytosis, demonstrating preferential uptake compared with quiescent cells.[90] Integration of folic acid modification with hydrogen peroxide–driven mesoporous silica nanomotors combines autonomous propulsion with M1 macrophage–specific targeting. Autonomous propulsion enhances tissue penetration, while catechol group incorporation provides complementary cartilage adhesion, prolonging joint retention for sustained catalytic activity at tissue degradation sites. This dual-targeting strategy achieves substantial reductions in joint swelling, synovial inflammation, and bone erosion in adjuvant-induced arthritis models.[91] Alternative receptor-targeting strategies exploit CD44 overexpression through hyaluronic acid modification. Natural CD44 affinity facilitates selective inflammatory cell binding while simultaneously activating antioxidant pathways and suppressing proinflammatory signaling, demonstrating that material selection can integrate recognition and immunomodulatory functions.[92] Advanced architectures combine multiple recognition modalities to enhance specificity. Biomimetic platforms incorporating macrophage-derived microvesicle camouflage with folate modification achieve dual-level targeting. Natural inflammation-homing properties combine with receptor-mediated recognition. Microvesicle coating confers prolonged circulation while reducing immune clearance, and subsequent folate-mediated binding ensures selective accumulation at inflammatory foci.[93]

Subcellular targeting addresses intracellular pathological processes driving oxidative stress beyond surface receptor engagement. Mitochondrial dysfunction represents a critical pathogenic mechanism in acute RA. Elevated ROS levels and hypoxia induce mitochondrial ROS accumulation, calcium overload, and metabolic dysregulation at primary sites of pathological oxidant generation.[94] Triphenylphosphine modification enables mitochondrial localization through lipophilic cationic properties that facilitate accumulation within the negatively charged mitochondrial matrix. Dual-driven selenium Janus single-atom nanomotors incorporating triphenylphosphine achieve autonomous diffusion into monocyte–macrophage mitochondria. Enhanced GPx catalytic activity efficiently scavenges excessive ROS and reactive nitrogen species while generating oxygen to restore redox balance.[95] Beyond acute ROS scavenging, mitochondrial targeting enables metabolic reprogramming that addresses fundamental energetic dysregulation underlying inflammatory macrophage activation. Nanozyme coatings featuring SOD and CAT activities restore mitochondrial function through efficient hydrogen peroxide–to–oxygen conversion and robust ROS scavenging (Figure 3a). Mitigation of mitochondrial ROS

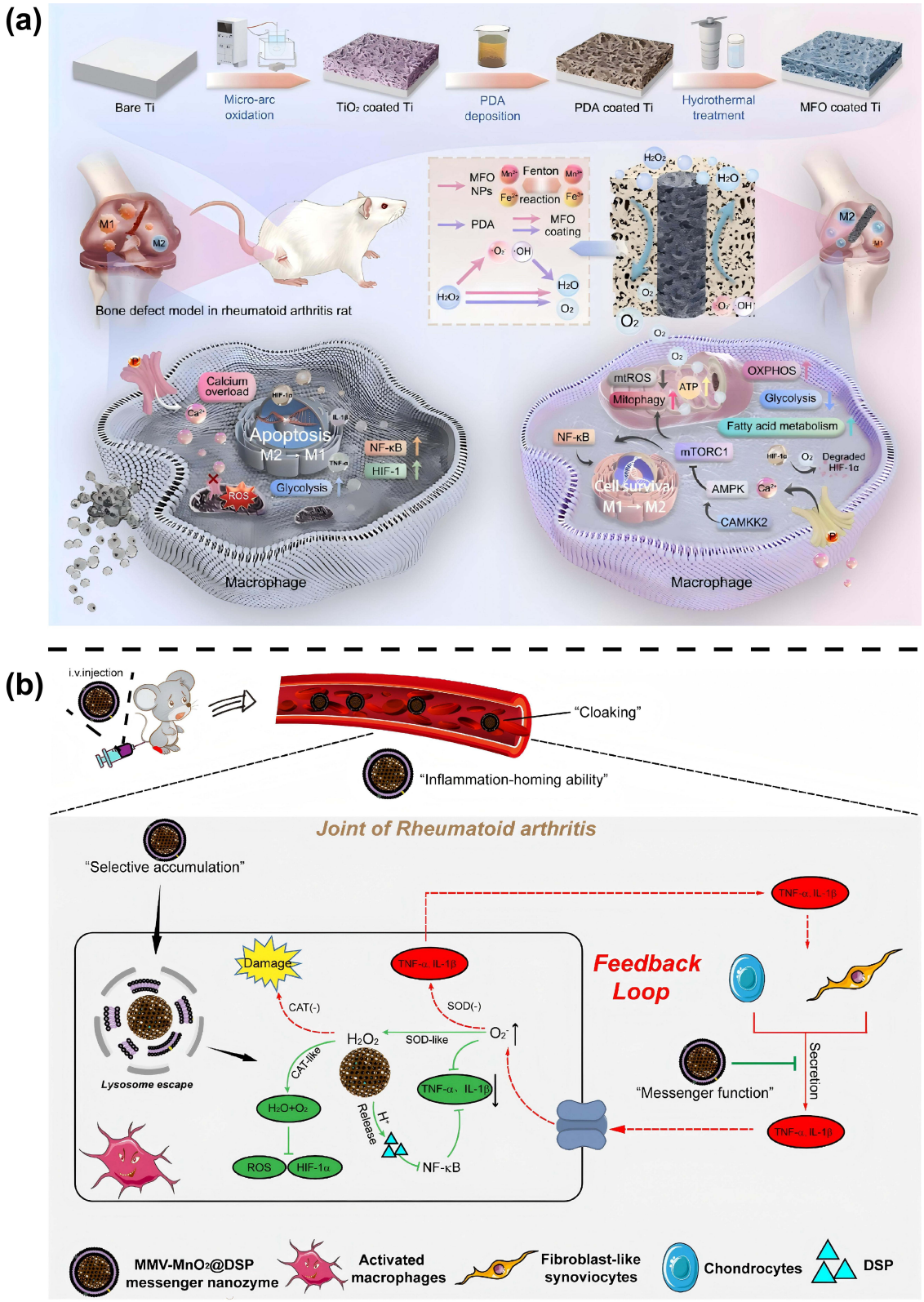

Figure 3 Targeted delivery through subcellular localization and biomimetic camouflage for the acute inflammatory phase of RA. (**a**) Nanozyme coating–mediated mitochondrial metabolic reprogramming 96 ↑, upregulation; ↓, downregulation. Copyright 2025, American Chemical Society. (**b**) Macrophage membrane-cloaked hollow MnO_2 nanozymes for inflammation targeting 100 ↑, upregulation; ↓, downregulation. Copyright 2023, American Chemical Society.

accumulation and intracellular calcium overload activates moderate mitophagy via the calcium–AMPK–mTOR signaling pathway, facilitating removal of dysfunctional mitochondria while preserving mitochondrial dynamics. Restored mitochondria subsequently enable metabolic pathway reprogramming from anaerobic glycolysis to aerobic oxidative phosphorylation, fundamentally altering the energetic state supporting inflammatory macrophage phenotypes and facilitating M2 polarization. These effects enhance osseointegration and improve joint mobility in adjuvant-induced arthritis models.[96]

Microenvironment-responsive strategies exploit distinct physicochemical signatures of inflamed joints for stimulus-triggered nanozyme activation.[97] These signatures include elevated ROS levels, acidic pH, and altered protein expression patterns. ROS-responsive delivery systems employ redox-sensitive linkages that undergo selective cleavage in oxidative environments, enabling targeted payload release at inflammatory sites while maintaining stability during systemic circulation. Representative platforms demonstrate successful M1 macrophage repolarization through cooperative catalytic ROS scavenging and inhibition of inflammatory signaling pathways.[98] pH-responsive mechanisms leverage acidic inflammatory microenvironments for controlled degradation. MOF systems demonstrate selective dissolution at inflammatory pH values, ensuring minimal premature drug loss during circulation and enabling burst release upon joint accumulation.[92] Biomimetic approaches transform traditionally problematic protein adsorption into targeting mechanisms through protein corona engineering. Human serum albumin presaturation reduces macrophage clearance while simultaneously leveraging albumin–SPARC binding for enhanced accumulation at inflammatory sites.[99] Macrophage membrane camouflage represents a sophisticated biomimetic strategy that confers natural inflammation-homing properties through membrane-associated adhesion molecules and chemokine receptors (Figure 3b). Macrophage-derived microvesicle coating of hollow manganese dioxide nanozymes imparts both inflammation-targeting capabilities and messenger functions, promoting cellular uptake by activated macrophages, FLSs, and chondrocytes. This approach effectively inhibits tumor necrosis factor-α and interleukin-1β feedback loops and facilitates macrophage repolarization toward M2 phenotypes. Micro-computed tomography confirms effective interruption of inflammatory progression in collagen-induced arthritis models.[100] The convergence of surface receptor recognition, subcellular localization precision, and microenvironment-responsive activation establishes multifaceted approaches that address hierarchical barriers from systemic circulation through tissue penetration to cellular uptake and subcellular localization, ensuring therapeutically relevant nanozyme concentrations at sites of pathological ROS generation during acute RA.

Synergistic Integration with Anti-Inflammatory Interventions

Contemporary nanozyme platforms integrate catalytic ROS elimination with complementary anti-inflammatory interventions to address the multifaceted pathology of acute RA. Pharmaceutical co-delivery enables simultaneous targeting of distinct pathological pathways, while direct modulation of inflammatory signaling regulates immune responses at the molecular level. Restoration of pathological microenvironmental conditions addresses the fundamental factors sustaining inflammatory progression. Collectively, these integrated approaches achieve comprehensive disease control that exceeds the capabilities of singular catalytic mechanisms.

