Advances in injectable drug delivery systems for the treatment of rheumatoid arthritis

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Key Words:
hydrogel, microspheres; intra-articular; nanomaterials; rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis is a chronic autoimmune disease characterised by inflammation and progressive joint damage, necessitating innovative therapeutic strategies. Conventional rheumatoid arthritis treatments, including disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, glucocorticoids, and biologics, often administered through systemic or intra-articular ways. These drugs often have low accumulation and/or retention in articular cartilage, causing dose-limiting toxicities and reduced efficacy. This review summarises recent advances in injectable drug delivery systems, specifically hydrogels, microspheres, and nanoparticles, highlighting their potential to enhance rheumatoid arthritis therapy. The outstanding potential of these systems was demonstrated; however, substantial research remains to be conducted to optimise their performance and safety.

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Introduction

Rheumatoid arthritis (RA) is a chronic, symmetrical, progressive autoimmune disorder that primarily involves the peripheral joints, mainly those in the hands, feet, and knees.[1] This is characterised by an inflammatory response that leads to synovitis and inflammatory cell infiltration, which in turn causes periarticular decalcification, cartilage degeneration, and bone erosion.[2] RA has long been considered an "immortal cancer", and epidemiologic surveys have shown that 0.5% to 1% of the world's population suffers from RA.[3]

RA begins as a condition characterised by ongoing cellular stimulation, which can lead to autoimmune reactions targeting joints or various other body parts.[4, 5] The symptoms observed in patients are driven by inflammation and joint injury, in which fibroblast-like synoviocytes play a crucial role.[6, 7] RA progression is often described in three stages: a non-specific inflammatory stage, amplified by T-cell activation in the synovium, followed by a chronic inflammatory stage, and finally a tissue damage stage mediated by cytokines like interleukin-1, interleukin-6, and tumour necrosis factor-α (TNF-α), respectively.[8, 9] At its core, the pathogenesis of RA is an autoimmune disease involves autoimmune responses triggered by T and B lymphocytes, which leads to synovial inflammation in response to macrophages, fibroblasts, osteoclasts, and other cells, resulting in irreversible joint damage in severe cases.[10]

Treatments for rheumatoid arthritis

Current treatments for RA primarily aim to alleviate pain, and discomfort of arthritis, and minimise joint damage, deformity, and loss of function, ultimately improving the patient's quality of life.[11] Early-stage RA is commonly treated with long-term oral or intra-articular injections of therapeutic drugs for pain relief. These drugs are typically categorised into four main groups: non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and biologics.[12]

Non-steroidal anti-inflammatory drugs are a mainstay in the early therapy of RA as they effectively inhibit cyclo-oxygenase, providing anti-inflammatory, analgesic, and anti-swelling effects.[13, 14] However, these drugs do not alter the course of the disease or prevent joint destruction, nor do they specifically target inflamed tissue. And their prolonged use is associated with gastrointestinal side effects, limiting their long-term use.[15, 16]

Glucocorticoids are effective in relieving arthritis symptoms and improving joint functions.[17] The main mechanism of glucocorticoids in the treatment of RA is that they follow blood circulation, diffuse to the cells, bind to the corresponding receptors on the cell surface, participate in the regulation of cytokine expression, and inhibit the release of pro-inflammatory factors by blocking the transcription of genes such as interleukin-1β, *TNF-α*, nuclear factor-kappa B (*NF-κB*), and so on, thus reducing the inflammatory response.[18] However, their advantages are short-lived.[19] Long-term use of these medications can lead to side effects such as hyperglycaemia and hypertension, and patients are resistant to the use of hormones.[20, 21]

Disease-modifying anti-rheumatic drugs, such as methotrexate (MTX), are effective in controlling RA progression, reducing synovial inflammation, and alleviating the ongoing lesions and damage of joints and cartilage.[22] Currently, DMARDs are the main drugs for the clinical RA treatment, functioning by curbing the production of antibodies and inflammatory mediators. This is achieved through the suppression of lymphocyte proliferation and dampening of inflammatory signaling pathways, ultimately aiming to slow down or halt the destruction of RA cartilage and bones.[23] MTX, known for its tolerability, cost-effectiveness, and therapeutic efficacy, is the most commonly prescribed DMARDs.[24, 25] It modulates the activity of various immune cells, including T cells, B cells, monocytes, neutrophils, synoviocytes to suppress inflammation and immune reactions. However, the use of MTX and other DMARDs can induce serious toxic side effects, highlighting the need for careful monitoring and management.[26-30] Additionally, the short half-life of these drugs necessitates frequent dosing, which may not always result in adequate drug concentration at the site of action. The long-term use of conventional drugs can lead to drug resistance and toxicity, such as gastrointestinal discomfort, hepatic, and renal toxicity.[31]

