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REVIEW

# Nanomedicine Strategies for Rheumatoid Arthritis: Precision Delivery and Immune Microenvironment Modulation

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**Abstract:** Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial inflammation, pannus formation, and progressive joint destruction. Despite their established clinical benefits, conventional antirheumatic drugs remain hampered by poor targeting precision, systemic toxicity, and inadequate immunomodulation of the dysregulated microenvironment. The recent development of nanomedicine technology offers transformative potential to address these therapeutic challenges. This review comprehensively examines the application of advanced nano-platforms in RA management, with particular focus on their dual roles in precision drug delivery and immune microenvironment remodeling. The discussion encompasses multifunctional nanomaterials that enable precise drug transport while actively regulating pathological processes through reactive oxygen species scavenging, hypoxia mitigation, and immune cell reprogramming. Additionally, the integration of diagnostic and therapeutic functions within nanomaterial systems represents a significant advancement in RA theranostics. Finally, translational challenges and future directions are critically analyzed to map the clinical development path for intelligent RA nanomedicine.

**Keywords:** rheumatoid arthritis, nanomaterials, targeted delivery, immune microenvironment, theranostics

## Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory autoimmune diseases globally, affecting approximately 0.5% to 1.0% of the world's population and imposing a substantial economic and healthcare burden on society.[1,2] Its core pathological alterations include abnormal hyperplasia of the synovial tissue, massive infiltration of inflammatory cells (such as macrophages, T cells, B cells), neovascularization (pannus), and the consequent degradation of articular cartilage and bone erosion.[3,4] The pathogenesis of RA is extremely complex, resulting from the interplay of genetic susceptibility, environmental factors, and immune system dysregulation. Among these, the imbalance in the pro-inflammatory cytokine network, overproduction of reactive oxygen species (ROS), formation of a local hypoxic microenvironment, and the appearance of autoantibodies collectively constitute a self-reinforcing inflammatory cycle that drives disease progression and chronicity.[5,6]

Current clinical treatment strategies for RA primarily rely on non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs, eg., methotrexate), biologic DMARDs (bDMARDs, eg., TNF-α inhibitors), and targeted synthetic DMARDs (tsDMARDs, eg., JAK inhibitors).[7] However, these therapies face significant limitations. Small-molecule drugs, including poorly water-soluble natural products such as celastrol, quercetin, and sinomenine, exhibit low bioavailability and a lack of targeting. This often necessitates high-dose, frequent administration, leading to systemic toxic side effects.[8–10] Moreover, a substantial proportion of patients eventually develop drug resistance or become non-responsive to even biologic therapies, while long-term use of existing drugs is frequently associated

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with cumulative organ toxicity, further underscoring the urgent need for more effective and safer treatment strategies. In contrast, biologics are not only expensive but may also lose efficacy due to immunogenicity or increase the risk of infection.[11] More critically, most existing drugs merely suppress inflammatory signals and struggle to fundamentally reverse the disordered immune microenvironment and repair damaged joint tissues, resulting in many patients failing to achieve long-term remission. Table 1 summarizes the key differences between conventional RA therapies and nanomaterial-based strategies.

The rapid development of nanomedicine offers revolutionary opportunities to overcome the above challenges. Nanomaterials leverage their unique size, high surface area, and tunable properties to serve as ideal platforms for drug delivery and disease intervention.[12,13] In the field of RA, nanomaterials significantly enhance drug enrichment in inflamed joints through both passive accumulation via the EPR (Enhanced Permeability and Retention) effect and active targeting strategies. Furthermore, they achieve intelligent controlled drug release by responding to specific pathological stimuli in the lesion microenvironment, including acidic pH, elevated ROS levels, and enzyme overexpression. This dual capability substantially improves therapeutic efficacy while simultaneously reducing adverse side effects.[14,15] Furthermore, many nanomaterials possess intrinsic bioactivities (eg., antioxidant, catalytic, immunomodulatory) enabling them to actively intervene in the pathological processes of RA, achieving synergistic "drug delivery" and "material biological effects".[16–18] This review is structured around a progression from precision targeted delivery, to active immune microenvironment remodeling, and finally to theranostic applications (Figure 1).

# Intelligent Nano-Delivery Systems: Enabling Precision and Controlled Therapy for RA

Achieving the specific enrichment and on-demand release of therapeutic agents in diseased joints is the cornerstone for improving RA efficacy and reducing toxic side effects. Nanotechnology, through ingenious carrier design and functionalization, endows traditional drugs with unprecedented "intelligent" attributes.

## Multi-Dimensional Targeting Strategies Enhance Lesion Accumulation

Nanoparticles utilize the pathophysiological characteristics of RA lesions to achieve multi-dimensional targeting from the tissue to the cellular level. Passive targeting relies on the EPR effect caused by enlarged gaps in the vascular endothelium of inflamed joints, allowing nanoparticles (typically 10–200 nm) to accumulate more readily in synovial tissue. Active targeting achieves higher precision navigation by modifying their surface with specific ligands. For instance, hyaluronic acid (HA) specifically binds to the CD44 receptor highly expressed on synovial macrophages and fibroblast-like synoviocytes (FLS), making it one of the most widely used targeting moieties for guiding nano-systems loaded with drugs like dexamethasone or celastrol to inflamed joints.[8,19,20] The folic acid (FA) receptor is overexpressed on activated

