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REVIEW

Advancing Arthritis Therapy: The Frontier of Targeted and Responsive Nanomedicine

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Abstract: Arthritis, a prevalent joint disorder with significant socioeconomic burden, poses considerable therapeutic challenges due to its complex pathophysiology and the limitations of conventional treatments, including systemic toxicity and poor intraarticular retention. Nanomedicine has emerged as a transformative platform to overcome these hurdles, offering precise drug delivery, prolonged retention, and multifunctional therapeutic capabilities. This review systematically summarizes the current landscape and future directions of nanomedicine for arthritis therapy. We first classify and analyze the rational design of four major nanotherapeutic platforms: lipid-based, polymer-based, inorganic, and bioinspired/biomimetic systems. Our discussion highlights their unique mechanisms for targeted delivery, controlled release, and microenvironmental modulation. Subsequently, we elucidate how these engineered nanoplatforms enable multifaceted therapeutic strategies, including immunomodulation, cartilage repair, pannus inhibition, and theranostics. The clinical translation status is critically assessed, acknowledging the promising early-phase validation of candidates like PEGylated liposomes, while also addressing the pivotal translational challenges spanning safety, manufacturing scalability, and biological barriers such as deep tissue penetration and disease heterogeneity. In conclusion, this review underscores the paradigm-shifting potential of nanomedicine in advancing arthritis management from symptomatic relief to disease-modifying interventions and outlines a roadmap for developing next-generation, intelligent nanotherapeutics.

Keywords: arthritis, nanomedicine, drug delivery, targeted therapy, biomimetic strategy, clinical translation

Introduction

Arthritis is a joint disease caused by factors such as inflammation, infection, degeneration, or trauma, clinically characterized by redness, swelling, heat, pain, and dysfunction of the joints.[1] Globally, arthritis affects hundreds of millions of people and is a leading cause of disability worldwide, with osteoarthritis (OA) and rheumatoid arthritis (RA) being the most common forms.[2,3] In China, arthritis affects over millions of individuals,[4] with osteoarthritis representing the most prevalent form, comprising more than 80% of all cases. Approximately 50% of the population aged 50 and above is affected by osteoarthritis, with prevalence rates rising to 90% in women and 80% in men aged 65 or older. Rheumatoid arthritis (RA), another major subtype, exhibits a prevalence of 0.34%–0.36% and affects an estimated 5 million patients in China.[5] Arthritis also imposes a significant socioeconomic burden,[6] characterized by high medication costs that dominate direct medical expenditures and substantial indirect costs, of which caregiver expenses account for 60.9%. With the ongoing trend of population aging, the burden of arthritis is projected to escalate further by 2046,[7] highlighting the imperative for more synergistic and precise interventions to mitigate this pressing public health challenge.

The pathophysiology of arthritis involves a systemic cascade initiated and amplified by synovial inflammation.[8] Upon abnormal immune activation, synovial lining cells release key pro-inflammatory cytokines such as TNF-α and IL-1β. These mediators not only directly stimulate synovial hyperplasia to form an inflammatory microenvironment but also induce chondrocytes and synovial fibroblasts to overexpress matrix metalloproteinases and aggrecanases, leading to structural degradation of the articular cartilage extracellular matrix.[9] In autoimmune arthritis, activation of $CD4^+$ T cells, particularly

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the Th17 subset, further drives B cells to produce autoantibodies, resulting in immune complex deposition and the recruitment of macrophages, neutrophils, and other inflammatory cells into the joint cavity.[10] This establishes a self-perpetuating cycle of inflammation. Throughout this process, reactive oxygen species (ROS), including superoxide anion ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\cdot}OH$), accumulate excessively. These are primarily generated by activated macrophages and neutrophils via the NADPH oxidase system (respiratory burst), as well as by dysfunctional chondrocytes within the joint. The accumulation of these oxidants further amplifying the inflammatory response by activating signaling pathways such as NF-κB, while also directly inducing chondrocyte apoptosis and oxidative damage to matrix components.[11] In the typical progression of RA, VEGF-mediated pathological angiogenesis promotes the transformation of synovial tissue into an invasive pannus structure, which erodes subchondral bone and ultimately leads to irreversible joint destruction and loss of function.[12] This complex, multi-faceted pathogenesis poses significant challenges for traditional therapeutic approaches, which often struggle to achieve comprehensive and sustained disease control.

Current clinical treatments, including anti-TNF biologics, JAK inhibitors, and corticosteroids, primarily target key inflammatory and immune pathways.[13] However, they face multiple practical limitations that constrain their long-term effectiveness and safety. Systemic administration exhibits low bioavailability at the joint site, which limits therapeutic efficacy and is often accompanied by systemic side effects, such as gastrointestinal reactions and hepatorenal toxicity.[14] Although intra-articular injections enable local delivery, drugs are rapidly cleared by synovial fluid, resulting in short retention times. This leads to frequent injections, elevated infection risk, and poor tissue specificity toward pathological tissues such as the synovium and cartilage.[15] These challenges highlight the urgent need to develop novel delivery systems or nanomedicines that are efficient, long-acting, and tissue-selective.

To address these critical gaps, nanomedicine has emerged as a promising solution, offering distinct advantages through rational design.[16–18] As summarized in Figure 1, these key strengths encompass: (1) enhanced targeting ability, which promotes selective drug accumulation at pathological sites such as inflamed synovium and damaged cartilage; (2) prolonged intra-articular drug retention, overcoming rapid synovial clearance to sustain local therapeutic action; (3) controllable or stimuli-responsive drug release, allowing on-demand delivery triggered by disease-specific cues such as pH, enzymes, or reactive oxygen species; and (4) co-delivery and multifunctional capacity, enabling combination therapies and the integration

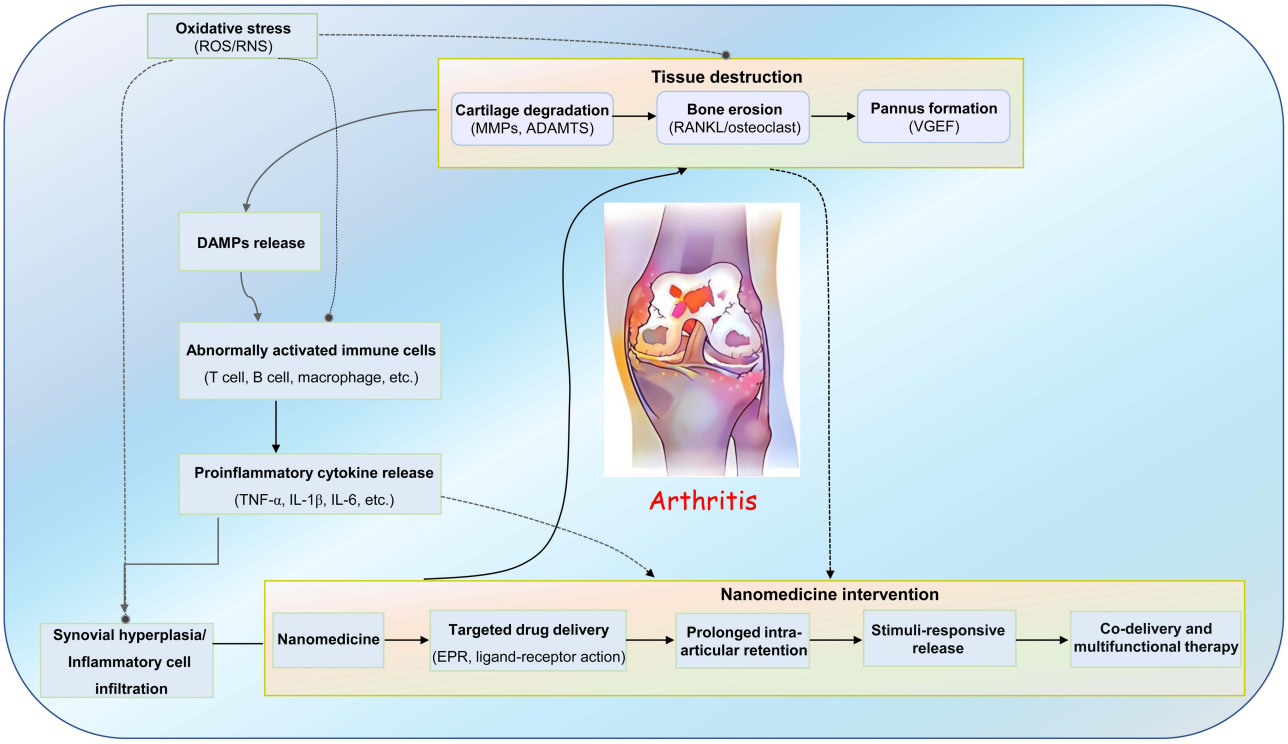

Figure 1 Schematic diagram of arthritis pathology progression and nanomedicine intervention mechanisms.

of diagnostic or regenerative functions within a unified platform. Collectively, these features establish nanomedicine as a transformative approach capable of overcoming the inherent limitations of conventional arthritis treatments.[19,20]

In this context, the present review comprehensively reviews the rational design of advanced nanomedicines for arthritis therapy, with a specific focus on the two most common and pathologically distinct modalities: RA and OA. It classifies current delivery platforms, including lipid-based, polymer-based, inorganic, and bioinspired/biomimetic systems, and analyzes their targeting strategies and stimuli-responsive release mechanisms. The review also evaluates the clinical translation progress of these nanotherapeutics and discusses key challenges in biocompatibility, scalability, and regulatory pathways. Finally, it outlines future directions for developing intelligent, multifunctional nanomedicines to achieve sustained and effective arthritis treatment.