Pharmaceutical integration enables synergistic therapeutic effects through the simultaneous targeting of distinct pathological pathways. Rapamycin co-delivery with manganese dioxide nanozymes exemplifies this strategy, wherein catalytic ROS elimination is combined with mTOR pathway inhibition to achieve comprehensive inflammatory control. Hydrogen peroxide–driven autonomous propulsion facilitates tissue penetration, while released rapamycin activates autophagy to clear dysfunctional mitochondria, thereby promoting M1-to-M2 macrophage polarization. Degradation products, including silicate ions and manganese ions, further inhibit osteoclastogenesis and promote cartilage regeneration. Methotrexate represents another extensively incorporated disease-modifying antirheumatic drug in nanozyme platforms, and multiple integration strategies demonstrate clear therapeutic advantages.[101] Programmable polymeric microneedle systems enable transdermal codelivery that avoids first-pass hepatic metabolism while achieving controlled release kinetics. These microneedle platforms provide dual functionality through ROS scavenging and manganese ion generation for MRI contrast, enabling real-time therapeutic monitoring alongside anti-inflammatory intervention. Validation in adjuvant-induced arthritis models demonstrates significant inhibition of acute joint inflammation, with

substantial reductions in paw swelling ratios and serum proinflammatory cytokine levels. These findings establish the synergistic benefits of combining chemotherapy with antioxidative therapy in early-stage RA management.[102]

Direct immunomodulatory functions achieved through active regulation of inflammatory signaling extend beyond drug codelivery. Cerium oxide nanozymes integrated with rhein within ROS-responsive hyaluronic acid micelles achieve dual-mechanism suppression, combining catalytic ROS decomposition with inhibition of the TLR4 signaling pathway to prevent amplification of inflammatory cascades. This combination successfully induces M1 macrophage repolarization, accompanied by substantial cytokine modulation and cartilage regeneration.[103] Genetic regulation through DNAzyme integration represents a further advanced approach. Cerium- and vanadium-based MOF nanozymes incorporating miRNA-155–cleaving DNAzymes achieve comprehensive inflammatory suppression through parallel mechanisms. Dual catalytic centers provide relay scavenging of $O_2^{\bullet -}$ radicals and H_2O_2, while DNAzymes simultaneously degrade overexpressed miRNA-155, leading to upregulation of SOCS1, SHIP-1, and Bcl-6 expression and subsequent suppression of proinflammatory cytokine production.[104] Inflammasome pathway targeting offers focused intervention on specific inflammatory mechanisms. Silver nanocomposite–loaded multiwalled carbon nanotube platforms exert anti-inflammatory effects by inhibiting NLRP3 inflammasome activation and reducing caspase-1–mediated prointerleukin-1β processing. CAT activity further enhances antioxidant capacity and protects renal function.[105] Immune tolerance induction through cuproptosis-mediated mechanisms represents an advanced strategy capable of establishing self-sustaining regulatory T cell expansion cycles, potentially enabling long-term RA remission beyond symptomatic control.[106]

Pathological microenvironmental conditions, including hypoxia, acidosis, and metabolic dysregulation, represent both consequences and perpetuators of inflammatory processes, providing a strong rationale for therapeutic strategies that address the fundamental conditions sustaining RA progression.[107] Oxygen generation through catalytic hydrogen peroxide decomposition represents a primary mechanism for alleviating hypoxia. Manganese dioxide– and ceria-based nanozymes demonstrate substantial increases in tissue oxygen saturation by converting abundant pathological hydrogen peroxide into therapeutic oxygen, thereby simultaneously eliminating harmful ROS and mitigating hypoxic conditions that drive hypoxia-inducible factor-1α–mediated inflammatory gene expression and metabolic reprogramming toward glycolytic pathways.[108] Ion-exchange strategies provide sophisticated microenvironmental modulation through in situ generation of bioactive therapeutic complexes. Copper silicate nanoparticles loaded with water-soluble zinc–curcumin exploit pH-responsive degradation in acidic arthritic regions to release copper ions, which subsequently replace zinc through ion-exchange reactions, forming highly antioxidative copper–curcumin complexes with superior ROS scavenging capabilities (Figure 4a). This dynamic transformation addresses oxidative stress in M1 macrophages while promoting transition toward the M2 phenotype. Released silicate components and zinc ions synergistically promote osteoblast biomineralization. Validation in mouse RA models demonstrates substantial alleviation of joint swelling and downregulation of proinflammatory cytokines. Micro-computed tomography confirms considerable bone tissue repair, illustrating how nanozyme platforms can simultaneously address inflammatory pathology and structural tissue restoration through coordinated catalytic and biomineralization mechanisms.[109]

Complementary approaches employ exogenous mitochondrial transfer alongside catalytic ROS scavenging to address fundamental energetic dysfunction underlying inflammatory cell activation. Polymer-modified DNA hydrogels co-delivering Prussian blue nanozymes and living mitochondria achieve comprehensive metabolic restoration through dual mechanisms (Figure 4b). Prussian blue provides exceptional ROS-scavenging capability that mitigates inflammatory responses, while transferred functional mitochondria restore cellular energy metabolism and reduce proinflammatory cytokine production. The DNA hydrogel matrix, modified with polymers to reduce synthesis costs and immunogenicity risks, ensures sustained support during tissue repair with finely tuned degradation kinetics. Validation in collagen-induced arthritis models demonstrates substantial reductions in paw swelling, clinical scores, and proinflammatory cytokine expression, accompanied by promotion of bone regeneration, illustrating the benefits of integrating endogenous ROS reduction with exogenous ROS clearance and metabolic restoration.[110]

The strategies detailed above collectively establish a hierarchical therapeutic framework for intervention during the acute inflammatory phase. Integration of catalytic performance optimization, targeted delivery, and synergistic anti-

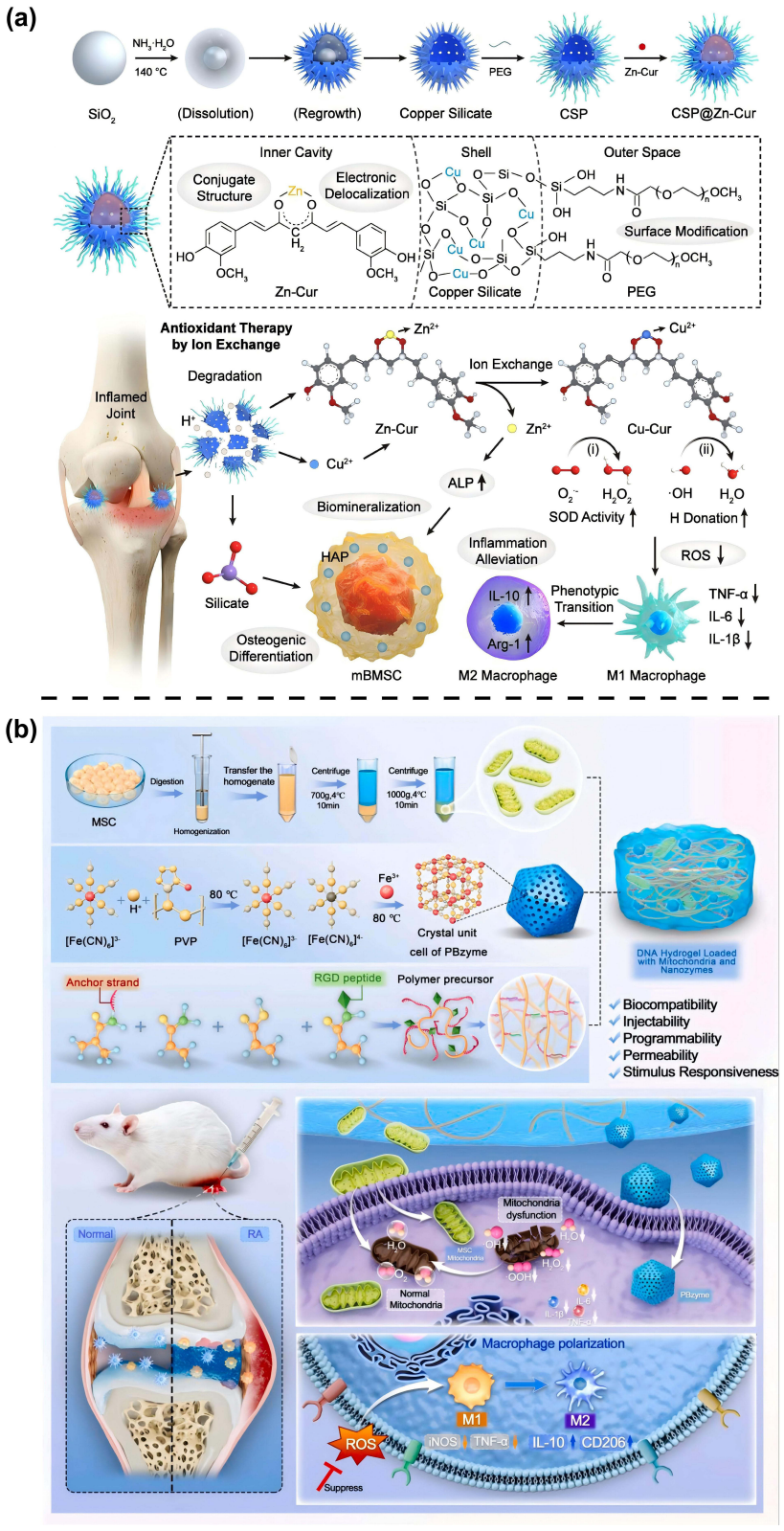

Figure 4 Synergistic integration of catalytic therapy with microenvironmental restoration for the acute inflammatory phase of RA. (**a**) Copper silicate nanoparticles employing an ion-exchange strategy for ROS scavenging and biomineralization 109 ↑, upregulation; ↓, downregulation. Copyright 2023, Wiley-VCH. (**b**) DNA hydrogels co-delivering Prussian blue nanozymes and living mitochondria 110 ↑, upregulation; ↓, downregulation. Copyright 2025, Elsevier.