**Table 1** Comparison of Conventional Therapies and Nanomaterial-Based Strategies for RA

| Feature | Conventional Therapies | Nanomaterial-Based Strategies |
|---|---|---|
| Main drug categories | NSAIDs, glucocorticoids, csDMARDs (eg., MTX), bDMARDs (eg., anti-TNF), tsDMARDs (eg., JAK inhibitors) | Liposomes, polymeric micelles, dendrimers, inorganic NPs, exosomes, etc. |
| Targeting specificity | Lacks specificity for inflamed joints; systemic exposure | Passive (EPR effect) or active (ligand-decorated) targeting to arthritic joints |
| Drug biodistribution | Widespread, leading to off-target effects | Preferential accumulation in inflamed synovium |
| Circulation half-life | Short (hours) for small molecules; longer for monoclonal antibodies (days) | Tunable from hours to days via PEGylation or matrix design |
| Dosing frequency | Frequent (daily to weekly) | Reduced (weekly or less) |
| Systemic adverse effects | Significant (GI, immunosuppression, infection risk, hepatotoxicity) | Reduced systemic toxicity; local drug release |
| Immune microenvironment modulation | Largely broad immunosuppression (except targeted biologics) | Can be engineered to repolarize macrophages, regulate Treg/Th17 balance, or respond to microenvironment signals (ROS, pH, enzymes) |
| Responsive delivery | Not applicable | On-demand drug release using stimuli-responsive nanocarriers |
| Clinical examples | Ibuprofen, prednisolone, MTX, etanercept, tofacitinib | Liposomal prednisolone (Lipraxon®), PEGylated liposomal doxorubicin (off-label), many candidates in clinical trials |