Nanotherapeutic Delivery Platforms for Arthritis

The success of modern drug delivery largely depends on the ability to transport therapeutic agents precisely and controllably to the disease targets. In the case of arthritis, a complex and localized disorder of the joint cavity, conventional administration strategies demonstrate limited therapeutic efficacy, primarily due to their failure to adequately overcome physiological joint barriers and adapt to the unique articular microenvironment. Nanoparticulate-based drug delivery systems have emerged as a transformative approach to overcome these limitations. Classified by material composition and intrinsic characteristics, nanocarriers employed in arthritis therapy can be categorized into four primary types: lipid-based nanosystems, polymer-based nanosystems, inorganic nanomaterials, and bioinspired/biomimetic nanovehicles (Figure 2).

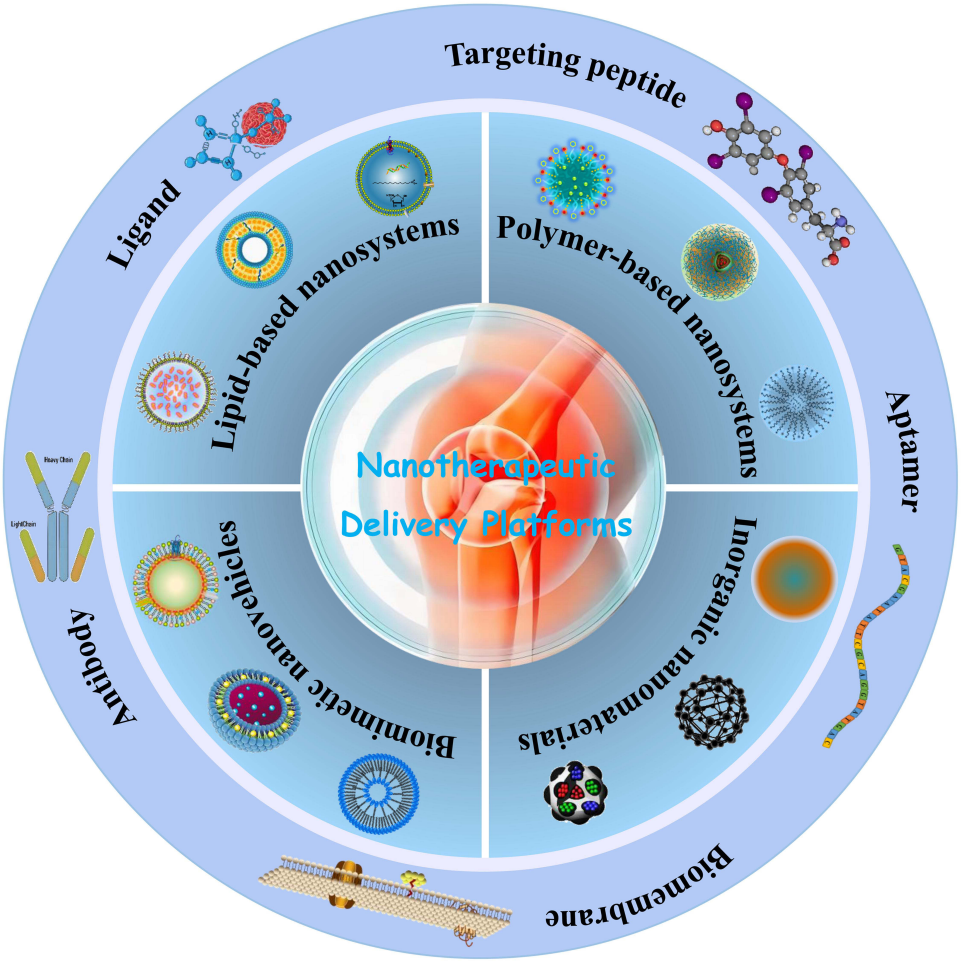

Figure 2 Engineered nanotherapeutic delivery systems for arthritis. Schematic representation of the four primary types of nanoplatforms—lipid-based, polymer-based, inorganic, and biomimetic nanosystems—all of which can be surface-engineered with targeting moieties such as ligands, peptides, aptamers, antibodies, or cell membranes to enhance joint-specific accumulation and therapeutic precision in arthritic tissues.

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Lipid-based nanosystems, represented by liposomes and lipid nanoparticles, possess inherent advantages in drug delivery due to their high affinity and biocompatibility with cell membranes.[21] The core strength of these systems lies in their amphiphilic nature, which enables efficient encapsulation of both hydrophilic drugs (within the inner aqueous compartment) and hydrophobic drugs (embedded in the lipid bilayer), while also providing a convenient interface for surface functionalization. In arthritis treatment, their application strategies are particularly sophisticated. Through adjusting lipid composition and particle size, they can significantly prolong drug retention time within the joint cavity.[22] For example, dexamethasone palmitate liposomes have been successfully translated into clinical use for long-acting intraarticular injections in RA. Furthermore, by modifying the lipid carrier surface with targeting ligands (such as RGD peptides), active targeting to inflamed synovium or macrophages can be achieved.[23] The most cutting-edge design involves endowing these systems with environmental responsiveness—for instance, constructing ROS-responsive liposomes that specifically rupture and release drugs only in the high reactive oxygen species environment of inflammatory sites, greatly enhancing the precision and safety of treatment.[24]

Polymer-based nanosystems, with their highly customizable chemical structures, serve as a potential platform for programmed drug release. Synthetic polymers, exemplified by PLGA, offer precisely tunable degradation periods.[25,26] This enables smooth drug release profiles ranging from weeks to months, perfectly aligning with the long-term management needs of chronic arthritis. Meanwhile, natural polymers demonstrate unique biological advantages. Positively charged chitosan can specifically adhere to the negatively charged cartilage matrix through electrostatic interactions, achieving natural cartilage targeting.[27] Hyaluronic acid, a natural component of joint synovial fluid, acts as an ideal ligand for CD44 receptor. It actively recognizes and targets activated inflammatory cells and synovial cells that overexpress CD44 in arthritis, making it a standout material for synovium-specific delivery.[28] These polymer nanoparticles are not merely inert carriers. Often, the materials themselves participate in synergistic therapeutic effects, contributing to anti-inflammatory or reparative processes.

Inorganic nanomaterials, with their unique and stable physicochemical properties (such as optical, magnetic, and catalytic capabilities), have opened new paradigms for arthritis treatment that go beyond simple drug delivery. For instance, mesoporous silica nanoparticles possess a large specific surface area and well-ordered pore channels, enabling not only efficient drug loading but also co-delivery of imaging agents, allowing for visualized monitoring of the treatment process (theranostics).[29–31] More revolutionary are photothermal agents like gold nanorods and black phosphorus nanosheets, which can efficiently generate heat under near-infrared light irradiation.[32,33] This heat can be directly used for photothermal ablation of abnormal synovial pannus or induce immunomodulation through thermal therapy. Additionally, cerium oxide nanoparticles exhibit potent enzyme-mimicking activity (nanozymes). Due to the mixed valence states (Ce^{3+}/Ce^{4+}) on their surface, they can continuously scavenge excess ROS in the joint by dismutating superoxide anion ($O_2^{-\cdot}$) via superoxide dismutase (SOD)-like activity and decomposing hydrogen peroxide (H_2O_2) via catalase (CAT)-like activity.[34] This dual antioxidase capacity allows them to intervene at the root of oxidative stress-driven inflammation and cartilage degradation, showcasing the novel concept of "catalytic therapy" that targets both the primary and secondary ROS species generated by activated immune cells.

Bio-derived nanosystems represent the pinnacle of biomimetic nanotechnology, leveraging the body's own components as delivery vehicles to achieve ultimate biocompatibility and intelligent targeting. Exosomes are natural nanovesicles secreted by cells, particularly those derived from mesenchymal stem cells, which are inherently rich in therapeutic nucleic acids and proteins.[35,36] They possess potent intrinsic anti-inflammatory and cartilage-repairing capabilities while serving as near-perfect natural carriers for loading exogenous drugs. Cell membrane camouflaging nanotechnology is even more innovative.[37,38] By enveloping synthetic nanoparticles with the cell membranes of macrophages or neutrophils, the resulting biomimetic nanoparticles perfectly inherit the chemotactic ability of the source cells toward inflammatory sites,[39] achieving inflammation targeting akin to "using the enemy against itself". Meanwhile, nanoparticles coated with chondrocyte membranes may enable homing to damaged cartilage, providing unprecedented precision tools for cartilage-specific repair.