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inflammatory mechanisms enables effective intervention before irreversible tissue damage accumulates. Catalytic optimization through single enzymatic platforms, external energy activation, and multienzymatic architectures provides foundational ROS elimination capacity to address the burst oxidative stress characteristic of disease onset. Targeted delivery ensures therapeutically relevant concentrations at inflammatory foci through receptor recognition, mitochondrial localization, and microenvironment-responsive activation, thereby overcoming hierarchical biological barriers while maximizing catalytic efficiency. Synergistic integration with pharmaceutical co-delivery, inflammatory signaling modulation, and microenvironmental restoration enables simultaneous intervention across oxidative stress, immune dysregulation, and metabolic dysfunction, interrupting self-amplifying cascades that would otherwise progress toward chronic disease phases. Representative platforms developed according to these principles are documented in Table 2, presenting enzymatic activities, targeting mechanisms, synergistic integrations, and therapeutic outcomes that illustrate the evolution from single-function ROS scavenging toward multifunctional systems capable of addressing the multidimensional pathology of acute RA.

Table 2 Representative Nanozyme Therapeutic Platforms for Acute Inflammatory Phase RA

Therapeutic Strategy	Platform	Nanozyme Component	Enzymatic Activities	Therapeutic Strategy	Key Therapeutic Outcomes	Ref.
Catalytic Optimization	R-DHLA-AuNCs-Ce	Ce-modified AuNCs	SOD/CAT	Passive accumulation	Superior to MTX, IL-6/TNF-α/IL-17↓	[81]
	Cerium oxide NPs	CeO_2 nanoparticles	CAT/SOD	Passive accumulation	Paw volume improved, arthritis scores↓, joints protected	[82]
	Au@CeO_2 core-shell	CeO_2 shell	CAT	Passive accumulation	sO_2↑, bone erosion eliminated	[83]
	UiO-66-NH_2/Mn_3O_4 /EGCG	Mn_3O_4 nanoparticles	CAT	Passive accumulation	Body weight recovery, ankle thickness↓	[84]
	UiO-66-NH_2/CeO_2 /Cel	CeO_2 nanozymes	SOD/CAT	Passive accumulation	Inflammatory infiltration↓, cartilage preserved	[85]
	PtPdCo-CQ nanocatalyst	PtPdCo nanoparticles	SOD/CAT/POD	HA-CD44 receptor targeting	Clinical scores↓, cartilage destruction prevented	[86]
	MFC-MSNs	$MnFe_2O_4$/CeO_2	Fenton/CAT/SOD	MSN drug carrier	Hypoxia improved, inflammation↓, pathological features ameliorated	[87]
	PdH nanocubes	PdH nanoparticles	CAT/SOD	Folic acid targeting	Arthritis index improved, paw thickness↓, Th17/Treg rebalanced	[88]
Targeted Delivery	Rapa-FMn@PMS nanomotors	MnO_2 nanozymes	SOD/CAT	Folic acid-M1 targeting, catechol-cartilage adhesion	Joint swelling↓, synovial inflammation↓, bone erosion↓	[91]
	FPD/MV/MTX@ZIF-8	ZIF-8 framework	pH-responsive release	MV camouflage, folate modification	Arthritis index↓, joint swelling↓, TNF-α/IL-1β↓	[93]
	Pd@MSe-TPP nanomotors	Selenium Janus SAzyme	GPx	TPP-mitochondrial targeting	Oxygen balance restored, cartilage degradation inhibited	[95]
	$MnFe_2O_4$ coating	$MnFe_2O_4$ nanoparticles	SOD/CAT	Implant coating	Osseointegration enhanced, joint mobility improved	[96]

(*Continued*)

Table 2 (Continued).

Therapeutic Strategy	Platform	Nanozyme Component	Enzymatic Activities	Therapeutic Strategy	Key Therapeutic Outcomes	Ref.
	HSA-MnO_2@MTX	Hollow MnO_2	CAT/SOD	HSA-SPARC binding	TNF-α/IL-1β↓, IL-10↑, hyperplasia controlled	[99]
	MMV-MnO_2@DSP	Hollow MnO_2	SOD/CAT	MMV inflammation homing	TNF-α/IL-1β loops inhibited, M2 polarization promoted	[100]
Synergistic Integration	MTX/PDA@MnO_2 microneedles	PDA@MnO_2	ROS scavenging	Transdermal delivery	Paw swelling↓, TNF-α/IL-1β levels↓	[102]
	HA@RH-CeO_x micelles	CeO_X nanozymes	SOD	ROS-responsive thioketal linker	M1:M2 ratio↑, TNF-α/IL-6↓	[103]
	Ce/V-MOF with DNAzymes	Ce/V dual centers	SOD/GPx	Passive accumulation	Bone volume ratio↑, inflammation↓	[104]
	Ag-MWCNT composite	Ag nanocomposites	CAT	Passive accumulation	Arthritic index↓, renal function protected	[105]
	CSP@Zn-Cur	Copper silicate	pH-responsive	Passive accumulation	Joint swelling↓, TNF-α/IL-1β/IL-6↓, bone repair	[109]
	DNA hydrogel/PB/Mito	Prussian blue	ROS scavenging	Polymer-modified hydrogel	Swelling↓, IL-1β/IL-6/TNF-α↓, bone regeneration promoted	[110]
	SOD nanomatrix	Polypropylene sulfide	CAT-mimicking	Folate receptor targeting	IL-6↓, antioxidant activity↑	[111]

Notes: ↑, upregulation; ↓, downregulation.

Abbreviations: ATO, atovaquone; BMCC, Cu-doped ZIF-8 biomimetic complex; BMD, bone mineral density; BV/TV, bone volume/tissue volume ratio; Ce6, chlorin e6; CQ4T, chlorin e6 tetra-tertiary amine; CS-CDs, chitosan-carbon dots; CuAP, Cu-coordinated polyphthalocyanine artificial peroxisomes; HIF-1α, hypoxia-inducible factor-1α; LDHB, lactate dehydrogenase B; MCG NMs, MnO_2-CQ4T-GOx nanomedicines; MCL, mycophenolate; MTX, methotrexate; Nrf2, nuclear factor erythroid 2-related factor 2; OIA, osteoarthritis-induced arthritis; PDA, polydopamine; PIDCT, proton-induced-delayed charge transfer; PMO, periodic mesoporous organosilica; RANKL, receptor activator of nuclear factor kappa-B ligand; SPARC, secreted protein acidic and rich in cysteine; SPX, sparfloxacin; UTMD, ultrasound-targeted microbubble destruction; ZIFC, ZIF-8 pyrolysis-derived carbon.

Nanozyme Therapeutics in Chronic Destructive Phase

Chronic destructive-phase RA exhibits fundamentally different patterns of ROS dysregulation and pathological mechanisms compared with acute inflammation. Persistent moderate oxidative stress over extended periods gradually depletes endogenous antioxidant capacity while driving matrix degradation through sustained activation of matrix metalloproteinases. ROS promote osteoclast differentiation and activation through upregulation of RANKL expression and downregulation of osteoprotegerin in synovial fibroblasts. Oxidative stress also perpetuates the transformed phenotype of FLSs, maintaining autonomous proliferation and tissue-invasive behavior through sustained activation of NF-κB and AP-1 transcription factors. Stabilization of hypoxia-inducible factor-1α under chronic oxidative stress drives pathological angiogenesis that supports pannus expansion. These established pathological structures necessitate sustained antioxidant protection over months to years, precision targeting to reach formed pannus and erosive bone surfaces, and multifunctional interventions that address both residual inflammation and structural repair requirements.

Sustained Catalytic Activity for Long-Term Protection

The transition from acute inflammation to chronic destruction in RA necessitates therapeutic platforms capable of maintaining catalytic efficacy over extended durations. Chronic RA management requires sustained intervention spanning months to years rather than the rapid intervention sufficient for acute phases. Such platforms must simultaneously maintain antioxidant protection against persistent oxidative stress and facilitate tissue regeneration in damaged regions. Unlike acute-phase treatment, which emphasizes rapid interruption of inflammatory cascades, chronic destructive

pathology demands prolonged ROS neutralization to prevent progressive matrix degradation while creating permissive microenvironments for limited structural repair.

Injectable hydrogels incorporating V_2CT_x MXenzyme as protective delivery vehicles for bone marrow–derived mesenchymal stem cells exemplify this approach (Figure 5a). The nanozyme component exhibits SOD-, CAT-, and GPx-like activities, effectively scavenging excessive ROS and reactive nitrogen species while generating oxygen through hydrogen peroxide decomposition. Integration of S-methylisothiourea within the hydrogel network provides additional therapeutic benefits through inhibition of inducible nitric oxide synthase. Together, these mechanisms create a favorable osteoimmune microenvironment conducive to bone regeneration. Therapeutic outcomes in severe rabbit RA models reveal substantial increases in bone volume–to–tissue volume ratios alongside macrophage polarization from the M1 to the M2 phenotype, validating the capacity of scaffold-integrated systems to orchestrate both catalytic protection and immunomodulation.[112] However, reliance on exogenous mesenchymal stem cell delivery introduces variables, including cell viability loss during storage, inconsistent engraftment efficiency across patients, and potential immunogenic responses that complicate clinical translation.