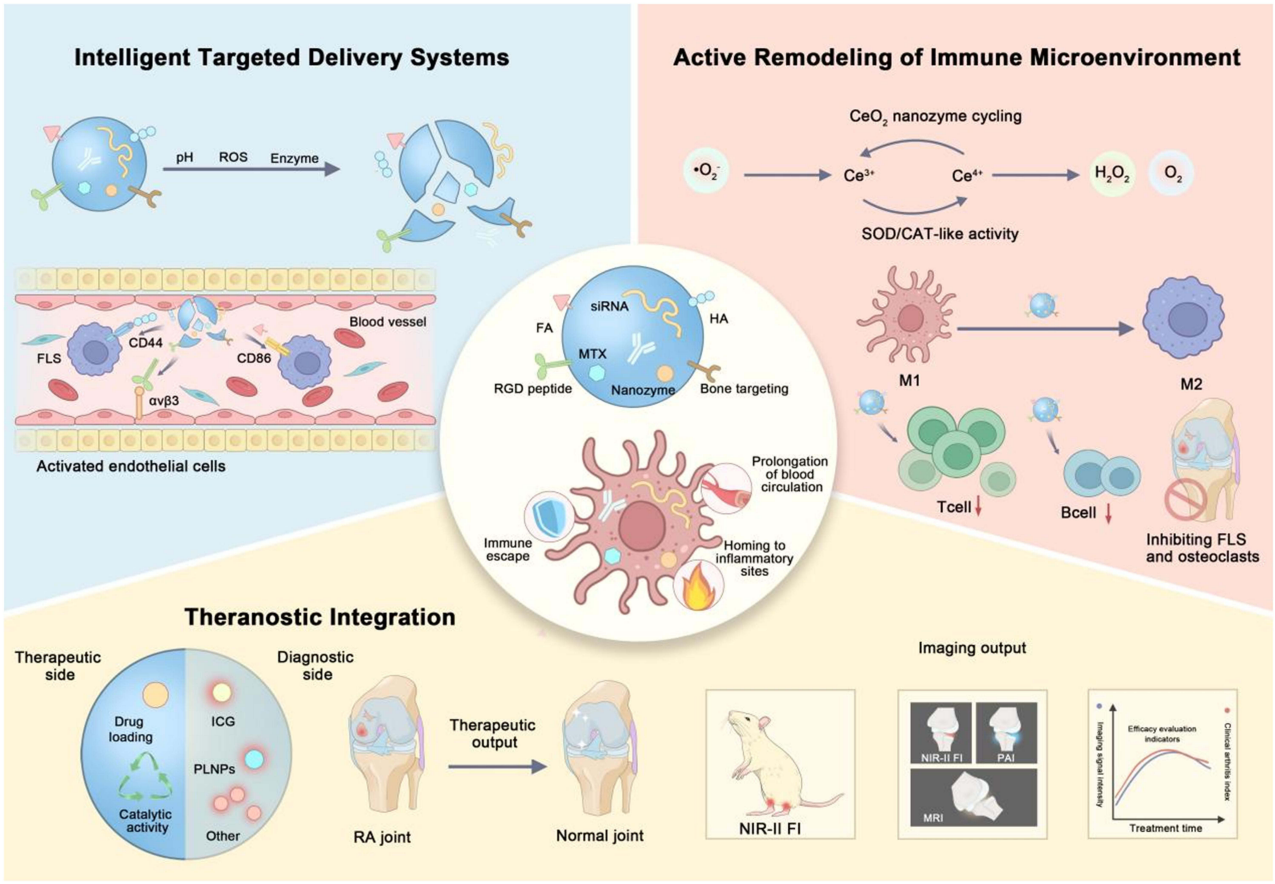


**Figure 1** Schematic overview of nanomaterial-based strategies for RA therapy. This illustration summarizes three core functionalities of advanced nanomedicine in RA: 1) Microenvironment-Responsive Drug Release: Nanocarriers are engineered to release their payload (eg., drugs, siRNA) specifically in response to pathological signals in the inflamed joint, such as acidic pH, elevated ROS, and overexpressed enzymes. 2) Precision Targeted Delivery: Nanoparticles achieve enhanced accumulation at the disease site through passive mechanisms (eg., the EPR effect due to leaky vasculature) and active targeting via surface ligands (eg., HA for CD44, FA for folate receptors, RGD for integrin αvβ3) that recognize overexpressed markers on synovial cells and immune cells (FLS, macrophages). 3) Theranostic Integration: Combining therapeutic agents with imaging probes (eg., ICG) enables concurrent treatment and real-time, multi-modal monitoring (NIR-II fluorescence, photoacoustic, and MR imaging) for precise efficacy evaluation.

M1-type macrophages. Thus, FA-modified nanoparticles can precisely recognize and internalize into these key pro-inflammatory cells, achieving precise strikes[21] (Figure 2i). Additionally, RGD peptides target integrin αvβ3, which is overexpressed on activated macrophages, osteoclasts, and FLS in inflamed joints, often used to enhance the cellular uptake of nanomedicines.[22] The surface-modified zoledronic acid confers dual functionality of bone targeting and anti-bone resorption, enabling both precise drug enrichment at the lesion site and synergistic therapeutic efficacy.[23]

A particularly ingenious strategy exploits the overexpression of SPARC (secreted protein acidic and rich in cysteine) in RA synovium by utilizing bovine serum albumin (BSA) as a targeting ligand, enabling site-specific drug delivery to inflamed joints.[25] Inspired by the unique biochemical architecture of natural proteoglycans in articular cartilage, Zhou's team[24] developed an innovative injectable lubricant by grafting chondroitin sulfate (CHI) onto drug-loaded chitosan nanoparticles (CS NPs) (Figure 2ii$_1$–Figure 2ii$_4$). This biomimetic brush-structured system presents a promising strategy for RA treatment, offering both effective lubrication and targeted drug delivery. Furthermore, the administration route critically influences the pharmacokinetic profile of nanomedicines. For instance, subcutaneously injected nanoparticles often exhibit a natural tropism for lymphatic accumulation.[26] Li et al[27] cleverly employed low molecular weight heparin (LMWH) as a key dual-function ligand. LMWH first specifically binds to P-selectin overexpressed on inflamed vascular endothelium, enabling vascular homing. After the nano capsules extravasate into the synovial tissue, LMWH precisely recognizes integrin αM on inflammatory macrophages, achieving cellular locking. This design not only enhances drug accumulation at the lesion but also enables spatiotemporal relay delivery from blood vessels to deep tissue.


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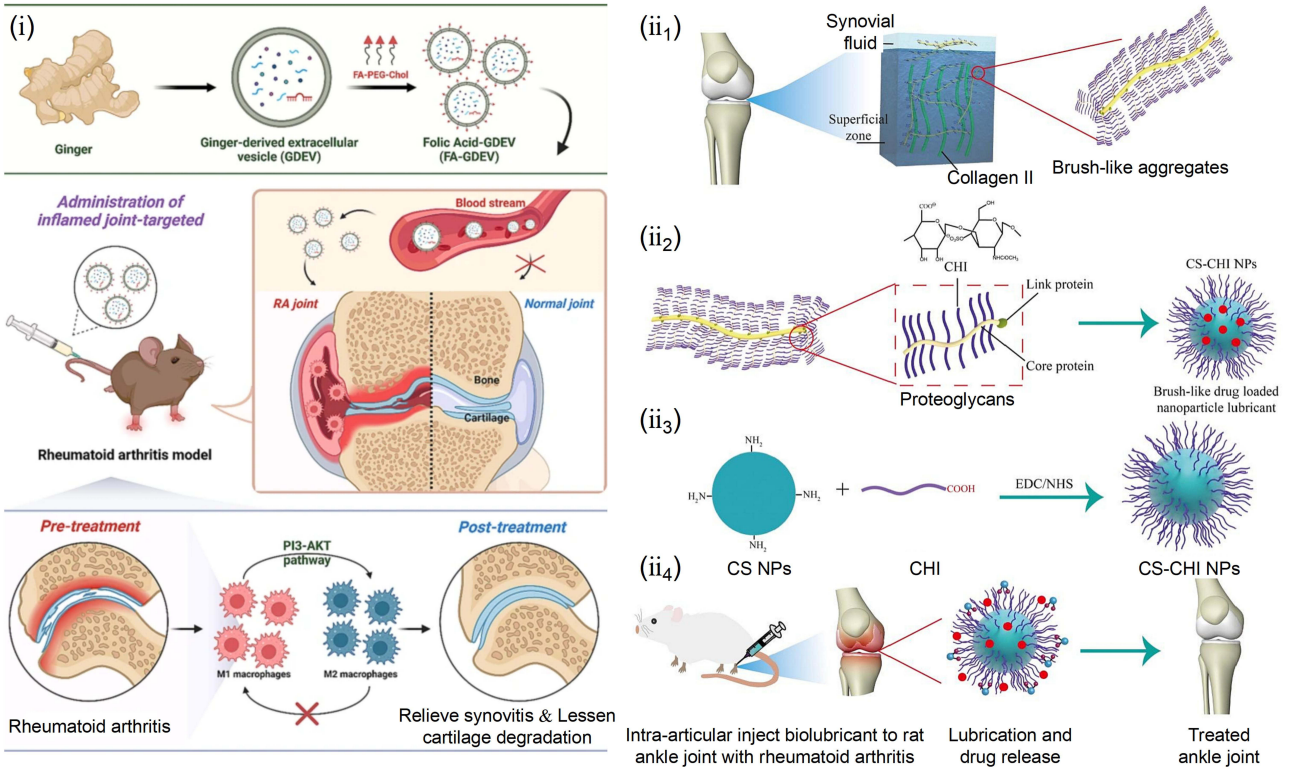