As summarized in Table 1, the four major classes of nanoplatforms each offer distinct advantages tailored to specific therapeutic needs. Collectively, they form a powerful and versatile "nanotechnology toolbox" for arthritis therapy. The membrane-mimicking properties of lipid-based systems, the programmable nature of polymer-based systems, the

Table 1 Comparative Features of Nanoplatforms for Arthritis Therapy

FeatureSystem	Lipid-Based	Polymer-Based	Inorganic	Bioinspired/Biomimetic
Representative systems	Liposomes; Lipid nanoparticles; Micro/nanoemulsions	PLGA nanoparticles; Chitosan; Polymeric micelles	Mesoporous silica; Gold nanoparticles; Nanoceria, Layered double hydroxide	Exosomes; Cell membrane-coated nanocarriers; Endogenous biomimetic systems (albumin/lipoprotein-mimetic)
Targeting/retention	High (surface modifiable with ligands, PEGylation)	Moderate-high (charge-mediated cartilage adhesion, HA targeting)	Moderate (size/shape dependent; EPR effect)	Very high (immune evasion, inflammatory chemotaxis, homologous targeting)
Drug release control	Moderate (stimuli-responsive liposomes; sustained release)	Excellent (tunable degradation; pH/ROS/enzyme responsive)	Moderate-High (pore structure; external stimuli: light/magnetic field)	High (microenvironment-triggered shedding; enzyme-responsive)
Regenerative potential	Low (primarily drug delivery)	Moderate (scaffolds, hydrogels, some polymers like HA have intrinsic bioactivity)	Moderate (ions like Mg^{2+}, Ca^{2+} promote bone/cartilage repair)	High (MSC-derived exosomes carry regenerative miRNAs/proteins)
Theranostic capability	Low (requires additional labeling)	Low-moderate (requires conjugation)	High (inherent optical/magnetic properties for imaging)	Moderate (can be engineered for imaging)
Key advantages	Biocompatible, clinically translated, versatile	Tunable release, smart responsiveness, material synergy	Multifunctional, catalytic therapy (nanozymes), photothermal effect	Ultimate biomimicry, active targeting, low immunogenicity
Limitations	Stability issues, rapid clearance (non-PEGylated)	Potential polymer degradation byproducts, complex synthesis	Long-term toxicity concerns, non-biodegradable (some)	Scalability challenges, batch variability, high cost
Recommended disease context	Acute inflammation/RA flares (rapid delivery of glucocorticoids); Sustained low-dose therapy	Chronic RA/OA (long-term immunomodulation); Combination therapy	Theranostics (image-guided therapy); Catalytic antioxidant therapy for OA; Photothermal ablation of pannus	Targeted immunotherapy; Cartilage regeneration; Personalized medicine

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multifunctionality of inorganic materials, and the ultimate biomimetic capabilities of bio-derived systems may address the challenges of drug delivery for arthritis from different dimensions.

Therapeutic Strategies and Action Mechanisms of Nanomedicines

The significance of nanomedicines in arthritis treatment extends beyond mere drug delivery, encompassing their capacity to enable precise and synergistic therapeutic interventions rooted in a profound comprehension of disease pathophysiology. The following sections, along with Figure 3, elaborate how nanomedicines, through multidimensional and intelligently engineered strategies, achieve comprehensive modulation of the intricate pathological cascades in arthritis.

Targeted Modulation of the Immune/Inflammatory Microenvironment

The core pathological feature of arthritis lies in immune system dysregulation and the persistence of chronic inflammatory responses. Nanomedicines can precisely intervene in this process, with designs directly targeting key cells and molecules within the inflammatory microenvironment. By specifically targeting M1-type pro-inflammatory macrophages, nanocarriers can deliver regulatory drugs to induce the transformation of these cells into anti-inflammatory and tissue-reparative M2-type macrophages,[40,41] thereby reshaping immune balance at its source.[42] For instance, nanomedicines have been engineered to deliver therapeutic agents such as celastrol, berberine, or specific nucleic acids (siRNA/miRNA) that modulate key signaling pathways.[23,43,44] These interventions often involve the activation of AMPK, or the inhibition of the NF-κB pathway, leading to a metabolic and functional shift in macrophages. This targeted delivery ensures that pro-inflammatory M1 macrophages are reprogrammed towards an anti-inflammatory M2 phenotype, enhancing the resolution of inflammation and promoting tissue repair in the arthritic joint. Simultaneously, nanoplatforms can precisely neutralize core inflammatory mediators, such as TNF-α, at the lesion site by efficiently loading or surface-modifying cytokine inhibitors, effectively blocking the cascade amplification of inflammation.[45,46] Furthermore, by delivering inhibitors of key signaling pathways such as the NLRP3 inflammasome,[47] nanomedicines can curb the initiation and progression of inflammation from upstream, achieving deep modulation of the immune microenvironment.

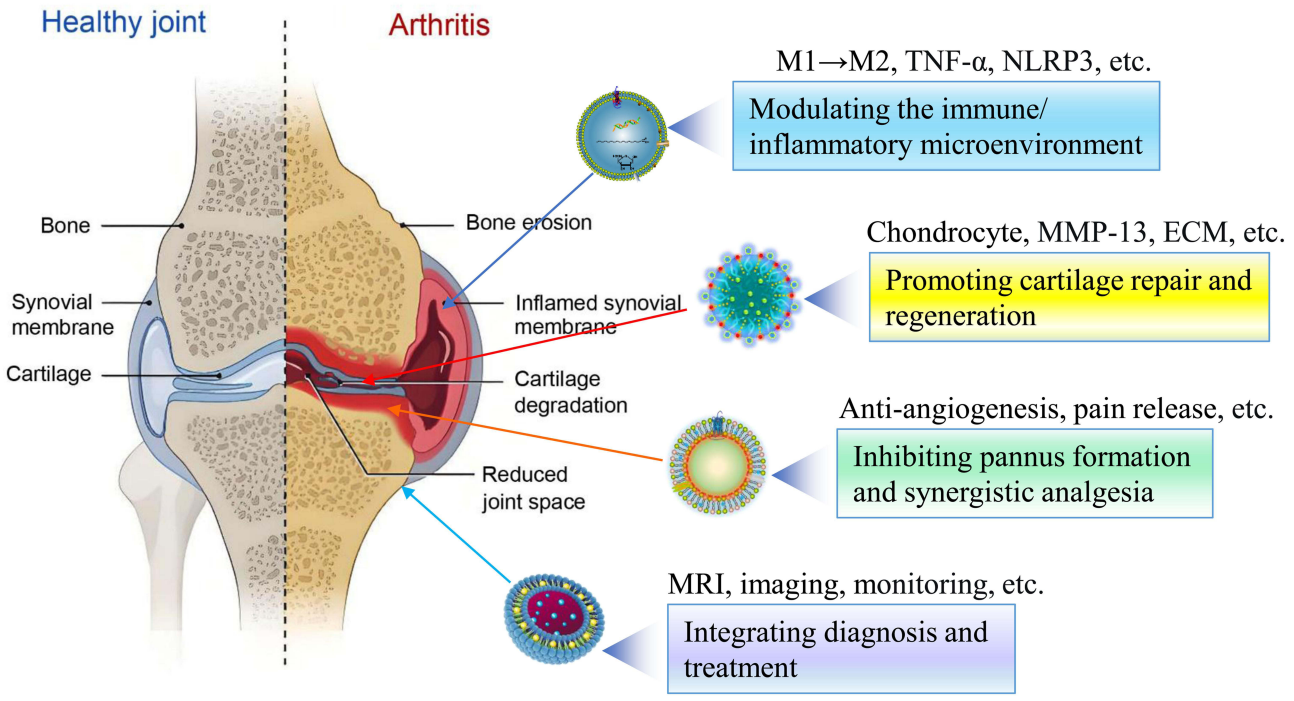

Figure 3 Multifaceted therapeutic strategies of nanomedicines in arthritis.