Building upon injectable platforms, three-dimensional printed composite scaffolds have advanced this concept by combining mechanical reinforcement with catalytic functionality for load-bearing applications in chronic RA joints requiring structural support. Metal-free antioxidant nanozymes derived from zeolitic imidazolate framework-8 pyrolysis are integrated into hybrid double-network hydrogels through additive manufacturing, providing cascading SOD- and CAT-like activities alongside broad-spectrum ROS scavenging capability. Theoretical calculations coupled with experimental validation reveal that CAT-like activity originates from synergistic catalytic interactions between graphitized pyridinic nitrogen and adjacent carbon atoms, representing a mechanistic departure from traditional metal-based catalysis.[113] Complementary bilayer hydrogel designs incorporating lithium manganese oxide–functionalized scaffolds expand therapeutic scope beyond antioxidant protection to include directed osteochondral regeneration through activation of adenosine monophosphate–activated protein kinase signaling pathways. These pathways promote osteoblast differentiation and upregulate osteogenic gene expression. Following extended treatment periods in rat osteochondral defect models, integrated repair characterized by improved bone microarchitecture parameters and substantial upregulation of cartilage matrix–related genes was achieved.[114] Specialized scaffold designs addressing site-specific biomechanical challenges include injectable bioadhesive and lubricating hydrogels integrating polyphenol-mediated single-atom nanozymes, which provide strong cartilage surface adhesion alongside excellent lubrication performance.[115] Nanozyme-reinforced hydrogels also serve as complementary platforms for stem cell delivery, protecting transplanted cells from oxidative damage and enhancing prosthetic interface osseointegration.[116]

Transitioning from bulk scaffold integration to miniaturized controlled-release platforms, dissolvable microneedle arrays and protein-based microspheres have emerged as alternative strategies capable of achieving sustained catalytic protection through programmed delivery kinetics suitable for chronic RA requiring repeated intervention. Cascade enzymatic systems combining SOD and CAT conjugated onto single nanoparticles enable proximity-dependent cascade reactions that effectively scavenge ROS and generate oxygen while simultaneously modulating macrophage phenotype. Codelivery of bone-protective pharmaceuticals through transdermal routes further enhances bioavailability.[117] Protein nanotube–crosslinked microspheres represent complementary microcarrier architectures, wherein manganese ion coordination with α-lactalbumin peptides forms nanotubes that are subsequently crosslinked to construct microspheres exhibiting dual peroxidase-like and CAT-like activities, thereby promoting macrophage repolarization following cellular uptake.[118]

Beyond externally controlled release mechanisms, intrinsic nanozyme design strategies focused on material composition and structural engineering have demonstrated the capacity for sustained catalytic activity without reliance on complex carrier systems while maintaining long-term therapeutic function in chronic RA environments. Two-dimensional MOF nanosheets exemplify this approach through periodically assembled active metal sites that mimic natural antioxidase coordination environments (Figure 5b). Manganese porphyrin coordination with zinc ions forms structures in which manganese sites replicate the active metal centers of human mitochondrial manganese SOD and human erythrocyte CAT. This biomimetic active-center design enables dual enzymatic activities, with superoxide disproportionation proceeding via outer-sphere proton-coupled one-electron transfer and H_2O_2 decomposition occurring through inner-sphere proton-coupled two-electron transfer. These platforms achieve therapeutic efficacy in adjuvant-

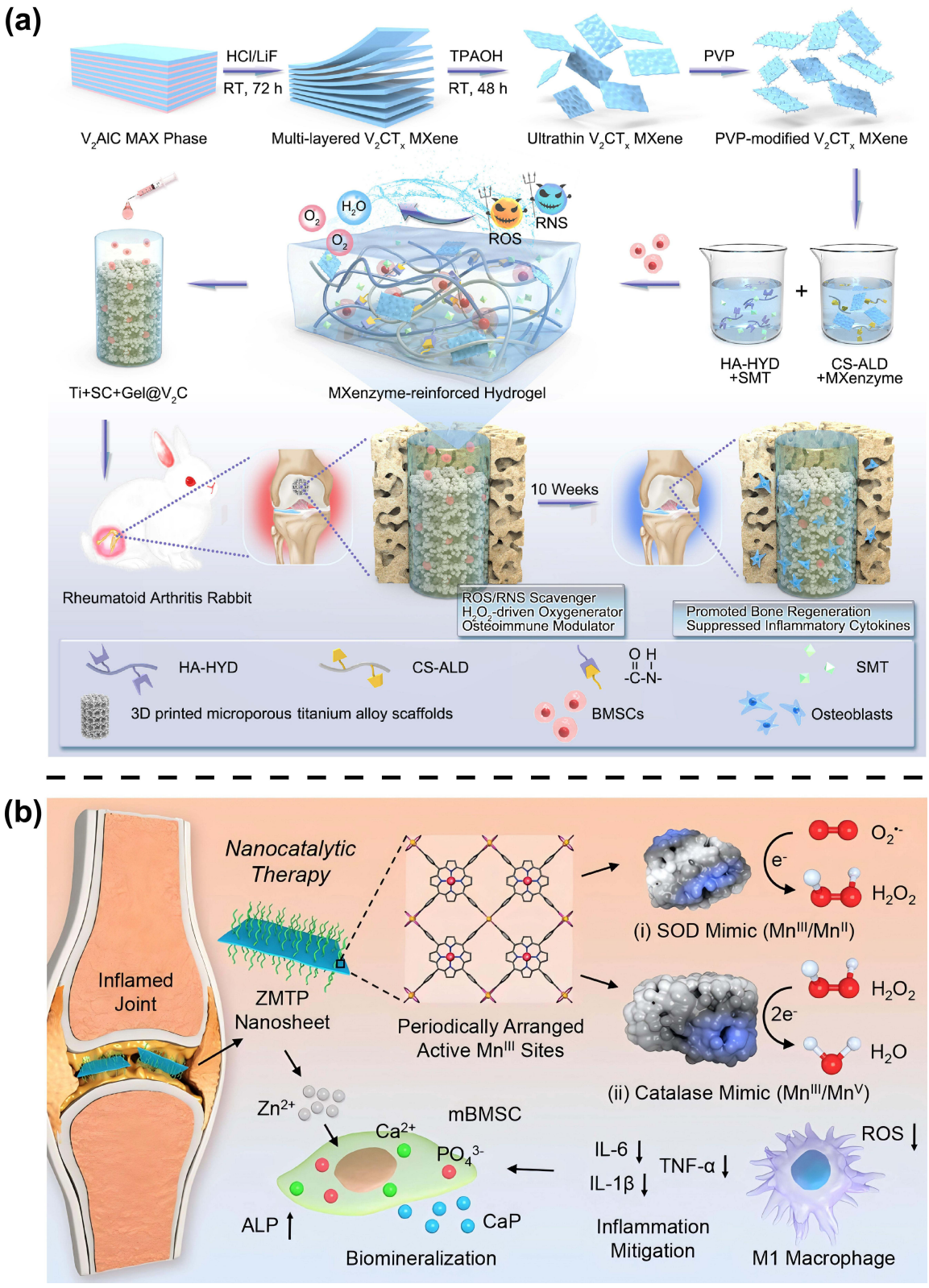

Figure 5 Sustained catalytic activity platforms for long-term protection in the chronic destructive phase of RA. (**a**) Injectable V_2CT_x MXenzyme-reinforced hydrogels for osteoimmune microenvironment regulation 112 Copyright 2026, Elsevier. (**b**) Two-dimensional metal–organic framework nanosheets with biomimetic active centers for dual enzymatic catalysis 119 ↑, upregulation; ↓, downregulation. Licensed under CC BY 4.0.

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induced arthritis models by promoting macrophage polarization, while zinc ion–mediated alkaline phosphatase upregulation facilitates biomineralization.[119] Platinum-doped zeolitic imidazolate framework-8 nanozymes demonstrate complementary advantages through superior CAT-like activity that efficiently decomposes hydrogen peroxide to generate oxygen, thereby alleviating joint hypoxia while inhibiting lipopolysaccharide-induced M1 polarization and downregulating hypoxia-inducible factor-1α and nuclear factor kappa-B expression.[120] Mechanistic investigations into sustained catalytic function reveal that bilirubin–platinum cooperative systems interrupt detrimental feedback loops between hypoxia and oxidative stress through complementary functions, wherein bilirubin eliminates ROS while platinum simultaneously scavenges ROS and generates oxygen. RNA sequencing analysis elucidates orchestration of hypoxic M1 macrophage repolarization toward the M2 phenotype through metabolic switching from glycolysis to oxidative phosphorylation.[121] Ferrihydrite nanoparticles further expand mechanistic understanding through a unique catalytic architecture in which tetrahedrally coordinated iron forms composite catalytic centers with adjacent hydroxyl groups, enabling cooperative hydrogen peroxide decomposition while promoting M1-to-M2 macrophage transition.[68]

Stability-enhancement strategies further extend the durability of nanozyme catalytic activity by activating endogenous antioxidant systems and regulating microenvironmental pH. Crystalline carbon antioxidase mimics engineered with controlled crystallinity exhibit superior cell permeability, enabling catalytic scavenging of intracellular ROS and reactive nitrogen species while activating nuclear factor erythroid 2–related factor 2–dependent cellular defense pathways. This activation leads to substantial upregulation of endogenous detoxifying and antioxidant enzymes, providing self-sustaining protection beyond exogenous catalytic activity.[122] Nanoceria-loaded magnesium aluminum layered double hydroxide platforms employ an alternative stabilization mechanism, wherein the mildly alkaline nature of layered double hydroxides neutralizes excessive hydrogen ion accumulation in RA microenvironments. This enhances ceria nanoparticle ROS-scavenging activity and promotes M2 macrophage repolarization. Subsequently released magnesium ions provide additional therapeutic benefits by inhibiting monocyte fusion and osteoclast formation while stimulating osteogenic activity.[123]

Precision Targeting of Pathological Structures

The chronic destructive phase of RA presents distinct targeting challenges compared with acute inflammation. Nanozyme platforms must selectively accumulate within fibrotic pannus tissue, penetrate dense cartilage matrices, and localize to sites of progressive bone erosion. The architectural complexity of established synovial pathology presents substantial delivery barriers. Neoangiogenic networks, activated FLSs, and organized immune cell infiltrates characterize this complexity. Traditional passive accumulation mechanisms relying on enhanced permeability and retention effects prove insufficient. Vascular normalization therapies or established fibrotic barriers restrict nanoparticle extravasation in chronic RA. Systemic clearance by reticuloendothelial organs substantially reduces the fraction reaching diseased joints.