Biologics represent a distinct class of therapeutic agents that have a predetermined specific action on cytokines or molecules involved in the inflammatory cascade response in RA.[32] Unlike the other therapeutic approaches discussed previously, biologics have a defined mechanism of action. This broad therapeutic class that can be split into several subgroups based on their function: co-stimulatory blockers (e.g., abatacept), TNF-α blockers (e.g., adalimumab), golimumab and infliximab, B-cell reductors (e.g., rituximab), and interleukin blockers (e.g., anabolic acid). They have disease-modifying properties but their use are often accompanied with side effects such as infection, elevated cholesterol and neutropenia.[33] This mode works by suppressing the pro-inflammatory cytokines overproduction at the site of inflammation in RA patients.[34] This suppression primarily targets the immune system, thereby increasing the patient's susceptibility to infections.[35] While biologics offer promising therapeutic options, ongoing research is essential to fully understand their potential risks, benefits, and economic implications.[36]

Intra-articular administration for rheumatoid arthritis

Intra-articular injection is a widely utilised treatment method for RA.[37, 38] This technique involves injecting medication directly into the joints, thereby enhancing its bioavailability and allowing the drug to reach the affected area directly, which not only shortens the recovery time of the patient. This targeted approach not only expedites patient recovery but also minimises the side effects typically caused by oral medication.[39] Currently, corticosteroids and hyaluronic acid are the most frequently used medications administered by intra-articular injection for pain management and joint lubrication.[40] However, the scientific consensus on intra-articular corticosteroid injections has not been harmonised, and the efficacy and safety of corticosteroids are controversial.[41] On the other hand, hyaluronic acid injections are known to provide lubrication, protect cartilage from mechanical degradation, possess anti-inflammatory effects, and increase proteoglycan and its synthesis.[42, 43] Furthermore, its viscoelasticity properties help cushion the joint, reducing friction, and maintaining joint space, which is crucial for joint function.[44]

Compared to oral medications, intra-articular injections can avoid first-pass effects and reduce systemic adverse effects.[45] Local injection of MTX directly affects synovitis, the basic lesion of RA, and is called "pharmacologic synovectomy". While this therapy offers benefits such as avoiding systemic side effects, they also come with challenges, including higher costs, potential discomfort, and the need for repeat injections, which can lead to persistent pain and increased risk of infection.[46] In addition, intra-articular injections bypass physiologic barriers, such as hard tissues, that prevent drug molecules from entering the synovial cavity at the site of arthritis. If the patient is unable to tolerate the medication or undergo the treatment, resulting in deterioration of the condition, the only way to treat the condition is with surgery, such as arthroscopic surgery, arthroplasty.[47] However, it is expensive and has the potential for recurrence, increasing patient suffering.[48]

The review aims to delve into the intricacies of intra-articular drug delivery systems utilised in the management of RA. The goal of these systems is to mitigate the adverse effects associated with high doses and to facilitate a precise, regulated delivery of medication. This approach is designed to optimise the efficacy of RA treatment (**Figure 1**).

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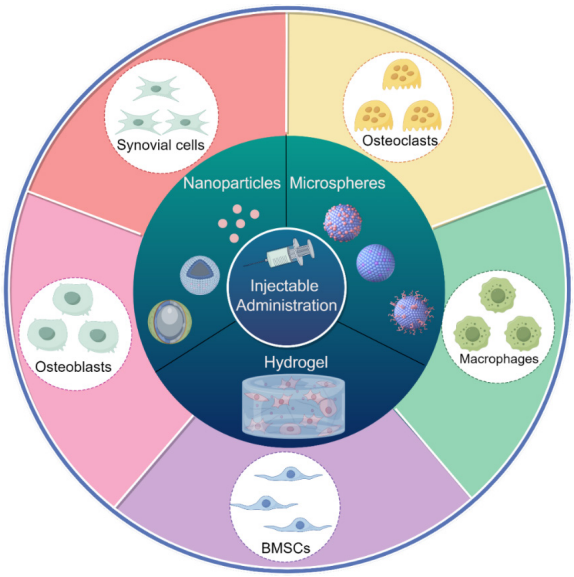

Figure 1. Cell biological behaviour of injectable drug delivery systems. Created with Figdraw. BMSCs: bone marrow mesenchymal stem cells.