Promotion of Cartilage Repair and Regeneration

Ideal arthritis treatment requires not only the inhibition of tissue destruction but also the active promotion of repair and regeneration of damaged cartilage. Nanomedicines demonstrate unique advantages in this field, serving as multifunctional platforms to support cartilage regeneration. By loading specific growth factors or genetic materials, nanocarriers can guide mesenchymal stem cells to home to the injury site and promote their differentiation into functional chondrocytes, thereby replenishing the lost cell population.[48,49] At the genetic level, nanocarriers can deliver protective genes to enhance the anabolic activity of chondrocytes or deliver gene-silencing tools to inhibit the overexpression of catabolic enzymes, achieving long-term regulation of cartilage homeostasis.[50,51] Additionally, injectable nanocomposite hydrogels can form a biomimetic three-dimensional microenvironment within the joint cavity, providing physical support and biochemical signals for cell adhesion, proliferation, and extracellular matrix secretion, synergistically promoting in situ tissue regeneration.[52]

Inhibition of Pannus Formation and Synergistic Analgesia

In inflammatory arthritis such as RA, the abnormal proliferation of synovial pannus is a key driver of joint destruction and is accompanied by significant pain. Nanomedicines provide targeted solutions for this. Through surface functionalization, nanoparticles can actively recognize and accumulate at neovascular sites, precisely delivering anti-angiogenic drugs to inhibit the growth of pathological pannus, thereby cutting off its "nutrient" supply to inflammation and destruction processes.[53] For pain management, nanotechnology-based sustained-release systems can maintain therapeutic levels of analgesic drug concentrations within the joint cavity, achieving localized analgesia lasting for weeks.[54] This not only significantly improves patients' quality of life but also reduces reliance on systemic analgesics and their associated side effects.

Orchestration of Theranostic Platforms

The inherent diverse physicochemical properties of nanomaterials make it possible to integrate diagnostic and therapeutic functions into a single platform, driving arthritis management toward precision and visualization. Theranostic nanoplatforms, by co-loading therapeutic drugs and imaging probes (such as MRI contrast agents or fluorescent dyes), enable non-invasive, real-time visualization of the distribution and targeting efficiency of nanomedicines within the joint.[55] More importantly, such platforms allow for the dynamic assessment of changes in lesions (such as the degree of inflammation reduction or cartilage repair) during treatment,[56] providing objective evidence for efficacy evaluation and laying the technical foundation for the individualized and dynamic adjustment of treatment plans.

Through the synergistic application of the above multifaceted strategies, nanomedicines are systematically transforming the treatment paradigm for arthritis, shifting from passive symptom relief to active intervention in disease progression. The intelligent integration and individualized implementation of these strategies represent the core direction for the future development of nanomedicine in arthritis.

Engineering Nanomedicines for Arthritis Therapy

The rise of nanotechnology is driving arthritis therapy toward greater precision and intelligence. Through the design of diverse platforms such as lipid carriers, polymeric nanoparticles, inorganic nanosystems, and bioinspired vehicles, efficient targeted delivery and programmed release of anti-inflammatory drugs can be achieved, which is providing a powerful tool to overcome the bottlenecks of traditional treatments.

Lipid-Based Nanoplatforms

As a pivotal drug delivery platform, lipid-based nanoplatforms encompass a wide range of lipid materials, from natural to fully synthetic ones, including phospholipids, triglycerides, and polymeric lipids.[57,58] Their inherent biocompatibility, biodegradability, and flexible modifiability for surface render them a cornerstone of nanomedicine engineering. In the field of arthritis therapy, these properties have been successfully translated into therapeutic advantages, enabling lipid nanocarriers to efficiently deliver drugs to inflamed joints and achieve precise treatment.[59]

Lipid-based nanoplatforms have emerged as versatile and effective delivery systems for targeted arthritis therapy, integrating various strategies to enhance therapeutic precision and reduce systemic toxicity. One prominent approach involves ligand-mediated active targeting, exemplified by VCAM-1-targeted methotrexate (MTX)-loaded lipid nanoparticles[60] and folate receptor-targeted MTX nanoemulsions,[61] which exploit receptor overexpression on activated synovial fibroblasts or macrophages for enhanced joint accumulation. Complementing this, endogenous albumin-hijacking strategies, such as dexamethasone-loaded liposomes functionalized with an albumin-binding domain, extend circulation and leverage albumin's natural tropism to inflammatory sites.[62] Furthermore, combination therapies co-delivering agents like curcumin and leflunomide within phytosomes demonstrate improved pharmacokinetics and synergistic anti-inflammatory effects.[63] These platforms collectively address key challenges in RA treatment, including poor bioavailability, non-specific distribution, and narrow therapeutic windows.

A significant advancement in this field is the development of biomimetic, microenvironment-responsive systems, with a notable example featuring a neutrophil-mimetic lipid nanoplatform. This sophisticated design cloaks leonurine and catalase co-loaded nanoliposomes with neutrophil membranes, inheriting their innate inflammation tropism for targeted joint delivery.[64] As illustrated in Figure 4. The system is engineered to be responsive to the reactive oxygen species (ROS)-rich arthritic microenvironment, where catalase converts hydrogen peroxide into oxygen, simultaneously alleviating hypoxia and triggering drug release. Moreover, the neutrophil membrane acts as a decoy, neutralizing pro-inflammatory cytokines and chemokines. In

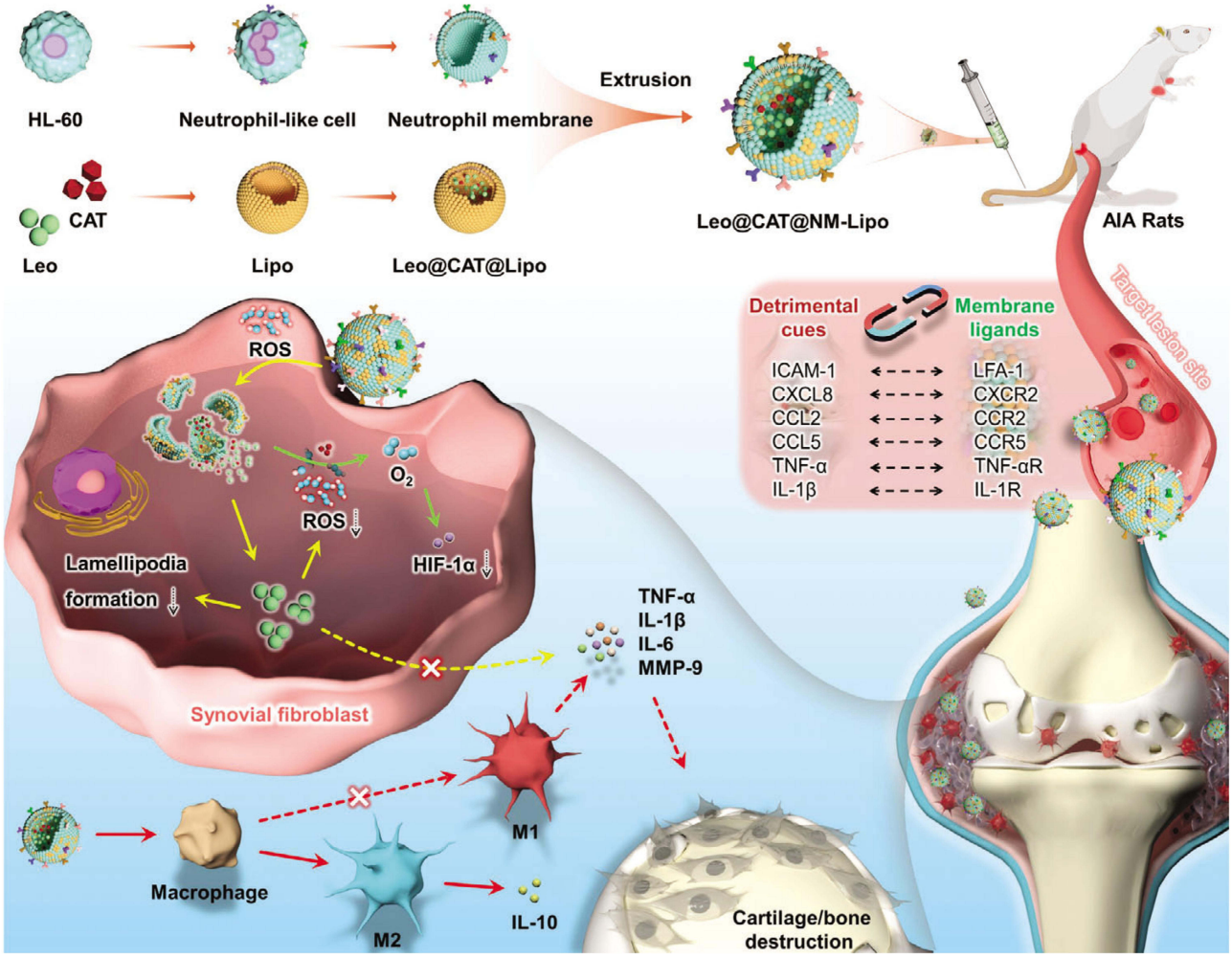

Figure 4 Engineering of multi-pronged nanoplatform (Leo@CAT@NM-Lipo) for synergistic therapy against rheumatoid arthritis via inflammatory lesion targeting, ROS-responsive drug release, ROS scavenging, immunoregulation, and hypoxia relief. Adapted from Tang Z, Meng S, Yang X, et al. Neutrophil-mimetic, ROS responsive, and oxygen generating nanovesicles for targeted interventions of refractory rheumatoid arthritis. Small. 2024;20(20):e2307379. http://creativecommons.org/licenses/by/4.0/.[64] licensed under CC-BY 4.0.

preclinical models, this multifunctional system synergistically alleviates joint swelling, reduces bone erosion, and repolarizes macrophages through combined anti-inflammatory, antioxidant, and immunomodulatory actions, showcasing a paradigm shift toward intelligent, feedback-responsive nanomedicine.