Biomimetic approaches leveraging cellular membrane camouflage have demonstrated superior targeting efficiency. These approaches exploit homotypic recognition mechanisms and enable evasion of immune clearance (Figure 6a). Macrophage membrane-cloaked metal–phenolic networks assembled through coordination interactions between epigallocatechin gallate and cerium ions exemplify this strategy. The membrane coating enables avoidance of phagocytic clearance by normal macrophages while simultaneously promoting accumulation in activated inflammatory cells. These systems exhibit SOD- and CAT-mimic activities that efficiently scavenge multiple types of ROS and reactive nitrogen species. Collagen-induced arthritis models show substantial reductions in serum interleukin-1β levels alongside a promoted M1-to-M2 macrophage phenotypic shift.[124] This approach demonstrates conceptual elegance by transforming immune surveillance mechanisms into targeting assets. However, practical challenges remain regarding membrane source standardization and scalability for clinical production.

Building upon membrane camouflage strategies, ligand-mediated targeting approaches have evolved to exploit pathological cell surface receptor overexpression. Cerium and manganese oxide nanoparticles modified with bovine serum albumin achieve M1 macrophage–specific targeting. These particles provide CAT-like and SOD activities that efficiently decompose hydrogen peroxide and clear $O_2^{\bullet -}$, •OH, and other ROS. The cerium–manganese synergistic effect promotes macrophage polarization from the M1 to the M2 phenotype through downregulation of proinflammatory cytokines alongside upregulation of anti-inflammatory factors. Integration into hyaluronic acid–based microneedles enables transdermal delivery that bypasses first-pass hepatic metabolism.[125] Complementary cascade targeting strategies

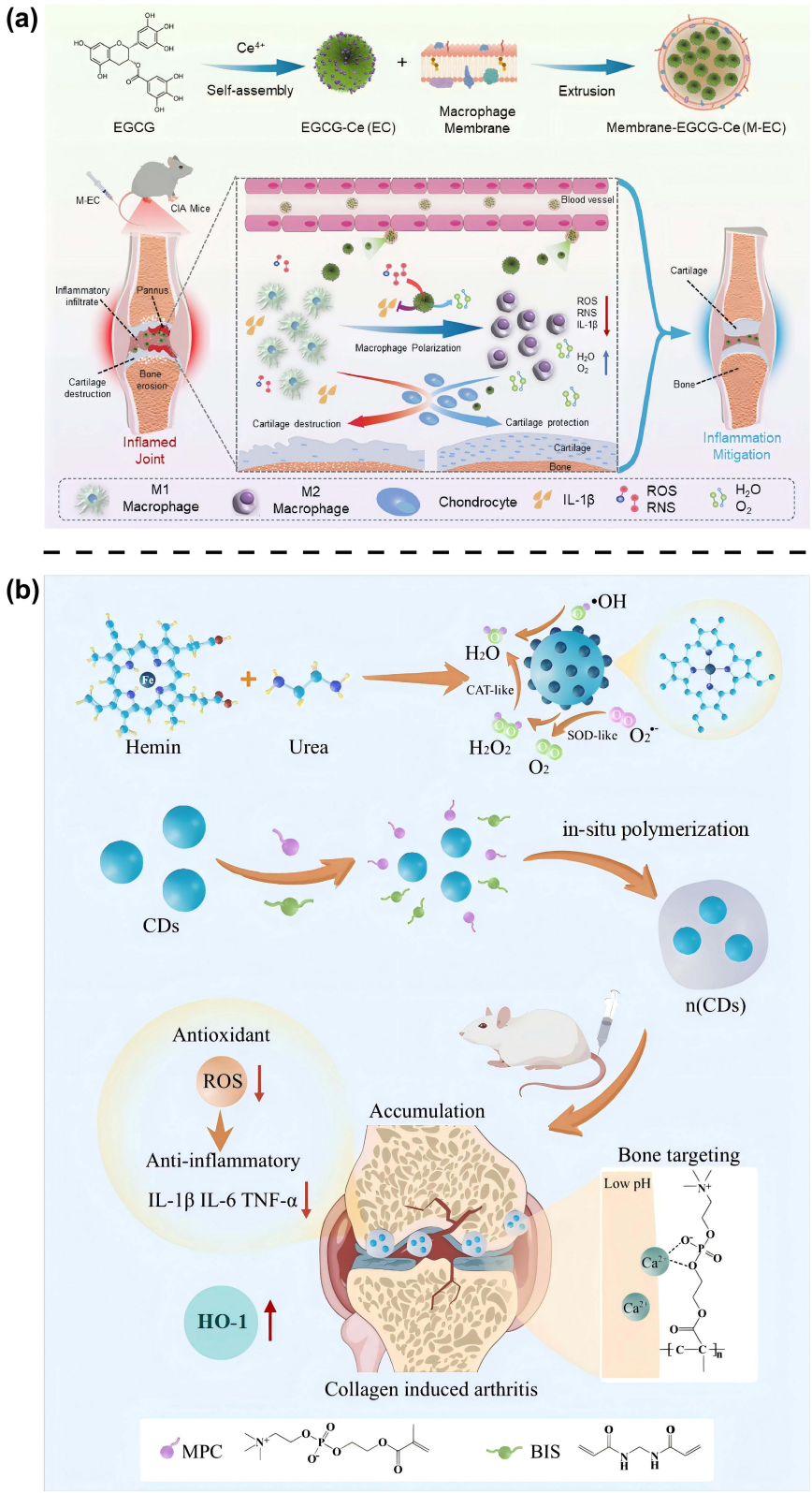

Figure 6 Precision targeting of pathological structures in the chronic destructive phase of RA. (**a**) Macrophage membrane-cloaked metal–phenolic networks for inflammation homing 125 ↑, upregulation; ↓, downregulation. Copyright 2023, American Chemical Society. (**b**) Bone-targeted carbon dot nanogels with phosphate modification for prolonged joint retention 129 ↑, upregulation; ↓, downregulation. Copyright 2025, Royal Society of Chemistry.

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employing tannic acid– and ferric ion–coordinated MOFs have achieved high-efficiency loading of anti–tumor necrosis factor-α small interfering RNA. Broad-spectrum radical scavenging capability eliminates diverse ROS and reactive nitrogen species, while rapid endosomal escape occurs through proton-sponge effects. Bovine serum albumin surface modification facilitates cascade targeting through binding to overexpressed secreted protein acidic and rich in cysteine in joint tissues, with scavenger receptor-mediated macrophage internalization providing complementary targeting.[126] However, reliance on secreted protein acidic and rich in cysteine as a targeting ligand raises concerns, as its expression occurs in multiple nonarticular tissues, including bone remodeling sites and wound-healing regions, potentially causing off-target accumulation and limiting therapeutic specificity.

Advanced biomimetic platforms incorporating self-sustaining feedback mechanisms have demonstrated enhanced therapeutic precision. These platforms dynamically respond to pathological microenvironments rather than relying on static targeting ligands. Macrophage membrane–coated nanoparticles integrating Prussian blue nanoenzymes with gene therapeutics establish positive-feedback drug release. CAT and SOD activities scavenge ROS while restoring glutathione levels, which subsequently promote disulfide bond cleavage in guanidinium-based polymers, releasing small interfering RNA that silences tumor necrosis factor-α expression.[127] This self-amplifying mechanism creates therapy-responsive delivery kinetics that intensify as pathological conditions are ameliorated. Nevertheless, the complexity of multicomponent systems introduces potential failure modes in which malfunction of any individual element may compromise overall therapeutic efficacy.

Whereas cellular targeting addresses immune and stromal components of synovial pathology, bone-directed strategies enable intervention at sites of structural destruction. These strategies exploit mineral-binding interactions specific to hydroxyapatite in bone tissue (Figure 6b). Bone-targeted carbon dot nanogels modified through phosphorylcholine polymerization form three-dimensional porous networks encapsulating multienzyme-active carbon dots exhibiting CAT, SOD, and •OH-scavenging activities. The critical innovation lies in surface phosphate group coordination with hydroxyapatite, achieving precise bone-targeting capability with prolonged joint retention. Localized ROS neutralization effectively suppresses synovial oxidative damage. Mechanistic studies reveal that these nanogels upregulate heme oxygenase-1 pathways, activating endogenous antioxidant defense systems while downregulating proinflammatory cytokine expression. This provides an important paradigm for oxidative stress–related bone disease precision nanomedicine treatment in chronic RA.[128] However, indiscriminate binding to all hydroxyapatite-containing structures raises questions regarding selectivity between diseased erosive bone surfaces and healthy skeletal sites, potentially limiting achievable concentration gradients between pathological and physiological bone.

The dense extracellular matrix architecture of established pannus tissue and calcified cartilage presents additional barriers that limit nanozyme bioavailability in deep pathological structures characteristic of chronic RA. Neutrophil-derived exosomes engineered with ultrasmall Prussian blue nanoparticles address this limitation by inheriting neutrophil targeting molecules that selectively accumulate in activated FLSs and achieve deep penetration into cartilage matrices. This enables neutralization of pro-inflammatory factors while scavenging ROS to exert anti-inflammatory effects[129] Complementary active propulsion systems employing hydrogen peroxide–actuated manganese dioxide nanomotors have demonstrated enhanced diffusion capability. Fuel-driven movement enables active tissue penetration, while CAT-like activity decomposes overproduced hydrogen peroxide in joint cavities to continuously generate oxygen. This relieves hypoxic synovial microenvironments characteristic of chronic RA while enabling nanomotor propulsion.[130]

Multifunctional Integration for Comprehensive Management

Multifunctional nanozyme platforms enable integration of complementary therapeutic modalities within single delivery systems for comprehensive chronic RA management. Physical ablation strategies, including photothermal and sonodynamic therapies, eliminate hyperproliferative pathological cells, while catalytic antioxidant functions provide sustained protection against persistent oxidative stress. Tissue regeneration promotion through growth factor delivery or scaffold integration addresses structural repair needs. Theranostic capabilities incorporating diagnostic imaging guide interventions and monitor therapeutic responses. Collectively, these integrated platforms address the established structural alterations and residual inflammation characteristic of the chronic destructive phase more comprehensively than monotherapy approaches.