**Figure 2** (i) FA-modified ginger-derived extracellular vesicles (FA-GDEVs) alleviate RA by targeting M1 macrophages and promoting M2 polarization via the PI3K-AKT pathway. Reproduced from reference[21] with permission from Journal of Nanobiotechnology, copyright 2025. ($ii_1$) Natural articular cartilage lubrication relies on brush-like proteoglycan aggregates in synovial fluid, consisting of a hyaluronic acid backbone and charged glycosaminoglycan side chains. ($ii_2$) Biomimetic drug-loaded nanoparticles (CS-CHI@DS NPs) were designed to replicate this structure, with a chitosan core for anti-inflammatory drug delivery and surface-grafted CHI side chains for hydration lubrication. ($ii_3$) CS-CHI NPs were synthesized via EDC/NHS-mediated coupling between amine groups on CS NPs and carboxyl groups of CHI. ($ii_4$) The resulting nanoparticles combine sustained drug release with enhanced lubricity, demonstrating significant potential for RA treatment. Reproduced from reference[24] with permission from Carbohydrate polymers, copyright 2023.

In recent years, cell membrane biomimetic technology has provided a revolutionary strategy for nanomaterial targeting. By coating nanoparticles with macrophage membranes,[28–31] neutrophil membranes,[32,33] erythrocyte membranes,[34] or FLS membranes,[35] the resulting biomimetic nanoparticles inherit the complex surface protein functions of the source cells. This not only enables effective evasion of immune system clearance and prolongs circulation time but also allows them to actively seek out and accumulate at inflammatory sites utilizing natural "homing" effects or homologous targeting capabilities, demonstrating exceptional targeting efficiency.[36] Furthermore, cell-derived vesicles inherently possess a dual functionality,[37] conferring both inherent therapeutic effects and intrinsic targeting capabilities (Figure $3i_1$ and $3i_2$).[38]

## Microenvironment-Responsive Intelligent Drug Release

The inflammatory microenvironment of RA possesses a series of unique biochemical signals, such as acidic pH, high levels of matrix metalloproteinases (MMPs), excessive ROS, and hypoxia. "Smart" nano-systems designed based on these signals enable on-demand, site-specific drug release, minimizing off-target effects.[22] For example, encapsulating drug-loaded nanocarriers within MMP-sensitive hydrogels allows for timed and localized drug release upon degradation by highly expressed MMP-2/9 in the inflamed joint (Figure 3ii).[39] Nanocarriers containing acid-sensitive chemical bonds like hydrazone or acetal can break under the acidic joint cavity environment (pH ~6.5), enabling rapid payload release.[40,41] Conversely, ROS-responsive carriers containing thioether or selenide bonds can be cleaved by excess $H_2O_2$ or other ROS, achieving oxidative stress-triggered drug release.[42] This synergistic design of multi-stimuli responsiveness forms the chemical basis for precision RA therapy.