Advances of Injectable Drug Delivery Systems

Hydrogels

Hydrogels, which are flexible and interconnected polymer networks, possess the ability to retain substantial volumes of liquids, pharmaceuticals, and biological compounds.[49] Their high water content, inherent to the polymerised cross-linked structure, shields the encapsulated substances from degradation with the body. This property has made hydrogel a staple in various applications, including the development of drug delivery systems for medical use, as well as in the field of tissue engineering.[50, 51]

Conventional intra-articular injections usually administer drugs in their free forms, which can rapidly escape from the synovium into the body's circulation and require frequent injections.[52] The emerging strategy of supramolecular *in situ* formation of hydrogels is showing promising.[53] The hydrogel reaction mixture is applied topically to the soft tissues surrounding the joints, cartilage, and synovial cavities. It specifically targets the affected area, thereby reducing the risk of systemic toxicity associated with anti-rheumatic and anti-arthritic drugs and avoiding adverse effects on biocompatibility, distribution, and pharmacokinetic profile due to factors such as metabolism or excretion.[54, 55]

The medicated hydrogels are reported to show stimuli-responsive, thermo-sensitive, site-specific, or pH-responsive properties. Wu et al.[56] prepared a thermosensitive hydrogel system using Soluplus (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol form) nanoparticles, which showed lower viscosity and a wider concentration range at 25°C in the sol-gel state and stronger gel strength at 37°C. These characteristics enabled a longer sustained release of tacrolimus *in vitro*, without the occurrence of an initial burst release. Additionally, this thermosensitive hydrogel system has been shown to maintain a longer retention of tacrolimus at the injection site *in vivo*. The thermosensitive system showed a slow release and improved therapeutic effect in an *in vivo* model.[56]

In another study, Wu et al.[57] designed a pH-sensitive hydrogel system using a naphthylacetic-glycine-phenylalanine-phenylalanine-lysine-glycine-arginine-histidine self-assembled into an injectable hydrogel at a specific concentration. The inherent tissue retention properties of the hydrogel, combined with the cationic nanoparticles, facilitate a rapid and sustained release of MTX coupled with cations stimulated by the acidic synovial microenvironment. This targeted release directly affects various cells in the synovium without any obstruction. Notably, with increasing peptide concentration, the cumulative drug release rate gradually decreased due to the small nanofiber lattice gaps unfavourable for drug exudation. On the other hand, the enhanced hydrogel stability made it difficult for the peptide to be solubilised by the release medium, thus reducing the drug release. This system demonstrates excellent pH responsiveness and major drug release characteristics, making it a promising approach for drug delivery.

Stimuli-responsive gas-generating sources and delivery systems based on biomaterials that enable on-demand and controllable release are promising approaches for RA therapy. Our team recently fabricated an innovative injectable hydrogel designed to modulate RA's immune responses while delivering medicinal agents (**Figure 2**).[58] This hydrogel, termed DNRS gel, is capable of on-demand degradation facilitated by the consumption of excess nitric oxide and the release of therapeutic hydrogen sulfide. This dual-gas mechanism leads to the restoration of endogenous gas balance, reduction of inflammation, and the reprogramming of macrophages towards the anti-inflammatory M2 phenotype. Moreover, the hydrogel has been shown to inhibit the formation of osteoclasts and to promote bone formation. In a rat model of collagen-induced arthritis, intra-articular injection of the hydrogel combined with MTX demonstrated significant improvements in inflammation, clinical symptoms, and the healing of bone erosion.[58]