The evolution of lipid nanoplatforms for arthritis thus reflects a trajectory from simple passive targeting to advanced bio-hybrid systems capable of active homing, microenvironmental sensing, and multi-modal therapy. By merging materials science with principles of immunology and cell biology, these platforms—from peptide-targeted nanoparticles to cell membrane-camouflaged vesicles—offer increasingly sophisticated solutions to overcome biological barriers and enhance site-specific efficacy.

Polymer-Based Nanoplatforms

Polymer-based nanoplatforms constitute a pivotal class of drug delivery vehicles, engineered from biocompatible and frequently biodegradable macromolecules including PLGA, chitosan, and PEG.[65] These systems are distinguished by their highly customizable architecture, enabling precise modulation of drug release profiles and straightforward conjugation of targeting moieties. In RA therapy, such design adaptability has been crucial for developing "smart" nanocarriers capable of responding to inflammatory cues and selectively accumulating in diseased joints, thus advancing therapeutic precision and safety.[66]

Polymer-based nanoplatforms have demonstrated considerable potential as versatile and effective delivery systems for targeted arthritis therapy, integrating multiple strategies to enhance therapeutic precision, improve bioavailability, and reduce systemic toxicity. One notable example involves the use of hyperbranched semiconducting polymer nanoparticles (HSP-PEG-NPs) for both imaging and therapy in RA.[67] HSP-PEG-NPs were engineered to co-deliver the radioisotope ^{99m}Tc for SPECT imaging and MTX for RA treatment. Upon intravenous administration, these nanoparticles selectively accumulated in inflamed joints via an EPR-like effect and showed significant RA alleviation with reduced systemic toxicity. Another innovative "drug in therapeutic polymer" strategy was reported by Yin' group, where sinomenine (Sin) was loaded into oxidation-responsive hyaluronic acid-based nanoparticles (PAM-HA@Sin NPs).[68] The PAM-HA carrier not only served as a drug vehicle but also exhibited intrinsic therapeutic effects, including ROS scavenging, joint lubrication, and cartilage binding via alendronate moieties. Further extending the concept of microenvironment-responsive polymer systems, a ROS-sensitive nanoplatform was developed for osteoarthritis (OA) therapy.[69] In this study, astaxanthin and rapamycin were co-encapsulated in thioketal-containing polymeric nanoparticles (NP@PolyRHApM) to reprogram macrophage polarization and mitigate oxidative stress. The nanoparticles disassembled under high ROS conditions in M1 macrophages, releasing astaxanthin to scavenge ROS and rapamycin to induce autophagy. This dual action promoted M1-to-M2 repolarization, reduced synovitis, and protected chondrocytes in an ACLT-induced OA mouse model. In another RA-targeted approach, a pH-responsive lipid-polymer hybrid nanoparticle system (Pae-PPNPs-DS) was designed to actively deliver paeoniflorin to macrophages via dextran sulfate-mediated targeting of scavenger receptor class A type I.[70] As reported, the nanoparticles released drug in acidic inflammatory environments and effectively modulated macrophage polarization by regulating the STAT signaling pathway. In CIA rats, Pae-PPNPs-DS reduced joint swelling, suppressed pro-inflammatory markers (TNF-α, IL-1β, iNOS), and promoted anti-inflammatory markers (IL-10, Arg-1), demonstrating the efficacy of combined active targeting and microenvironment-triggered release. Meanwhile, in addition to the MMP-sensitive macrophage-targeted CoQ10 delivery system that utilizes PEG cleavage for PS-mediated phagocytosis,[71] another multifunctional polypyrrole-based platform (PPy–FePi–MTX NPs) has been developed to enhance RA therapy by simultaneously inducing apoptosis and ferroptosis in M1 macrophages.[72] These "smart" polymer-based designs demonstrate how nanoplatforms can integrate microenvironmental responsiveness, multimodal therapeutic actions, and precise targeting to effectively eliminate inflammatory macrophages and improve RA treatment.

Most recently, several studies have further demonstrated the versatility and therapeutic potential of polymer-based nanoplatforms for arthritis treatment through innovative design strategies. For instance, Wu et al[73] reported a redox- and gene-regulating polymeric nanoparticle system for osteoarthritis (OA) therapy. The platform was constructed from antioxidant TEMPO-PEG-PLGA and cationic PEG-PLG A-OA9, enabling co-delivery of the ROS scavenger tetramethylpiperidoxyl (TEMPO) and MMP-13-targeting siRNA (siMMP-13). The nanoparticles effectively neutralized excess reactive oxygen species and silenced catabolic gene expression in chondrocytes. In a DMM-induced OA mouse

model, the system showed strong anti-inflammatory and cartilage-protective effects, attenuating cartilage degradation and subchondral bone remodeling. Impressively, a self-anti-inflammatory polymer nanocarrier based on caffeic acid was developed for enhanced RA therapy.[74] The caffeic acid-derived polyphenol polymer (PCOH) was used to construct nanoparticles for the delivery of MTX. These MTX@PCOH NPs exhibited rapid accumulation and prolonged retention in inflamed joints of collagen-induced arthritis (CIA) mice via the EPR effect. PCOH NPs inhibited LPS-stimulated iNOS expression and pro-inflammatory macrophage polarization in vitro. In vivo, even at a low MTX dose (2.5 mg/kg), MTX@PCOH NPs significantly alleviated joint swelling, reduced bone erosion, and decreased levels of pro-inflammatory cytokines (TNF-α, IL-1β, iNOS), demonstrating synergistic therapeutic effects between the active carrier and the drug with minimal systemic toxicity (Figure 5).

Together, these studies chronicle the transformative progression of polymer-based nanoplatforms from passive carriers to sophisticated, multifunctional systems capable of active targeting, microenvironmental sensing, and combined therapeutic-imaging functions. By leveraging materials chemistry, immunology, and disease biology, polymer nanoplatforms offer promising strategies to overcome biological barriers, enhance site-specific efficacy, and improve outcomes in arthritis therapy.

Inorganic Nanoplatforms

Inorganic nanoplatforms serve as a potential alternative to their organic counterparts in arthritis treatment, characterized by their tunable morphology, superior physicochemical stability, and multifunctional capabilities.[75] These nanomaterials, such as mesoporous silica nanoparticles, selenium nanoparticles, gold nanoparticles, ion nanoparticles, and layered double hydroxides, offer unique advantages including high drug-loading capacity, controllable degradation profiles, and responsiveness to external stimuli (eg., pH, redox, or magnetic fields). In the context of arthritis therapy, these platforms have been engineered to not only deliver anti-inflammatory drugs with enhanced pharmacokinetics, but also to integrate diagnostic imaging (eg., via MRI or photoacoustic contrast) and photothermal or catalytic therapeutic functions. This convergence of targeting, treatment, and imaging within a single inorganic carrier underscores its potential for developing combined theranostic strategies in managing joint inflammation and damage.[76]

In parallel with the advances in polymer-based delivery systems, inorganic nanoplatforms have emerged as highly promising candidates for arthritis therapy. These platforms often combine structural versatility, catalytic functions, and inherent immunomodulatory or osteogenic effects, enabling multifunctional approaches to treat complex arthritic conditions. One characteristic case is the use of hydroxyapatite (HA)-based nanoparticles for targeted RA therapy.[77] The engineered nanocarrier functionalized with hyaluronic acid and loaded with MTX and teriflunomide not only halted the disease progression and promoted articular regeneration, but also reduced the hepatotoxicity caused by traditional treatments. This system exemplifies how inorganic carriers can be surface-engineered for active targeting and combination drug delivery. Another innovative approach leverages mesoporous silica hybrid nanoparticles for combined phototherapy, hypoxia-activated chemotherapy, and RNA interference in RA.[78] The photosensitizer PCPDTBT-loaded mesoporous silica nanoparticles coated with branched polyethyleneimine-folic acid (PEI-FA) to co-deliver tirazapamine and Mcl-1 siRNA. Under NIR irradiation, the nanoplatform enabled photothermal/photodynamic therapy, hypoxia-activated drug release, and gene silencing, collectively promoting apoptosis in activated macrophages and ameliorating RA symptoms in vivo. Similarly, metal–natural product coordination complexes have been designed to counteract oxidative stress and modulate immune responses in RA.[79] The synthesized ultrasmall iron–quercetin natural coordination nanoparticles (Fe–Qur NCNs) preserved the antioxidant capacity of quercetin while concurrently demonstrating improved water solubility and biocompatibility. These nanoparticles effectively scavenged ROS, inhibited NF-κB activation, promoted M2 macrophage polarization, and reduced osteoclastogenesis, leading to significant alleviation of joint inflammation and bone erosion in a collagen-induced arthritis model. For osteoarthritis therapy, magnesium oxide (MgO)-based nanocomposites have shown promise in promoting cartilage–bone synergy. Zheng et al[80] engineered microspheres loaded with nano-MgO for intra-articular delivery of Mg^{2+} ions. The sustained release of Mg^{2+} enhanced chondrogenic differentiation, inhibited osteoclast formation, and activated the PI3K/AKT pathway. Lately, a sophisticated inorganic nanocatalytic platform, nanoceria-loaded magnesium–aluminum layered double hydroxide (LDH–CeO_2) system, has been reported for RA therapy.[81] It strategically targets two key pathological features of RA:

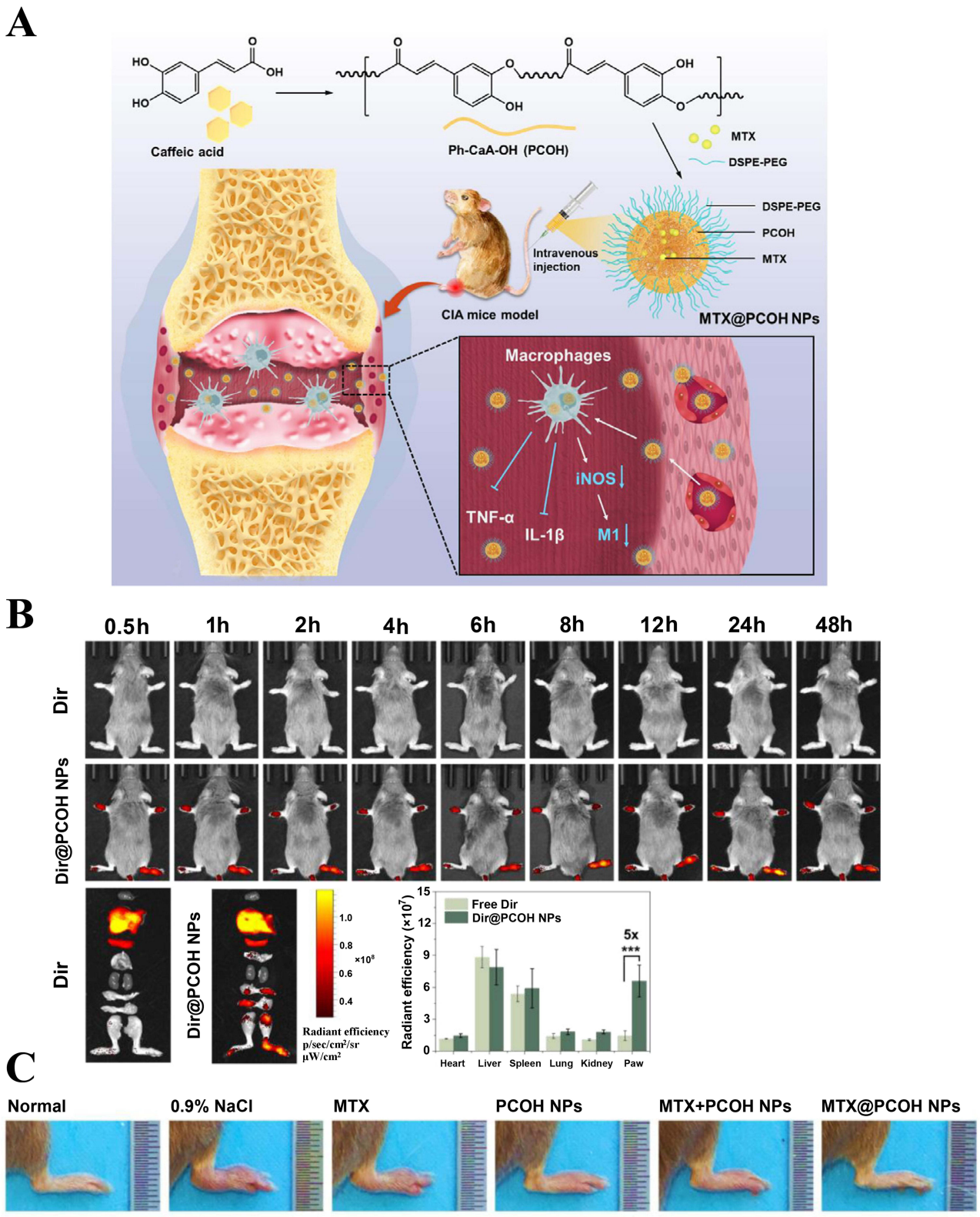

Figure 5 Engineering MTX@PCOH NPs for arthritis rheumatoid treatment: (**A**) Schematic of PCOH NPs and MTX@PCOH NPs aggregating in inflamed joints; (**B**) Biodistribution of Dir@PCOH NPs in vivo in CIA mice (n = 3, ***$P < 0.001$, unpaired Student's *t*-test); and (**C**) Representative hind paw images of different groups on day 51 after treatment. Adapted from Dai C, Wang L, You X, et al. Coffee-derived self-anti-inflammatory polymer as drug nanocarrier for enhanced rheumatoid arthritis treatment. Chin Chem Lett. 2025;36:109869. http://creativecommons.org/licenses/by/4.0/.[74] licensed under CC-BY 4.0.

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acidic microenvironment and oxidative stress. The alkaline LDH neutralizes osteoclast-derived H^+, restoring the antioxidant activity of CeO_2 nanoparticles in acidic conditions. Concurrently, released Mg^{2+} drives M2 macrophage polarization and osteogenesis, while CeO_2 scavenges ROS to reinforce anti-inflammatory repolarization.

In the context of OA, inorganic nanoparticles have also shown systemic and local therapeutic efficacy. Gold nanoparticles (GNPs) have been shown to mitigate OA progression via modulation of the "microbiota–gut–joint" axis.[82] In an ACLT-induced murine model, oral administration of GNPs significantly attenuated cartilage degradation and subchondral bone loss, effects attributed to their ability to beneficially reshape gut microbial composition. Likewise, polydopamine-coated selenium nanoparticles (PDA-SeNPs) demonstrate enhanced chondroprotective effects in OA.[83] The PDA coating improves their stability and biocompatibility, which in turn better supports chondrocyte viability, upregulates chondrogenic markers, scavenges reactive oxygen species, and promotes cartilage repair. Applying this inorganic paradigm in RA, iron-doped carbon dots synthesized from traditional Tibetan medicinal materials (magnetite and medicated leaven) also exhibit noticeable therapeutic efficacy.[84] Orally administered MM-CDs significantly alleviated joint swelling, inflammatory infiltration, and bone-cartilage damage in a Freund's adjuvant-induced RA model, performing comparably to MTX (Figure 6). Mechanistically, MM-CDs suppress neutrophil-driven inflammation by downregulating NETosis markers, promoting apoptosis, and reducing autophagy-related proteins, thus disrupting the autophagy–NETosis axis. Importantly, no hepatorenal toxicity was detected, highlighting their favorable safety.

The abovementioned cases illustrate the versatility and therapeutic potency of inorganic nanoplatforms in arthritis treatment. By integrating catalytic, ionic, structural, and targeting functionalities, inorganic systems can simultaneously address multiple pathological processes, such as oxidative stress, acidosis, immune dysregulation, and bone erosion, offering a robust and multifunctional arsenal against both RA and OA.

Bioinspired/Biomimetic Nanoplatforms

Bioinspired/biomimetic nanoplatforms represent a transformative frontier in arthritis therapy, engineered by emulating natural biological structures and processes such as cell membranes, viral capsids, or inflammatory tropism.[85] These systems are distinguished by their innate ability to evade immune clearance, selectively engage with pathological cells, and dynamically respond to the arthritic microenvironment. In RA treatment, this biomimetic design has been pivotal for creating intelligent nanomedicines that achieve precise targeting of inflamed joints and context-specific drug release, thereby significantly enhancing therapeutic efficacy while minimizing systemic toxicity.

Bioinspired nanoplatforms have evolved beyond simple drug carriers to become sophisticated systems capable of precise subcellular targeting. A representative example involves engineering platelet microparticle membrane (PMMs)-camouflaged nanoparticles to deliver all-trans retinoic acid (ATRA) directly to the Golgi apparatus of pathogenic synovial fibroblasts in RA.[86] This strategy exploits the natural affinity of PMMs for inflamed sites and RA synovial fibroblasts (RASFs), while a conjugated Golgi-targeting peptide ensures retrograde transport to the specific organelle. The ensuing structural disruption of the Golgi by ATRA effectively shuts down the secretion of critical pathogenic proteins (eg., IL-6, MMPs), thereby attenuating synovitis and bone erosion in vivo. Similarly, for OA treatment, a decorin-derived cartilage-binding peptide was used to functionalize lipid nanoparticles, granting them high affinity for the type II collagen-rich extracellular matrix.[87] This modification not only enabled prolonged retention within the avascular cartilage but also facilitated deep penetration into the dense matrix, allowing for sustained release of chondrogenic factors (TGF-β3 and kartogenin) to recruit endogenous stem cells and promote hyaline-like cartilage regeneration in full-thickness defects.