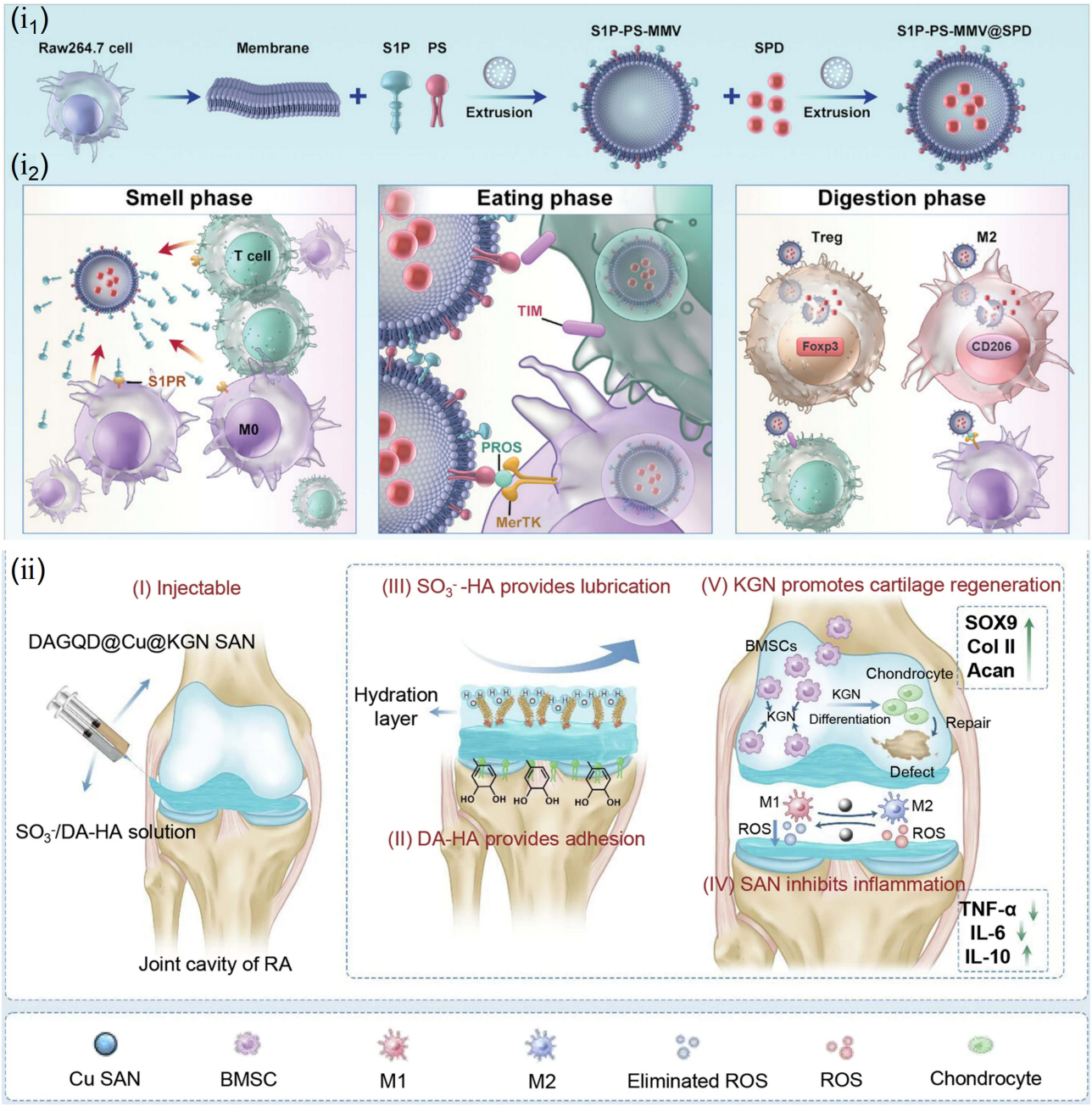


**Figure 3** Synthesis and immunomodulatory mechanism of efferocytosis mimicking nanovesicles S1P PS MMV@SPD. ($i_1$) Schematic illustration of EMNV fabrication. ($i_2$) Interactions between EMNVs and immune cells, demonstrating the three-phase process: find me signal recognition, eat me signal mediated phagocytosis, and post digestion immune reprogramming in both macrophages and T lymphocytes. Reproduced from reference[38] with permission from Wiley, copyright 2024. (ii) Multifunctional DAGQD@Cu@KGN-$SO_3^-$/DA-HA hydrogel for synergistic RA therapy. The injectable hydrogel undergoes rapid in situ gelation within the joint cavity (I), providing robust bioadhesion and sustained lubrication (II, III). The incorporated single-atom nanozyme (SAN) actively scavenges ROS to alleviate inflammatory responses (IV), while the controlled release of kartogenin (KGN) promotes bone marrow mesenchymal stem cell recruitment and chondrogenic differentiation, enabling cartilage regeneration (V). Reproduced from reference[39] with permission from Nature Communications, copyright 2025.

## Nanomaterial-Mediated Remodeling of the RA Immune Microenvironment

Transcending their traditional role as mere drug delivery vehicles, nanomaterials, particularly those with catalytic activity (nanozymes), can actively intervene in and remodel the pathological microenvironment of RA, offering a new paradigm for correcting immune imbalance at its root.[43]


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## Scavenging ROS and Alleviating Hypoxia

The excessive accumulation of ROS and the consequent hypoxic microenvironment are key drivers sustaining chronic inflammation, promoting pannus formation, and activating osteoclasts in RA.[44] Nanozymes, with their multiple enzyme-mimicking activities, show tremendous potential in this regard. Cerium Dioxide ($CeO_2$) nanozymes, due to their $Ce^{3+}/Ce^{4+}$ switchable valence states, can mimic superoxide dismutase (SOD) and catalase (CAT) activities, effectively scavenging $O_2^{-}$• and $H_2O_2$.[45,46] Manganese Dioxide ($MnO_2$) nanozymes not only eliminate ROS but also react with $H_2O_2$ to produce oxygen, simultaneously alleviating oxidative stress and hypoxia.[47–49] Others like Prussian Blue (PB),[43] Metal-Organic Frameworks (MOFs),[16] and precious metal nanodots (eg., Au)[50] are also widely developed for antioxidant and oxygenation therapy in RA. For instance, Ce/V-MOF nanozymes effectively eliminate ROS and promote macrophage polarization towards the anti-inflammatory M2 phenotype through synergistic dual catalytic centers.