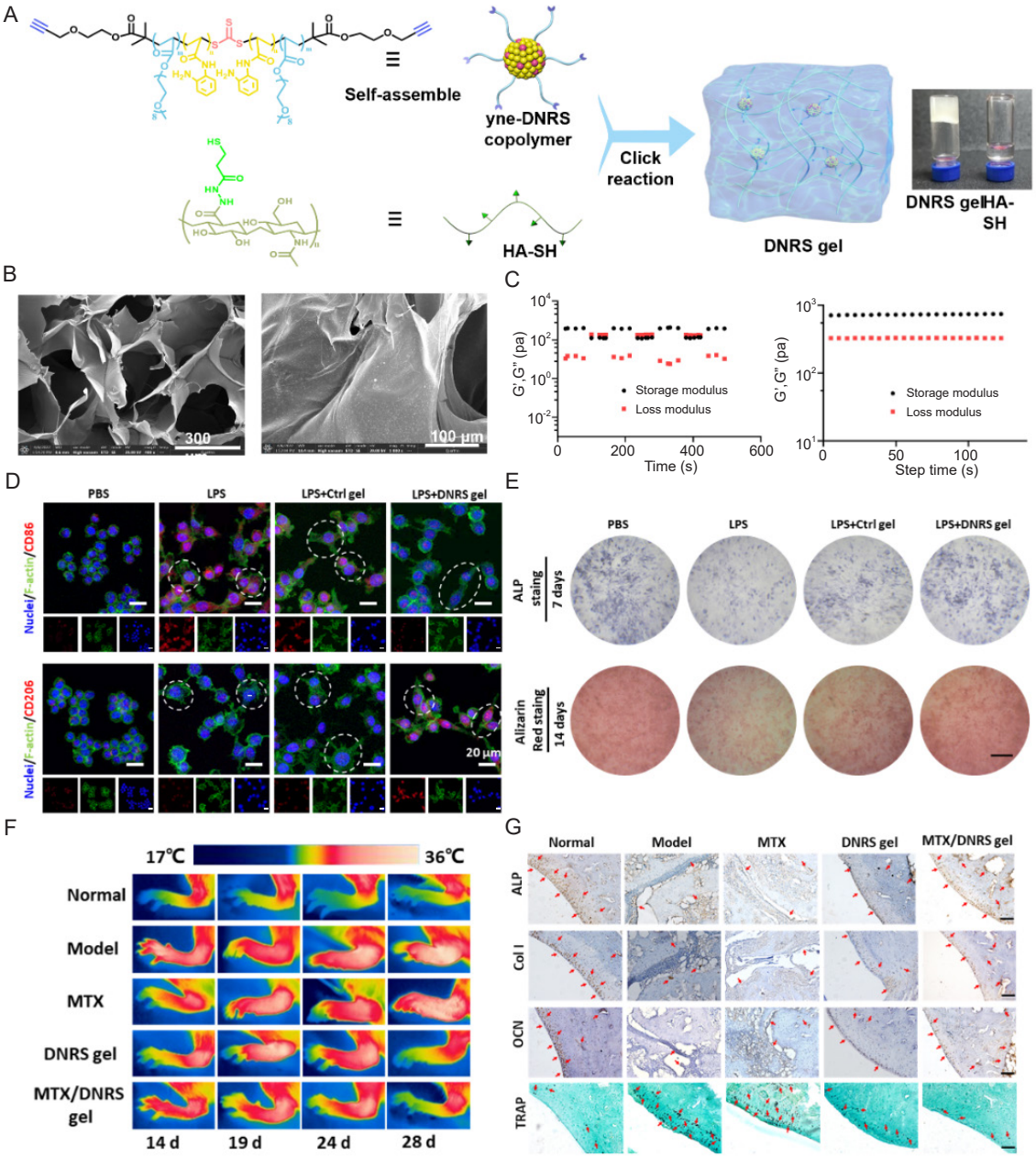

Figure 2. Characterisation of DNRS gel and treatment for RA. (A) The polymerisation mechanism and photograph of DNRS gel. (B) SEM images of DNRS gel. Scale bar: 300 μm (left), 100 μm (right). (C) Step-strain oscillatory theology and time-sweep rheological properties of DNRS gel. (D) Representative fluorescent images of CD86 and CD206 in macrophages after different treatments. Dashed circle represents a decrease in the red fluorescence of CD86. Scale bar: 20 μm. (E) ALP staining and alizarin red staining of osteoblasts after treatment with different conditional media. Scale bar: 500 μm. (F) Thermographic images of inflammatory joints after various treatments. (G) ALP, Col I, and OCN expression levels and TRAP-stained osteoclasts in the joints in different groups. Scale bar: 100 μm. Reprinted from Geng et al.[58] ALP: alkaline phosphatase; COL-1: type I collagen; OCN: osteocalcin; G′: storage modulus; G″: loss modulus; HA: hyaluronic acid; MTX: methotrexate; SEM: scanning electron microscope; SH: sulfhydryl functional group; TRAP: tartrate resistant acid phosphatase.

Recent studies have indicated that neutrophils can abnormally form neutrophil extracellular traps, which, through a variety of mechanisms, enhance the immunogenicity of cartilage components and thus damage articular cartilage. Wang et al.[59] constructed a DNase hydrogel that is capable of digesting neutrophil extracellular traps structures and reducing the expression of inflammatory cytokines *in vivo* (**Figure 3**). This approach addresses the challenge of the short half-life of proteins such as DNA in RA treatment. This study shows that hydrogels can serve as a versatile delivery system, capable of transporting not only conventional RA medications but also synergised protein drugs. These protein drugs, which have a short half-life and are typically unsuitable for intra-articular injection, can now be effectively administered through hydrogel systems. This innovation significantly broadens the therapeutic options available for the treatment of RA.