Upconversion nanoparticle-based platforms exemplify synergistic approaches through near-infrared light–triggered multimodal therapy (Figure 7a). Ceria CAT-like activity decomposes accumulated hydrogen peroxide into oxygen and

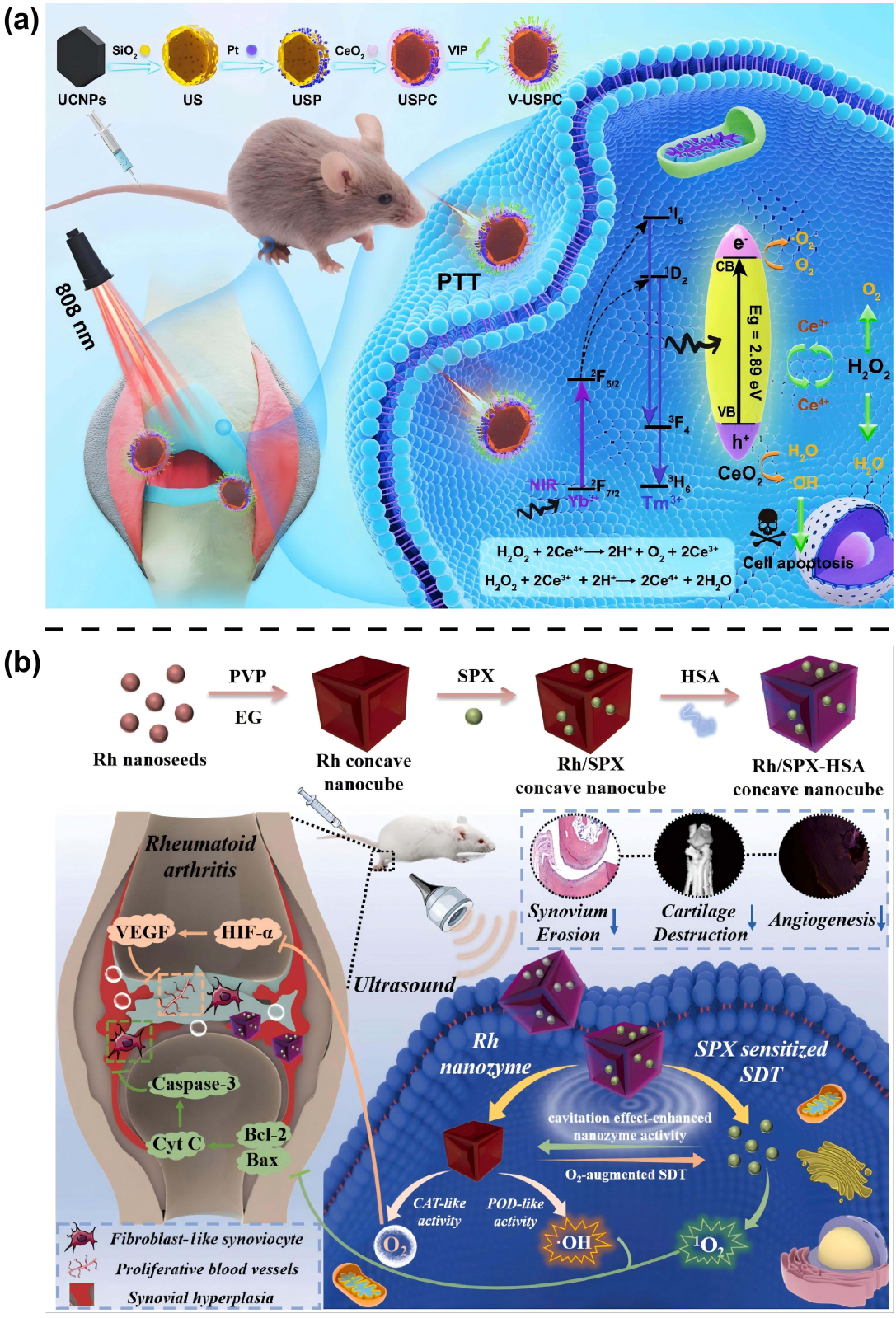

Figure 7 Multifunctional integration of physical ablation with catalytic therapy for chronic-phase RA management. (**a**) Upconversion nanoparticle-based platform for near-infrared–triggered multimodal therapy 132 Copyright 2022, Elsevier. (**b**) Sparfloxacin-doped rhodium nanozymes for oxygen-augmented sonodynamic therapy 136 ↓, downregulation. Copyright 2021, Elsevier.

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water, alleviating hypoxia and downregulating hypoxia-inducible factor-1α expression characteristic of chronic RA microenvironments. Upconversion nanoparticles convert near-infrared photon energy to ultraviolet light, triggering ceria to form electron–hole pairs and catalyze water to generate •OH for photodynamic therapy. Platinum nanoparticle–mediated photothermal therapy further enhances therapeutic efficacy through localized hyperthermia, inducing apoptosis in hyperproliferative synoviocytes and inflammatory macrophages. Collagen-induced arthritis models demonstrate substantial improvements in clinical parameters with imaging confirmation of effective inhibition of bone destruction.[131] However, reliance on near-infrared–to–ultraviolet upconversion introduces energy-efficiency concerns, as the anti-Stokes shift process exhibits inherently low quantum yields, potentially necessitating prolonged irradiation or elevated laser powers that may cause thermal damage to superficial tissues before achieving therapeutic depths in chronic RA joints.

Photothermal ablation strategies have been refined through targeting approaches that achieve selective inflammatory cell elimination. Hyaluronic acid–modified platinum–tellurium nanorods actively target inflammatory macrophages via specific binding between hyaluronic acid and CD44 receptors overexpressed on activated macrophages in chronic RA. Laser irradiation generates localized hyperthermia sufficient to induce inflammatory macrophage apoptosis, while platinum particles simultaneously provide multienzymatic ROS-scavenging activities.[132] Complementary polydopamine-based platforms have demonstrated near-infrared–responsive synergy, in which photothermal conversion generates localized hyperthermia causing M1 proinflammatory macrophage death at lesion sites. The low-pH inflammatory microenvironment stimulates polydopamine dissociation, exposing manganese trioxide nanozymes exhibiting SOD and CAT activities alongside methotrexate release that inhibits synovial fibroblast proliferation.[133] Advanced platforms employing iron–cobalt Prussian blue analogs have expanded photothermal-enhanced chemodynamic therapy. Ceria CAT-like activity decomposes hydrogen peroxide to generate oxygen, while cerium redox cycling enhances Fenton and Fenton-like reactions. Polydopamine-mediated photothermal therapy not only directly ablates M1 macrophages but also accelerates catalytic oxidation processes through temperature-dependent reaction kinetics.[134]

Beyond photothermal modalities, integration of sonodynamic therapy has emerged as an alternative physical intervention strategy. Sonodynamic therapy offers superior tissue penetration depths for deep-seated pathological structures without the optical scattering and absorption limitations that constrain light-based therapies in chronic RA joints (Figure 7b). Sparfloxacin sonosensitizer–doped concave cubic rhodium nanozymes address hypoxic microenvironment limitations through dual enzymatic activities. Peroxidase-like activity generates •OH, while CAT-like activity decomposes hydrogen peroxide to produce oxygen. Sparfloxacin functions as a sonosensitizer to generate singlet oxygen under ultrasound activation, with rhodium nanozyme–produced oxygen further enhancing sparfloxacin-mediated singlet oxygen generation to achieve oxygen-augmented sonodynamic therapy. In addition, ultrasonic cavitation effects enhance rhodium nanozyme activity by increasing catalytic site accessibility through mechanical perturbations, while generated ROS provide additional substrate for continued catalytic processing. Human serum albumin modification achieves secreted protein acidic and rich in cysteine–mediated targeting to inflammatory joints. Collagen-induced arthritis models show substantial reductions in synovial hyperplasia and inhibition of cartilage destruction, alongside downregulation of hypoxia-inducible factor-1α expression.[135]

Theranostic integration represents the culmination of multifunctional platform development. Diagnostic imaging capabilities guide therapeutic interventions while monitoring treatment responses in chronic RA requiring sustained management. Cerium- and selenium–co-doped carbon dot–based self-cascading antioxidant nanozymes combined with fluorophore-conjugated anti-microRNA achieve synergistic monitoring and amelioration. These systems mimic natural antioxidant enzyme defense mechanisms, with cerium active centers executing SOD-like activity and adjacent selenium components sequentially decomposing hydrogen peroxide through GPx-like activity. Simultaneously, they serve as genetic material transfer carriers, enabling macrophage subphenotype identification via microRNA ratiometric imaging for real-time assessment of therapeutic responses.[136] Macrophage membrane-cloaked copper-coordinated polyphthalocyanine–based artificial peroxisomes further advance theranostic capabilities by integrating ROS scavenging and macrophage reprogramming with photoacoustic imaging guidance. Ultrasound-targeted microbubble destruction technology enhances nanoparticle tissue penetration and cellular uptake in fibrotic chronic RA tissues.[137] Advanced platforms employing homology-activated ultrasensitive mechanisms have achieved precise near-infrared fluorescence– and

magnetic resonance imaging–guided dynamic therapy. Manganese dioxide–chlorin e6 tetra-tertiary amine–glucose oxidase nanomedicines construct manganese dioxide–to–manganese ion reaction systems that undergo ultrasensitive responsive degradation through multistimuli processes, enabling both therapeutic function and imaging contrast generation.[138] Janus bifunctional nanoplatforms composed of ceria–platinum nanozyme subunits and periodic mesoporous organosilica subunits represent culminating examples of chronic-phase multifunctional integration. Their compartmentalized dual-subunit architecture achieves ROS scavenging while delivering loaded pharmaceuticals that block receptor activator of nuclear factor κB ligand–induced osteoclast differentiation, with incorporated imaging agents conferring diagnostic capability for early disease detection and treatment monitoring in chronic RA progression.[139]

The approaches outlined above establish comprehensive therapeutic paradigms for chronic destructive phase intervention that address fundamentally different pathological demands through sustained catalytic activity, precision targeting, and multifunctional integration. Scaffold-integrated systems and controlled-release platforms provide prolonged antioxidant defense while facilitating tissue regeneration through maintained delivery of catalytic components over extended periods. Precision targeting through biomimetic camouflage, ligand-mediated recognition, and bone mineral affinity enables therapeutic concentration at sites of irreversible structural alterations, including fibrotic pannus, degraded cartilage, and eroded bone surfaces. Multifunctional integration combining physical ablation with catalytic protection, metabolic remodeling with structural repair, and therapeutic intervention with diagnostic guidance achieves comprehensive management of persistent inflammation and progressive destruction. Representative platforms developed according to these stage-specific design principles are systematically documented in Table 3, presenting platform architectures, catalytic mechanisms, targeting strategies, and therapeutic outcomes that illustrate the evolution toward integrated systems addressing multidimensional chronic pathology.