A central theme in biomimetic nanomedicine is the repurposing of natural cell membranes to bestow nanoparticles with complex biological functions. This is vividly demonstrated in strategies for RA immunotherapy. For instance, erythrocyte membranes were used to camouflage self-assembled nanoparticles of celastrol and bilirubin, significantly extending systemic circulation and reducing immunogenicity.[43] Further functionalization with hyaluronic acid added active targeting to inflamed joints. This design synergized STING pathway inhibition with reactive species clearance to remodel the joint microenvironment. Another approach utilized the homologous targeting capability of fibroblast-like synoviocyte membrane proteins, fusing them with liposomes loaded with chrysin.[88] These biomimetic vesicles efficiently honed to inflamed synovium, where drug release inhibited the HIF-1α/iNOS/NLRP3 inflammatory axis. Aligned with

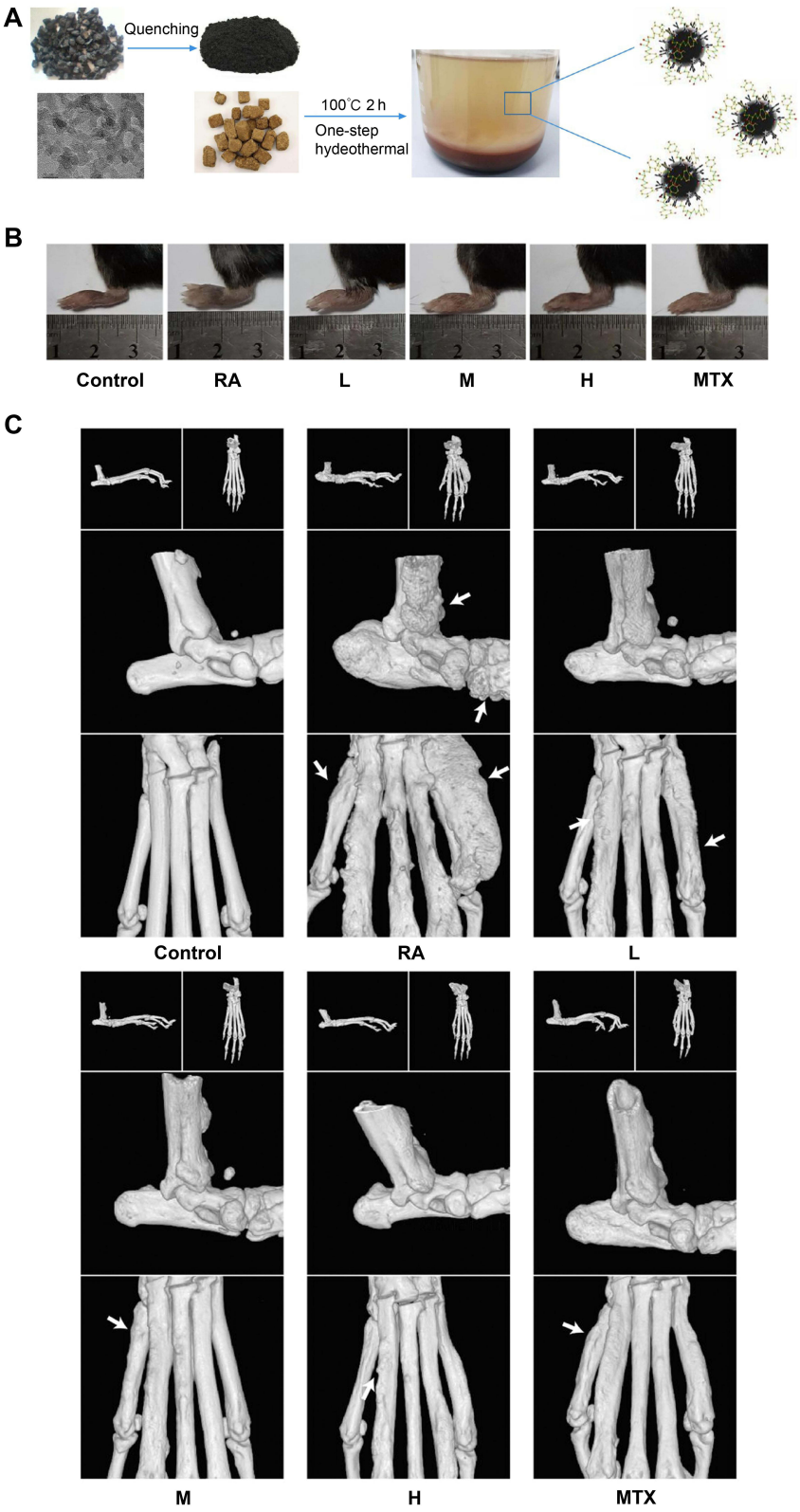

Figure 6 Fe-doped carbon dots fabricated from magnetite and medicated leaven (MM-CDs) alleviated rheumatoid arthritis: (**A**) Preparation of MM-CDs; (**B**) Photos of the mouse ankle joint treated with MM-CDs at low (L), medium (M) and high (H) dose or methotrexate (MTX); and (**C**) 3D images of the hind paw and ankle joint, arrows indicating bone erosion. Adapted from Wang H, Wang L, Yan A, et al. Fe-doped carbon dots alleviated rheumatoid arthritis by inhibiting neutrophil NETosis and autophagy. ACS Biomater Sci Eng. 2025;11;3666−3681. http://creativecommons.org/licenses/by/4.0/.[84] licensed under CC-BY 4.0.

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this biomimetic membrane-coating strategy, Zhang et al[89] developed a dual-engineered plant-derived exosome-like nanovesicles (MOE@EM) for RA therapy. UV irradiation of *Morinda officinalis* roots enhanced MOE yield, antioxidant activity, and M1-to-M2 macrophage repolarization via Wnt/β-catenin suppression. Erythrocyte membrane camouflage further reduced immunogenicity, prolonged circulation, and promoted joint accumulation via the EPR effect, ultimately alleviating arthritis symptoms and modulating synovial immunity without systemic toxicity in vivo.

Perhaps the most dynamic application involves macrophage membranes used as a reversible cloak. These membranes provide long circulation and inflammation targeting but are strategically shed within the oxidative joint milieu.[90] The shedding is triggered by oxygen bubbles generated from catalase-mediated decomposition of excess H_2O_2, subsequently exposing a cationic core for efficient macrophage uptake and siRNA delivery. This elegantly solves the inherent conflict between stealth and cellular internalization in membrane-coated systems. The most advanced frontier involves integrating multiple therapeutic components into a single, cooperative biomimetic platform that performs sequential, synergistic actions. A paradigm was manifested by macrophage membrane-coated, nanozyme-incorporated metal-organic frameworks (mZPMG NPs).[91] This platform executes a "dual-pronged attack" on RA by simultaneously targeting hyperproliferative synovial fibroblasts and the inflammatory immune microenvironment. The system features a ZIF-8 core that co-encapsulates MTX and glucose oxidase (GOx), along with surface-anchored platinum nanoparticles (Pt NPs) serving as a nanozyme, cloaked with a macrophage membrane to ensure targeted delivery to inflamed joints. Upon localization, Pt NPs scavenge ROS that alleviates oxidative stress and inflammation while generating oxygen. This oxygen relieves hypoxia and fuels GOx to convert glucose into gluconic acid and H_2O_2, thereby starving glycolytic cells through glucose depletion. Following this biomimetic strategy, a complementary platform based on cerium oxide nanozymes (MCB@MMs) was recently developed.[92] It employs a BSA-templated core co-encapsulating MTX and Ce nanozymes, which is camouflaged with a macrophage membrane for targeted delivery. The Ce^{3+}/Ce^{4+} redox center mimics SOD/CAT activity to scavenge ROS and generate oxygen, thus alleviating hypoxia and suppressing the HIF-1α/MAPK inflammatory pathway. This effect synergizes with MTX to promote M1-to-M2 macrophage repolarization and remodel the synovial immune microenvironment. The macrophage membrane coating further enhances joint-specific accumulation and mitigates immunogenicity. In AIA rats, MCB@MMs demonstrated pronounced efficacy in alleviating arthritis symptoms and suppressing bone erosion (Figure 7), underscoring the therapeutic potential of integrating traditional drugs, functional nanozymes, and biomimetic membrane strategies for reprogramming the RA microenvironment.

The progression of biomimetic nanoplatforms for arthritis therapy, as evidenced by above studies, reveals an evolution from simple targeted delivery systems to sophisticated, multifunctional constructs that mimic biological processes, respond to pathological microenvironments, and execute combined therapeutic actions. These platforms collectively offer promising avenues for developing more effective, targeted, and safe treatments for arthritis.