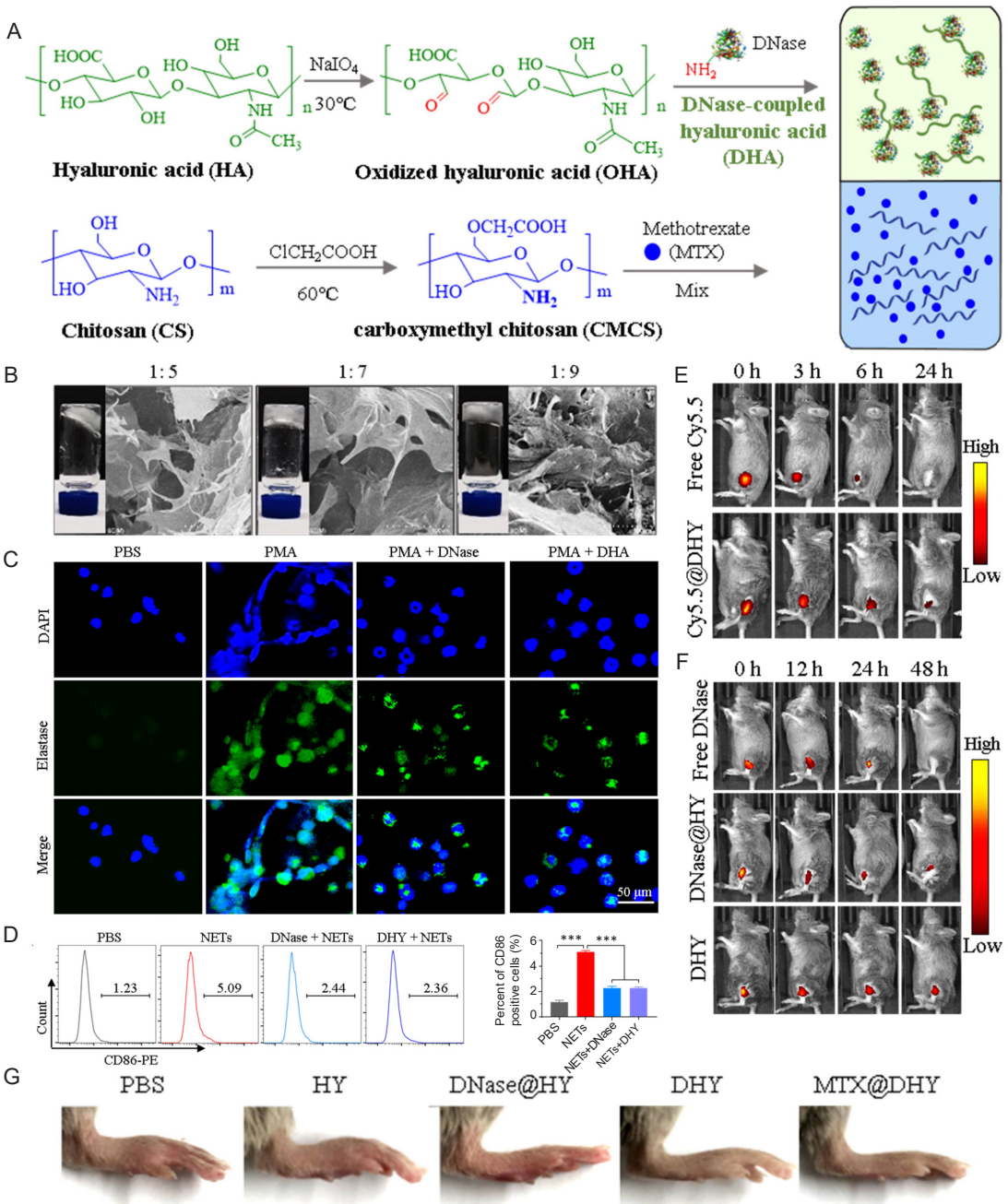

Figure 3. (A) Schematic preparation of MTX-loaded DNase-functionalised hydrogels. (B) Tube inversion experiments and SEM images of DHY with different mass ratio of DHA and CMCS. (C) *In vitro* NETs digestion mediated by DHA. (D) RAW264.7 cells were cultured in the lower chamber and incubated with NETs upon different treatments (upper chamber) for 48 hours. The CD86 of M1 macrophage marker was determined by flow cytometry. (E, F) Determination of fluorescence intensity for *in vivo* controlled release behaviour of DHY. (G) *In vivo* therapeutic effect of DHY in a collagen-induced arthritis mouse model. Reprinted from Wang et al.[59] CMCS: carboxymethyl chitosan; CS: chitosan; DAPI: 4′,6-diamidino-2-phenylindole; DHA: DNase-coupled hyaluronic acid; DHY: DNase-functionalised hydrogel; HA: hyaluronic acid; HY: nonfunctional hydrogel; MTX: methotrexate; NETs: neutrophil extracellular traps; OHA: oxidised hyaluronic acid; PBS: phosphate buffered saline; PMA: 1-methoxy-2-propyl acetate; SEM: scanning electron microscope.

In summary, hydrogel drug delivery systems offer a controllable and responsive approach to medication administration. They can be tailored to respond to changes in temperature, pH, etc, which enhances their retention time in the body and facilitates a more targeted and sustained release of drugs.[55] This approach greatly improves the problems of traditional therapies in terms of untargetability and short drug half-life. Hydrogels that encapsulate drugs have demonstrated significant anti-inflammatory capabilities and have shown to be more therapeutically effective than free drugs.[60] Moreover, the slow-release effect of hydrogel systems can significantly reduce the discomfort associated with frequent injections.[61] Hydrogel also

exhibits resistance to deformation under mechanical stress, a property that is essential for alleviating joint pain.[60] When injected into the joint cavity, hydrogels absorb body fluids, swell, and form a cushion-like support. This support minimises direct bone-to-bone contact, further reducing joint pain and inflammation.[62, 63] Overall, hydrogel drug delivery systems present a promising avenue for improving the treatment of RA, offering a versatile platform for drug administration that is both effective and patient-friendly.