Clinical Translation and Future Perspectives

The stage-oriented nanozyme therapeutic framework demonstrates substantial preclinical promise for addressing the pathophysiological heterogeneity characteristic of RA progression.[143] Literature analysis reveals that investigations targeting chronic destructive phase pathology considerably outnumber those focused on acute inflammatory interventions. This distribution reflects the clinical reality that RA manifests predominantly as a chronic progressive disease requiring sustained therapeutic intervention. However, translation from laboratory investigations to clinical implementation confronts interconnected challenges that require systematic resolution. These challenges encompass comparative evaluation against established therapies to determine appropriate clinical positioning, long-term safety characterization essential for chronic disease management, and translational barriers including disease model validity and manufacturing scalability. Coordinated resolution of these fundamental questions is necessary before the therapeutic potential documented in preclinical studies can be realized in RA patient populations.

Comparative Positioning Against Standard RA Therapies

Evaluating nanozyme therapeutics against established treatment modalities provides essential context for understanding their potential clinical positioning and for identifying critical knowledge gaps requiring resolution.[144] From an efficacy perspective, nanozyme platforms address oxidative stress through catalytic mechanisms fundamentally distinct from the immunomodulatory approaches employed by DMARDs, biological agents, and JK inhibitors.[145] Preclinical evidence demonstrates therapeutic benefits in RA animal models, with selected platforms achieving outcomes comparable to methotrexate or biological agents in reducing inflammatory markers and structural damage. However, direct head-to-head comparisons remain limited. More critically, nanozyme efficacy in human RA remains entirely unvalidated through clinical trials. This represents a fundamental knowledge gap distinguishing nanozyme platforms from therapies supported by decades of clinical evidence.

Safety profile assessment reveals stark contrasts in knowledge depth between established therapies and nanozyme platforms. Methotrexate-associated hepatotoxicity risks, immunogenicity profiles of biological agents, and infection susceptibilities associated with immunosuppression are thoroughly characterized through extensive clinical use.[146] Established monitoring protocols enable clinicians to manage these known risks effectively. In contrast, nanozyme long-term safety profiles, particularly under the chronic administration required for RA management, remain largely

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Table 3 Nanozyme Therapeutics for Chronic Destructive Phase RA

Therapeutic Strategy	Platform	Nanozyme Component	Enzymatic Activities	Therapeutic Strategy	Key Therapeutic Outcomes	Ref.
Sustained Activity	Hybrid double network hydrogel	ZIFC (ZIF-8 pyrolysis-derived)	Cascading SOD, CAT	3D printing integration with bioactive hydrogel	Rapid antioxidant defense activation, remarkable bone regeneration in cranial defects	[113]
	$LiMn_2O_4$-functionalized hydrogel	$LiMn_2O_4$	CAT, SOD, GPx	Bilayer architecture targeting cartilage and subchondral bone	Integrated repair after 12 weeks, BV/TV improved, Col II/aggrecan↑	[114]
	Injectable hydrogel with SAN	DAGQD@Cu@KGN single atom nanozyme	SOD, CAT, •OH scavenging	DA-HA bioadhesion, SO_3-HA lubrication, sustained KGN release	Efficacy in CIA rats and OIA rabbits, cartilage repair promoted	[115]
	PSC@IGU dissolvable microneedles	SOD-CAT conjugated PCL NPs	Cascading SOD→CAT	Proximity-dependent cascade, transdermal IGU delivery	Joint hypoxia relief, synovial inflammation↓, bone erosion prevented	[117]
	ZIF-8@Pt	Pt-doped ZIF-8	Superior CAT-like	Intra-articular injection	Intracellular ROS↓, LPS-induced M1 polarization inhibited, HIF-1α/NF-κB p65↓, IL-1β/TNF-α/CRP↓	[120]
	BSA-BR-Pt NPs	Bilirubin + Pt	Synergistic ROS elimination, O_2 generation	Enzyme-catalyzed interruption of hypoxia-oxidative feedback	Superior to MTX, paw thickness↓, joint diameter↓, synovitis score↓, bone erosion↓, hypoxic M1→M2 orchestration	[121]
	Crystalline carbon (crys-CAM)	Controlled crystallinity carbon	Artificial SOD	Superior cell permeability for intracellular ROS/RNS scavenging	Self-sustaining protection, paw swelling↓, cartilage damage↓, bone erosion↓, innate anti-inflammatory immunity restored	[122]
Precision Targeting	TFSB (TA-Fe^{3+} MOFs loading siRNA)	TA-Fe^{3+} coordination	Broad-spectrum RONS scavenging (H_2O_2, O_2^-, •OH, NO)	BSA-SPARC binding, scavenger receptor internalization, proton-sponge endo/lysosome escape	Arthritis score improved, paw thickness↓, synergistic RONS scavenging and siRNA therapy	[126]
	uPB-Exo (neutrophil-derived exosomes with uPB NPs)	Ultrasmall Prussian blue	ROS scavenging	Neutrophil targeting molecules inheritance, selective FLS accumulation, deep cartilage penetration	Targeted synovitis, Th17/Treg balance regulation, joint damage↓, arthritis severity suppressed	[129]
Multifunctional Integration	MTX-Mn_3O_4@PDA	Mn_3O_4 + PDA	SOD, CAT	Low pH inflammatory environment triggers PDA dissociation	Toe swelling↓, synovial inflammation↓, bone erosion↓, cartilage degeneration↓, NIR-driven synergistic treatment	[133]
	F-PCP (FA-Fe-Co PBA@CeO_2@PDA)	CeO_2 (CAT-like) + Fe-Co PBA	CeO_2 CAT-like, Ce^{4+}/Ce^{3+} enhances Fenton/Fenton-like	Folic acid targeting	Arthritis index↓, paw thickness↓, synovial inflammation controlled, photothermal-enhanced catalytic strategy	[134]

	CS-CDs@Cy5-anti-miRNA-155	Ce-Se co-doped carbon dots	Ce SOD-like ($\bullet O_2^-$ $\rightarrow H_2O_2$), Se GPx-like (H_2O_2 decomposition)	CS-CDs as Cy5-anti-miRNA-155 carriers	Joint swelling↓, bone erosion↓, cartilage destruction↓, synergistic self-cascading ROS scavenging and anti-inflammatory cytokine inhibition	[136]
	CuAP (macrophage membrane-cloaked Cu-polyphthalocyanine)	Cu-coordinated polyphthalocyanine	Mimics SOD, CAT	Macrophage membrane camouflage, UTMD enhances tissue penetration	Arthritis score improved, joint swelling↓, bone destruction inhibited, synovial hyperplasia↓, cartilage degradation↓	[137]
	RuO_2@BSA-ATO nanogels	RuO_2	POD-like	BSA-based endogenous platform	Paw thickness↓, arthritis index↓, NIR-II photoacoustic imaging for precise diagnosis, targeted ablation	[140]
	CuS@ZnS core-shell	CuS@ZnS heterostructure	LDHB-mimetic (LA oxidation), PIDCT pathway	980 nm laser irradiation	Arthritis score improved, paw volume↓, bone destruction prevented, metabolic remodeling	[141]
	A-nanoceria (albumin-CeO_2-ICG)	Cerium oxide	SOD, CAT, POD	SPARC-mediated inflammation targeting, albumin biomineralization	Comparable to MTX efficacy, superior targeting, toxicity↓, image-guided therapy	[142]

Notes: ↑, upregulation; ↓, downregulation.

Abbreviations: ATO, atovaquone; BMCC, Cu-doped ZIF-8 biomimetic complex; BMD, bone mineral density; BV/TV, bone volume/tissue volume ratio; Ce6, chlorin e6; CQ4T, chlorin e6 tetra-tertiary amine; CS-CDs, chitosan-carbon dots; CuAP, Cu-coordinated polyphthalocyanine artificial peroxisomes; HIF-1α, hypoxia-inducible factor-1α; IGU, iguratimod; KGN, kartogenin; LDHB, lactate dehydrogenase B; MCG NMs, MnO_2-CQ4T-GOx nanomedicines; MCL, mycophenolate; Nrf2, nuclear factor erythroid 2-related factor 2; OIA, osteoarthritis-induced arthritis; PDA, polydopamine; PIDCT, proton-induced-delayed charge transfer; PMO, periodic mesoporous organosilica; RANKL, receptor activator of nuclear factor kappa-B ligand; RONS, reactive oxygen and nitrogen species; SPARC, secreted protein acidic and rich in cysteine; SPX, sparfloxacin; UTMD, ultrasound-targeted microbubble destruction; ZIFC, ZIF-8 pyrolysis-derived carbon.

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unexplored. Questions regarding metal-based nanozyme tissue accumulation, potential immune responses to nanomaterial exposure, and the biological effects of degradation products require systematic investigation before clinical translation becomes feasible. With respect to administration convenience, nanozyme platforms incorporating sustained-release formulations or scaffold integration could theoretically reduce dosing frequency compared with biological agents requiring injections every two to four weeks. This potential advantage would be particularly beneficial for chronic destructive phase patients. However, intra-articular delivery requirements for many nanozyme formulations introduce procedural complexity that may limit widespread implementation.