## Regulating Immune Cell Fate and Function

The phenotypic polarization of macrophages (from pro-inflammatory M1 to anti-inflammatory M2) is a central link in RA treatment.[51] Nanomaterials can achieve this precise regulation through various mechanisms.[52–54] Beyond indirectly promoting M2 polarization by scavenging ROS and alleviating hypoxia, some nano-systems directly intervene in cellular metabolic pathways. For example, nanomotors loaded with Rapamycin can drive the M1-to-M2 transition by activating autophagy to clear dysfunctional mitochondria (Figure 4i).[55] The Metal-Amino Acid Framework (MAF) nano-platform pZFH-MTX-Pt simultaneously delivers methotrexate (depleting M1 cells) and platinum nanodots (promoting repolarization), realizing a dual-effect strategy of "depletion and reconstruction". Furthermore, consuming glucose in the microenvironment via glucose oxidase (GOx) can inhibit the abnormally active glycolysis, thereby suppressing the proliferation and function of FLS and M1 macrophages.

Inducing immune tolerance is the ultimate goal in curing autoimmune diseases. Nanomaterials also show astonishing potential in this area. By delivering oligonucleotides (eg., DNAzyme cleaving miRNA-155, miRNA-124, TNF-α siRNA), nanoparticles can precisely regulate intracellular signaling pathways to suppress inflammation. More cutting-edge approaches involve using DNA origami technology to construct nanodevices that can precisely arrange CD95L ligands at inflammatory sites, activating CD95 death signaling to specifically induce apoptosis of infiltrated activated immune cells, thereby establishing local immune tolerance.[58] Similarly, hybrid nanoparticles displaying autoantigens (eg., glucose-6-phosphate isomerase, GPI) can concurrently induce antigen-specific tolerance in both B cells and T cells, effectively preventing and delaying RA onset in animal models.[59]

# Theranostic Nano-Platforms

Integrating diagnostic and therapeutic functions into a single nano-platform is a crucial direction for achieving precise RA management, real-time efficacy monitoring, and dynamic treatment adjustment. Such platforms typically co-load imaging agents and therapeutic components, enabling "see and treat" capabilities.

For instance, the Janus nanoplatform (Janus-CPS) utilizes $CeO_2$-Pt nanozymes to eliminate ROS and loads the anti-osteoclastogenic drug michelol (MCL) for synergistic therapy, while also loading indocyanine green (ICG) to achieve second near-infrared window (NIR-II) fluorescence imaging of RA lesions. This allows for highly efficient treatment concurrent with very early lesion detection (Figure 4ii).[56] Near-Infrared Persistent Luminescence Nanoparticles (NIR-PLNPs) can luminesce for an extended period after the excitation light ceases, completely avoiding tissue autofluorescence interference, enabling ultra-high signal-to-noise ratio autofluorescence-free imaging. This guides precise photothermal therapy while monitoring treatment outcome via the persistent luminescence signal.[60] Additionally, some NO-activated PA probes (Figure 4iii)[57] or ultrasound-responsive nanozymes can convert disease severity-related biomarker concentrations (eg., NO, $H_2O_2$) into imageable signals, thereby achieving disease visualization and simultaneous therapy. This theranostic strategy signifies that RA management is entering a new era of precision medicine.