Microspheres

Microsphere represents a particulate dispersion system where a drug is either dispersed or adsorbed within a polymer or polymeric matrix. Among the various carrier materials used for the preparation of microspheres, hydrogel microspheres stand out in drug delivery systems due to their obvious properties. Hydrogel microspheres are nanoscale, three-dimensional mesh structures that are formed through physical or chemical cross-linking of hydrophilic or amphiphilic polymer chains. This distinctive structure endows them with the property of swelling but not dissolving, which effectively protects the encapsulated drug.[64] The small particle size, high loading capacity, and slow-release nature of the drug enable a gradual release of the drug with the body to achieve better efficacy.[65]

One of the primary challenges with intra-articular drug injection is the leakage of the drug from the joint cavity and its rapid entry into the systemic circulation. To address this, a strategic approach is to encapsulate the drug into a particle system with an adequate size.[66, 67] Particle size is a key factor in intra-articular drug delivery, large particles tend to have longer retention time at the injection site, which can improve drug efficacy. However, excessively large particles can potentially irritate the synovial tissue, leading to synovial inflammation. Conversely, particles that are too small may escape from the joint cavity too quickly.[68] Particles smaller than 10 μm (1–4 μm is optimal) can be phagocytosed by synovial macrophages. Through the macrophage-mediated controlled release of the drug, these particles can sustain drug release in the synovial tissues and improve the therapeutic efficacy of the drug administered by intra-articular injection, without triggering the neutrophilic reaction.