Cost considerations and manufacturing scalability present additional uncertainties. Nanozyme synthesis procedures generally involve more complex processing than small-molecule pharmaceuticals, potentially resulting in higher production costs.[147] Whether these costs would exceed those of biological agents, which already represent substantial healthcare expenditures, remains unclear in the absence of large-scale manufacturing data. Nanozyme therapeutics are therefore best positioned as mechanistically complementary options potentially valuable for specific patient populations rather than as wholesale replacements for established therapies. Candidate populations may include refractory patients with inadequate responses to current immunomodulatory treatments, individuals unable to tolerate standard therapy adverse effects, or chronic destructive phase patients requiring sustained localized intervention where nanozyme stability advantages could provide therapeutic value. The stage-oriented framework offers rational guidance for matching therapeutic approaches to disease characteristics. However, realizing this potential requires addressing substantial safety characterization needs, validation requirements, and translational barriers.

Key Challenges for Clinical Translation

Long-term safety characterization represents the most critical barrier confronting nanozyme therapeutic development for RA management. Metal-based nanozymes incorporating cerium, manganese, iron, and other transition metals dominate current platforms due to their robust catalytic activities.[148] However, the metabolic pathways governing these materials in biological systems remain incompletely elucidated. Cerium oxide nanoparticles may undergo gradual dissolution, releasing cerium ions that could accumulate in the liver and spleen over extended periods. Manganese-based platforms raise concerns regarding potential accumulation in brain tissue, given the documented neurotoxicity of manganese via other exposure routes. Iron oxide nanozymes, while generally considered biocompatible based on their use as approved MRI contrast agents, could potentially overwhelm physiological iron homeostasis mechanisms during the chronic high-dose administration required for sustained RA management. Comprehensive pharmacokinetic characterization, including absorption kinetics following different administration routes, distribution volumes, clearance rates, and elimination half-lives, remains incomplete for most nanozyme platforms.[149] Intra-articular injection, the primary delivery route for many RA nanozyme formulations, presents unique pharmacokinetic challenges, as joint clearance mechanisms differ substantially from systemic circulation. Current preclinical evaluations typically span weeks to months, timeframes insufficient to detect gradual tissue accumulation or subclinical organ dysfunction that may only manifest after years of repeated administration. Comprehensive biodistribution studies tracking nanozyme fate over durations matching chronic RA treatment requirements, coupled with sensitive biomarkers capable of detecting early organ stress, are essential before clinical translation becomes ethically justifiable.

Immune system interactions with nanomaterials introduce additional safety concerns particularly relevant to RA applications, where immune dysregulation already characterizes the underlying disease.[150] Nanoparticle surfaces can activate complement cascades through both classical and alternative pathways, generating anaphylatoxins that trigger inflammatory responses potentially exacerbating, rather than ameliorating, joint inflammation. Repeated nanozyme administration carries the risk of immune sensitization through neutralizing antibody development, which could progressively reduce therapeutic efficacy or trigger hypersensitivity reactions. Excessive nanoparticle uptake by macrophages could theoretically induce macrophage activation syndrome, a life-threatening complication characterized by cytokine storm and systemic inflammation.[151] Nanozyme degradation products represent another incompletely characterized safety dimension. Although metal ions released from degrading platforms may exhibit biological activities, including antimicrobial effects or signaling functions, their long-term accumulation could disrupt cellular processes or generate oxidative stress that paradoxically counteracts the intended therapeutic antioxidant effects.

Beyond safety characterization, disease model validity presents substantial translational uncertainty. As discussed in disease staging characterization, RA animal models exhibit temporal and pathological patterns that differ from human disease.[152] These limitations complicate efficacy prediction, as therapeutic responses demonstrated under standardized experimental conditions may not reliably translate to the heterogeneous clinical presentations characteristic of human RA. Substantial inter-patient variability in disease trajectories, autoantibody profiles, and genetic susceptibility further challenges extrapolation from uniform animal model cohorts to diverse patient populations. Manufacturing challenges intensify as synthesis scales from laboratory batches to the clinical trial quantities required for human studies. Multistep nanozyme synthesis processes requiring precise control over particle size, crystallinity, and surface properties become increasingly difficult to maintain at larger scales. Batch-to-batch consistency in catalytic activity, a critical quality attribute for therapeutic nanozymes, currently lacks standardized analytical methods enabling robust characterization across laboratories and production facilities. Regulatory pathways present additional uncertainty given challenges in nanozyme classification between traditional pharmaceuticals and medical devices. Food and Drug Administration (FDA) frameworks for nanomaterial-based therapeutics continue to evolve, with potential classification requiring evaluation under both drug and device paradigms.[153] Investigational New Drug applications for nanozyme therapeutics would necessitate comprehensive Chemistry, Manufacturing, and Controls documentation addressing nanomaterial-specific challenges, including catalytic activity standardization, particle size distribution control, and surface property reproducibility. The absence of established protocols creates regulatory ambiguity that complicates development planning and resource allocation.

Future Research Directions

Addressing safety characterization needs requires long-term biodistribution studies tracking nanozyme tissue accumulation over durations consistent with chronic RA treatment requirements. Such studies must extend beyond current preclinical timeframes to detect gradual metal accumulation or subclinical organ dysfunction that may only manifest after prolonged exposure. Development of sensitive biomarker panels capable of detecting early signs of hepatic, renal, or neurological stress would enable identification of safety concerns before irreversible damage occurs.[154] Standardized immunogenicity assessment protocols specifically designed for nanomaterial therapeutics would facilitate consistent evaluation across nanozyme platforms. These protocols should characterize antibody responses, complement activation patterns, and immune sensitization following repeated administration. Systematic investigation of degradation product toxicology requires identification of breakdown products, determination of their tissue distribution, and evaluation of their biological activities at concentrations achieved during chronic RA management.

Improving translational predictability requires biomarker-based patient stratification strategies to identify subpopulations most likely to benefit from nanozyme therapeutics.[155] Oxidative stress markers, including lipid peroxidation products and antioxidant enzyme activities, may distinguish RA patients whose disease involves prominent oxidative components potentially responsive to catalytic intervention. The stage-oriented framework established in this review provides conceptual guidance for such stratification, suggesting that chronic destructive phase patients with established structural damage represent an appropriate initial target population in which sustained antioxidant protection may demonstrate clinical value. Integration of imaging biomarkers enabling noninvasive disease stage assessment would facilitate patient selection while providing pharmacodynamic endpoints for clinical trials. Establishing consensus criteria for disease stage designation applicable across experimental and clinical contexts would further enable consistent study design and facilitate cross-study comparisons. These translational bridges between preclinical models and clinical applications are essential for designing informative early-phase trials.

Broader infrastructure development would further accelerate clinical implementation. Regulatory guidance addressing nanozyme classification and characterization requirements would reduce development uncertainty. Establishment of reference materials with well-characterized catalytic activities and physicochemical properties would enable standardization across laboratories and facilitate quality control during manufacturing scale-up.[156] Collaborative networks linking academic researchers, clinical investigators, and industry partners could enable sharing of biodistribution datasets and toxicology findings, accelerating knowledge accumulation while reducing redundant efforts. International harmonization of characterization methods and safety assessment protocols would further facilitate global development efforts. The

convergence of advancing materials science capabilities with deepening understanding of RA pathophysiology creates opportunities for stage-oriented nanozyme therapeutics to progress toward clinical implementation, potentially offering patients treatment options more closely matched to individual disease characteristics.

Conclusions

RA progression through distinct pathophysiological states establishes a fundamental rationale for stage-oriented nanozyme therapeutic strategies that address qualitatively different pathological demands during acute inflammatory versus chronic destructive phases. The approaches detailed throughout this review demonstrate that nanozyme platforms can be rationally engineered to meet stage-specific requirements through integration of optimized catalytic activities, targeted delivery mechanisms, and synergistic therapeutic modalities. Accumulated preclinical evidence establishes proof-of-concept for stage-oriented nanozyme therapeutics across multiple animal models. However, critical knowledge gaps must be addressed before clinical implementation becomes feasible. Comprehensive characterization of long-term safety profiles, particularly for metal-based platforms requiring chronic administration, represents the most immediate need. Development of predictive biomarkers enabling patient stratification would identify subpopulations most likely to benefit from catalytic intervention, thereby enhancing clinical trial efficiency. Establishment of standardized analytical methods for catalytic activity characterization and batch-to-batch quality control remains essential for manufacturing scalability. Collectively, these gaps define research priorities requiring coordinated investigation across materials science, clinical medicine, and regulatory science disciplines.

Translation from preclinical validation to clinical application follows a stepwise pathway requiring progressive evidence accumulation. Initial Phase I trials must establish safety profiles and pharmacokinetics in small patient cohorts, likely focusing on refractory chronic destructive phase patients for whom conventional therapies have failed and acceptable risk–benefit ratios favor novel interventions. Phase II efficacy studies would evaluate clinical and imaging endpoints demonstrating disease activity reduction and structural damage prevention, ideally incorporating the stage-oriented framework for patient selection and outcome assessment. Comparative Phase III trials against established therapies would ultimately determine clinical positioning and inform treatment guidelines. Regulatory pathways for nanozyme therapeutics will require collaborative framework development between sponsors and regulatory agencies to address classification challenges and establish characterization requirements appropriate for this emerging therapeutic class. The convergence of advancing materials science capabilities with deepening understanding of RA pathophysiology and emerging precision medicine technologies creates realistic opportunities for stage-oriented nanozyme therapeutics to progress toward clinical implementation. These platforms may ultimately offer patients treatment options better aligned with individual disease characteristics and trajectories than currently available uniform interventions.

Abbreviations

ACPA, Anticitrullinated protein antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; DMARD, Disease-modifying antirheumatic drugs; FLS, Fibroblast-like synoviocytes; MAPK, Mitogen-activated protein kinase; MRI, Magnetic resonance imaging; NADPH, Nicotinamide adenine dinucleotide phosphate; RA, Rheumatoid arthritis; RANKL, Receptor activator of nuclear factor kappa B ligand; RF, Rheumatoid factor; ROS, Reactive oxygen species; VEGF, Vascular endothelial growth factor.

Data Sharing Statement

No new data were created or analyzed in this study.

Author Contributions

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

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Disclosure

The authors declare no competing interests in this work.

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