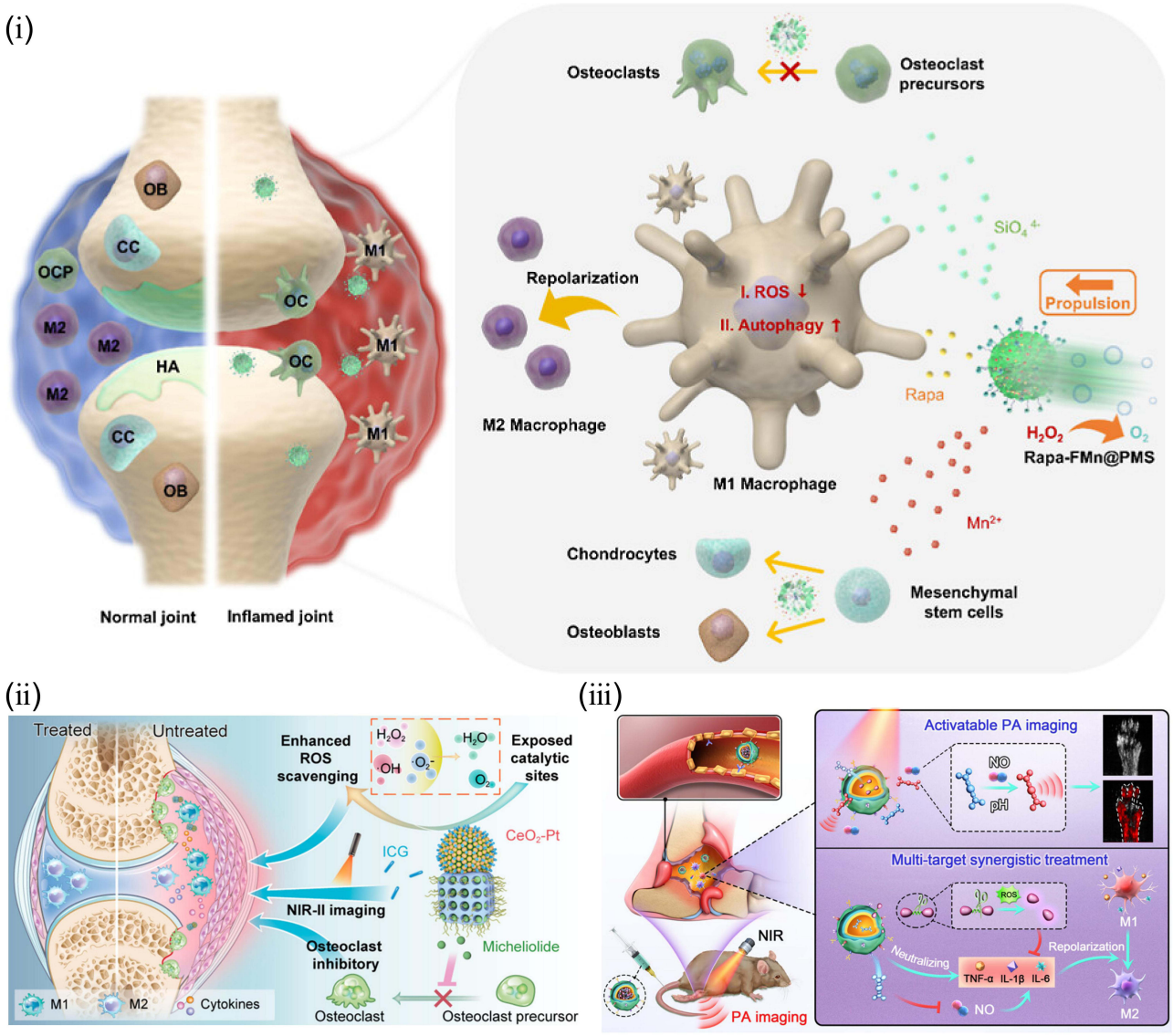


**Figure 4** (i) Application of rapamycin-loaded mesoporous silica nanomotors (Rapa-FMn@PMS) for synergistic RA therapy. Reproduced from reference[55] with permission from ACS Nano, copyright 2025. (ii) The schematic illustrates the structure of the asymmetric nanoparticle and its dual functionality in enabling early diagnosis through advanced imaging techniques while providing synergistic therapy via ROS scavenging and anti-inflammatory effects. Reproduced from reference[56] with permission from ACS Nano, copyright 2023. (iii) Schematic illustration of the theranostic nanoagent for NO-activatable PA imaging and synergistic treatments of RA. Reproduced from reference[57] with permission from ACS Nano, copyright 2024.

## Conclusion

In summary, nanomaterial technology has profoundly transformed the paradigm of RA treatment and research. Through sophisticated nano-engineering design, researchers have successfully constructed various efficient and intelligent multi-functional nano-platforms. These platforms successfully overcome the long-standing limitations of conventional anti-rheumatic drugs, including poor targeting, low bioavailability, and systemic toxicity. More importantly, their intrinsic catalytic and biological activities enable them to actively intervene in and remodel the pathological microenvironment of RA. This represents a therapeutic philosophy upgrade from mere "anti-inflammation" to "immune homeostasis reconstruction". Evolving from simple drug encapsulation carriers to complex regulators of immunometabolism and cell fate, nano-strategies demonstrate unprecedented precision, versatility, and synergy. The introduction and practice of the theranostic concept further seamlessly integrate early disease diagnosis, precision treatment, and efficacy monitoring, heralding a new era of more intelligent and personalized clinical management for RA. Achieving this vision, however,


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**Table 2** Summary of Representative Targeting Ligands, Biomimetic Strategies, and Smart Responsive Nanoplatforms for RA Therapy

| Category | Platform Type | Target or Responsive Signal | Ref. |
|---|---|---|---|
| Active targeting ligands | HA | CD44 (overexpressed on macrophages, FLS) | [8, 19, 20] |
| | FA | Folate receptor (activated M1 macrophages) | [21] |
| | RGD peptide | Integrin αvβ3 (activated macrophages, osteoclasts, FLS) | [22] |
| | Zoledronic acid | Bone tissue/anti-bone resorption | [23] |
| | LMWH | P-selectin-integrin αM (spatiotemporal dual targeting) | [27] |
| | BSA | SPARC (overexpressed in RA synovium) | [25] |
| Cell membrane biomimetic coating | Macrophage | Natural inflammatory "homing" effect | [28–31] |
| | Neutrophil | Inflammatory tropism | [32, 33] |
| | Erythrocyte | Prolonged circulation, immune evasion | [34] |
| | FLS | Homologous targeting | [35] |
| Microenvironment-responsive release | MMP-sensitive hydrogel | MMP-2/9 (highly expressed in inflamed joints) | [39] |
| | Acid-labile bond (hydrazone, acetal) nanocarriers | pH ~6.5 (acidic joint cavity) | [40, 41] |
| | ROS-responsive carriers (thioether/selenide bonds) | $H_2O_2$ and other ROS | [42] |
| Immunomodulatory nanoplatform | Rapa-FMn@PMS (mesoporous silica nanomotors) | M2 polarization via autophagy induction | [55] |
| | S1P PS MMV@SPD (efferocytosis-mimicking nanovesicles) | "Find me"/"eat me" signals | [38] |
| Theranostic platform | Janus-CPS (CeO2-Pt Janus nanoparticles) | ROS scavenging+anti-osteoclast+NIR-II imaging | [56] |
| | Near-infrared persistent luminescence nanoprobes (NIR-PLNPs) | Persistent luminescence after excitation (autofluorescence-free imaging) | [60] |
| | NO-activatable photoacoustic probe | NO (biomarker of RA inflammation) | [57] |