Clinical Translation Status and Challenges

The clinical translation of nanomedicines for arthritis has entered a pivotal, early-stage clinical validation phase. This is exemplified by the first completed randomized controlled trial (2022, NCT00241982) of intravenous pegylated liposomal prednisolone (Nanocort).[93] This Phase II study demonstrated superior Week 1 "European League Against Rheumatism" (EULAR) response rates compared to standard intramuscular methylprednisolone. It successfully validated the concept of using long-circulating liposomes for targeted glucocorticoid delivery, enhancing therapeutic efficacy without significantly increasing overall systemic adverse events, though a higher incidence of infusion-related hypersensitivity reactions was noted. While this trial represents a milestone as the first proof-of-concept in a substantial patient cohort, no nanodrug has achieved global regulatory approval for routine clinical use in arthritis. The broader field remains in pre-clinical exploration for osteoarthritis. Furthermore, results from another completed trial on oral gold nanoparticles (NCT05347602) are yet to be reported (https://clinicaltrials.gov). Key challenges for successful translation include mitigating nanocarrier-specific safety concerns such as hypersensitivity, ensuring scalable manufacturing and rigorous quality control for complex nano-formulations, and improving patient's compliance beyond intravenous administration.

Advancing beyond these translational hurdles, the next frontier for nanotherapeutics involves overcoming the profound biological barriers within the arthritic joint itself, which encompasses three core scientific challenges. The first is achieving deeper tissue penetration to deliver therapeutics through the dense, avascular cartilage matrix in osteoarthritis, with

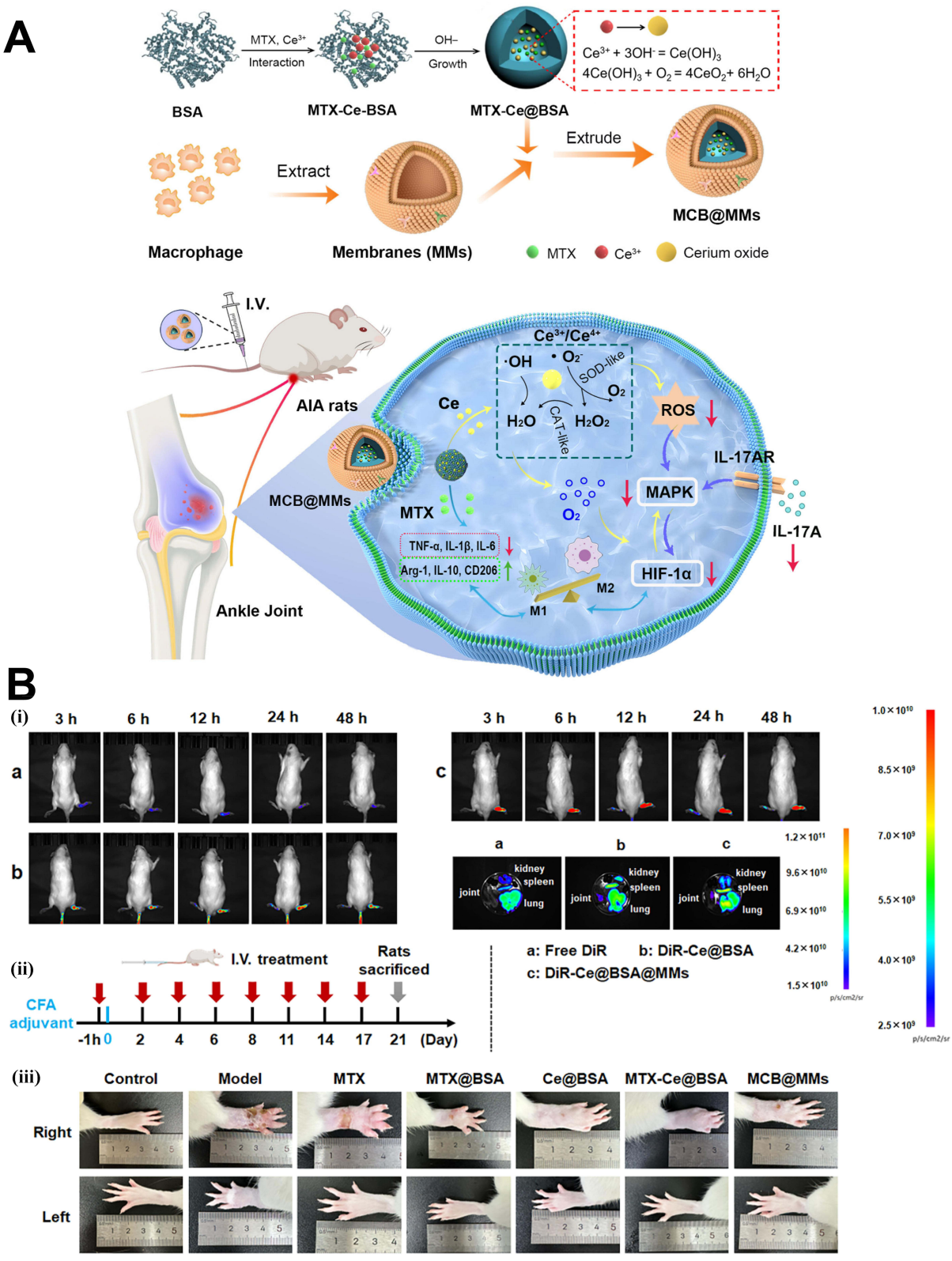

Figure 7 Engineering methotrexate and cerium oxide self-assembly nanoparticles with surface modification by macrophage membrane (MTX-Ce@BSA@MMs) for RA therapy: (**A**) Schematic of MCB@MMs preparation and therapeutic mechanisms; (**B**) In vivo imaging and evaluation of therapeutic effects in AIA rats: (i) biodistribution of nanodevices in vivo and ex vivo fluorescence imaging of major organs and representative images of rat hind paws post-treatment; (ii) the treatment protocol for AIA rats; and (iii) representative images of rat hind paws post-treatment. Adapted from Lv L, Qiu X, Chen W, et al. Oxygen-self-supplying biomimetic nanozymes synergize with methotrexate to reprogram macrophage polarization for rheumatoid arthritis therapy. Acta Biomater. 2026;209:566–582. http://creativecommons.org/licenses/by/4.0/.[92] licensed under CC-BY 4.0.

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strategies under investigation including the design of smaller, charge-modulated nanoparticles or the use of enzymes for transient matrix disruption. The second is the critical need for precise cellular and sub-cellular targeting, moving beyond broad inflammation targeting by incorporating ligands specific to overexpressed receptors on pathogenic cell types like activated synovial macrophages, and even engineering nanoparticles to deliver cargo to specific organelles such as mitochondria. The third and final challenge is navigating the highly heterogeneous and dynamic disease microenvironment, which demands that future nanomedicines be "smart" and stimuli-responsive, capable of releasing their payload only in the presence of specific pathological signals like elevated ROS or enzymes, thereby adapting to variations across disease stages, patient subsets, and joint micro-regions. Consequently, future translation efforts must therefore focus not only on advancing leading candidates like Nanocort into Phase III trials but also on pioneering these next-generation, biologically intelligent platforms to enable smarter targeting and less invasive delivery routes.

Conclusion and Future Prospective

Nanomedicine is fundamentally redefining the therapeutic landscape for arthritis, moving beyond conventional broad-spectrum approaches to enable localized, multi-targeted interventions. Through the rational design of versatile nanoplatforms, such as lipid-based, polymeric, inorganic, and biomimetic systems, key drawbacks of traditional therapies, including poor bioavailability, rapid clearance, and off-target effects, are being systematically overcome. These engineered systems achieve enhanced drug delivery, sustained intra-articular retention, stimuli-triggered release, and combinatorial therapeutic effects, allowing for holistic management of disease processes spanning immune dysregulation, cartilage degradation, and synovial hyperplasia. While early-stage clinical trials, such as the Nanocort study, provide encouraging proof of concept, the full translational potential of these technologies depends on resolving critical hurdles related to long-term safety, scalable production, and the ability to navigate complex joint microenvironments. The ongoing refinement of adaptive and intelligent nanosystems thus positions nanomedicine as a cornerstone of next-generation, precision-based strategies aimed not merely at symptom palliation but at durable disease modification.

Looking ahead, the evolution of arthritis nanomedicine will be steered by two interconnected frontiers: personalized nanomedicine and combinatorial multi-modal therapy. Future platforms will utilize patient-specific biomarkers such as synovial fluid profiles or genetic signatures to tailor nanocarrier properties, including targeting ligands and release profiles, for individualized efficacy. Simultaneously, the integration of multi-modal strategies within a single platform will be central, enabling the co-delivery of complementary agents (eg., biologics with small-molecule drugs, or therapeutics with imaging probes) to concurrently suppress inflammation, promote repair, and allow treatment monitoring. Through the convergence of biomarker science, advanced materials, and immunology, next-generation nanotherapeutics are poised to deliver adaptive, patient-specific combination therapies aimed at achieving sustained remission and functional restoration in arthritis.

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Disclosure

The authors report no conflicts of interest in this work.

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