requires parallel efforts to establish standardized safety evaluation protocols and clear regulatory guidelines for nanomedicine-based RA therapies. In addition to these therapeutic advances, establishing standardized safety evaluation protocols and clear regulatory guidelines is essential to facilitate the clinical translation of nanomedicine-based RA therapies. A summary of representative targeting ligands, biomimetic coating strategies, and smart responsive nanoplatforms discussed in this review is provided in Table 2. This table categorizes these approaches into active targeting, cell membrane biomimetics, microenvironment-responsive release, immunomodulatory platforms, and theranostic systems, along with their corresponding targets or responsive signals and key references. Although most of the exciting findings currently remain in the pre-clinical exploration stage, the immense therapeutic potential and disruptive advantages they exhibit have brought unprecedented dawn to the future clinical treatment of RA.

## Prospects and Challenges

Despite the explosive growth and broad prospects of nanomaterial research in the RA field, their successful ultimate translation into clinical therapies still faces a series of severe challenges, which also point to key future development directions.

First, pharmacokinetics and in vivo fate. The absorption, distribution, metabolism, and excretion of nanomaterials remain poorly characterized for most novel platforms. Unlike small molecules, nanoparticles often exhibit prolonged circulation time and preferential accumulation in the reticuloendothelial system (liver, spleen), but their joint-specific pharmacokinetic profiles, especially the relationship between synovial drug concentration and therapeutic effect, are rarely reported. Standardized methods to quantify nanocarrier biodistribution and degradation kinetics in arthritic joints are urgently needed to guide rational design.

Second, biosafety and immune toxicity are the primary hurdles for the clinical translation of nanomedicines. Most pre-clinical studies report good biocompatibility of nanomaterials in short-term experiments. However, their potential organ toxicity (eg., liver and kidney burden) and immunogenicity, which arise from biodistribution, degradation behavior, metabolic pathways, and long-term accumulation in vivo, require more systematic and rigorous long-term evaluation. Of particular concern is the unintended activation of the complement system or the induction of anti-nanomaterial antibodies, which could lead to accelerated clearance, loss of efficacy, or even adverse reactions upon repeated administration. Future efforts need to establish more standardized and human-relevant complex models (eg., organoids, humanized animal models) for safety assessment.

Thirdly, there is a contradiction between the complexity of nano-platforms and the feasibility and economy of large-scale production. Multifunctional, multi-component nano-systems (eg., biomimetic membrane coating, peptide targeting, stimulus responsiveness), while exhibiting excellent performance, often involve complicated synthesis steps, making batch-to-batch consistency and stability difficult to guarantee, with high production costs.[61] Developing simple, controllable, and reproducible "green" preparation processes and strengthening scale-up studies from laboratory gram-scale to factory kilogram-scale are crucial for industrialization.

Fourthly, a deeper understanding of RA pathogenesis will drive the design of more precise next-generation nanomaterials. Future work needs to focus more on antigen-specific immune tolerance therapies and personalized nano-schemes tailored to different disease subtypes and stages (early active phase vs. late fibrotic phase).[62] Utilizing cutting-edge technologies like single-cell sequencing and proteomics to decipher patient immune microenvironment heterogeneity will aid in designing more targeted "precision nanomedicine" strategies. Concurrently, investigating the role of multi-system interactions such as neuro-immune-skeletal in RA and developing corresponding nano-regulatory strategies is an emerging direction.

Finally, a clear clinical translation pathway is paramount. Future research should pay more attention to validating the efficacy and safety of nano-therapies in large animal models (eg., dogs, non-human primates), which are more predictive of human responses than rodent models. Simultaneously, actively exploring optimal routes of administration (eg., weighing the local advantages of intra-articular injection against the systemic coverage of intravenous administration), strengthening early communication with regulatory agencies, and establishing evaluation standards suitable for nanomedicines are all indispensable steps in moving them from the laboratory to the bedside.

To move beyond a sequential compilation of successful examples and provide a more balanced assessment, this section highlights several underdiscussed considerations. First, simpler systems such as PEGylated liposomes, polymeric micelles, and albumin-based nanoparticles, although less sophisticated than multifunctional platforms, offer distinct advantages in scale-up feasibility, batch-to-batch consistency, lower cost, and clearer regulatory pathways, and have already achieved clinical use or advanced trials for other diseases. Second, beyond synthetic nanomaterials, emerging alternatives like naturally derived exosomes, plant-based nanoparticles, inorganic nanodots, and protein nanocages possess intrinsic bioactivities that may complement or surpass synthetic systems. Third, future comparative syntheses should directly contrast different strategies head to head under standardized models, reporting not only efficacy but also translational metrics such as manufacturing yield, storage stability, and toxicity upon repeated dosing. Such comparative approaches will better guide the rational selection of RA nanomedicines.

In conclusion, with the deep integration of materials science, immunology, clinical medicine, and artificial intelligence, we have reason to expect that safer, more intelligent, efficient, and affordable nanotheranostic platforms will inevitably be developed, ultimately bringing new hope and the potential for a definitive cure to tens of millions of RA patients worldwide.

## Data Sharing Statement

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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## Disclosure

The authors declare no conflict of interest.

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