Intra-articular injection of anti-RA medicines is a common method used today, the short half-life of these drugs in inflamed joints poses a challenge. A recent study has introduced a responsive hydrogel, essentially a smart "self-driven" drug delivery system (MTX-polymer-lipid hybrid hydrogel microspheres), in which MTX was encapsulated within hydrogel microspheres and injected directly into the matrix in the joint. The composition is crafted to detect the inflammatory enzyme matrix metalloproteinase, a crucial protease involved in the pathology of RA.The hydrogel microspheres are programmed to release MTX in response to elevated levels of matrix metalloproteinase, thereby ensuring controlled drug release only when the joint is inflamed. The formulation is stable in the joint environment but is subject to breakdown due to inflammation.[69] This targeted release strategy not only protects patients from side effects when the disease is in remission but also reduces the need for frequent repeat injections into the joint.

Li et al.[70] have pioneered the development of a locally injectable, long-lasting nano-microcomplex consisting of biodegradable hyaluronic acid and releasable gene and artemisinin, designed to enhance the treatment efficacy in RA (**Figure 4**). Intra-articular injection of this nano-microcomplex marks a significant advancement, as it achieves sustained activity of gene therapy combined with the therapeutic efficacy of artemisinin, providing a long-term treatment strategy first time for RA. This intra-articular injection of TNF-α small interfering RNA/artemisinin co-delivery nano-microcomplex based on dimeric artesunate-phospholipid conjugate/dimeric artesunate-choline conjugate lipid complex and microfluidic microspheres will be one of the most effective gene/drug co-delivery systems for RA treatment.

In order to realise a long-term slow release of drug, researchers have conducted a study to prepare hyaluronic acid methacrylate hydrogel microspheres loaded with oligomeric silsesquioxane-diclofenacsodium nanoparticles. The microspheres hyaluronic acid methacrylate@oligomeric silsesquioxane-diclofenacsodium were prepared by microfluidic technology, a method known for its precision and manipulation. The constructed hydrogel microspheres were non-toxic, effectively improved the local inflammatory microenvironment and significantly promoted the proliferation of chondrocytes. This enhancement in chondrocyte activity is beneficial for promoting cartilage regeneration and facilitating the repair of osteoarthritis.[71]

Injecting hydrogel microspheres directly into the affected joints is a targeted approach that minimises systemic toxicity.[72, 73] For instance, certain drugs with low water solubility, such as cyanosaponin A, present a challenge in direct intra-articular injection due to their solubility limitations. Cyanosaponin A, derived from natural Chinese medicine, has been used for treating knee injuries and alleviating joint pain. However, its poor solubility has restricted its clinical application. By encapsulating cyanosaponin A within hydrogel microspheres, its therapeutic effects can be effectively realised (**Figure 5**).[74]

To sum up, the adaptable nature of hydrogel microspheres permits the adjustment of both materials and manufacturing techniques. This adaptability enables the regulation of drug release pace and duration. Such tailoring enhances the effectiveness of therapy and addresses the issues associated with conventional frequent dosing regimens. By decreasing the number of doses required, it also enhances patient adherence to treatment protocols.[75]

Nanoparticles

The emergence of nanotechnology has garnered increasing attention and has provided new avenues for diagnosis and treating major diseases, including RA.[76, 77] Studies have shown that nanoparticles present obvious advantages in the management of RA, particularly in drug targeting and slow-release delivery systems.[78] By delivering bioactive compounds with enhanced bioavailability directly to the target site, nanoparticles can potentially improve the efficacy and safety of RA therapies, as well as reduction. In addition, the small size and high surface area of nanomaterials contribute to increased solubility and intracellular uptake of active substances.[79]

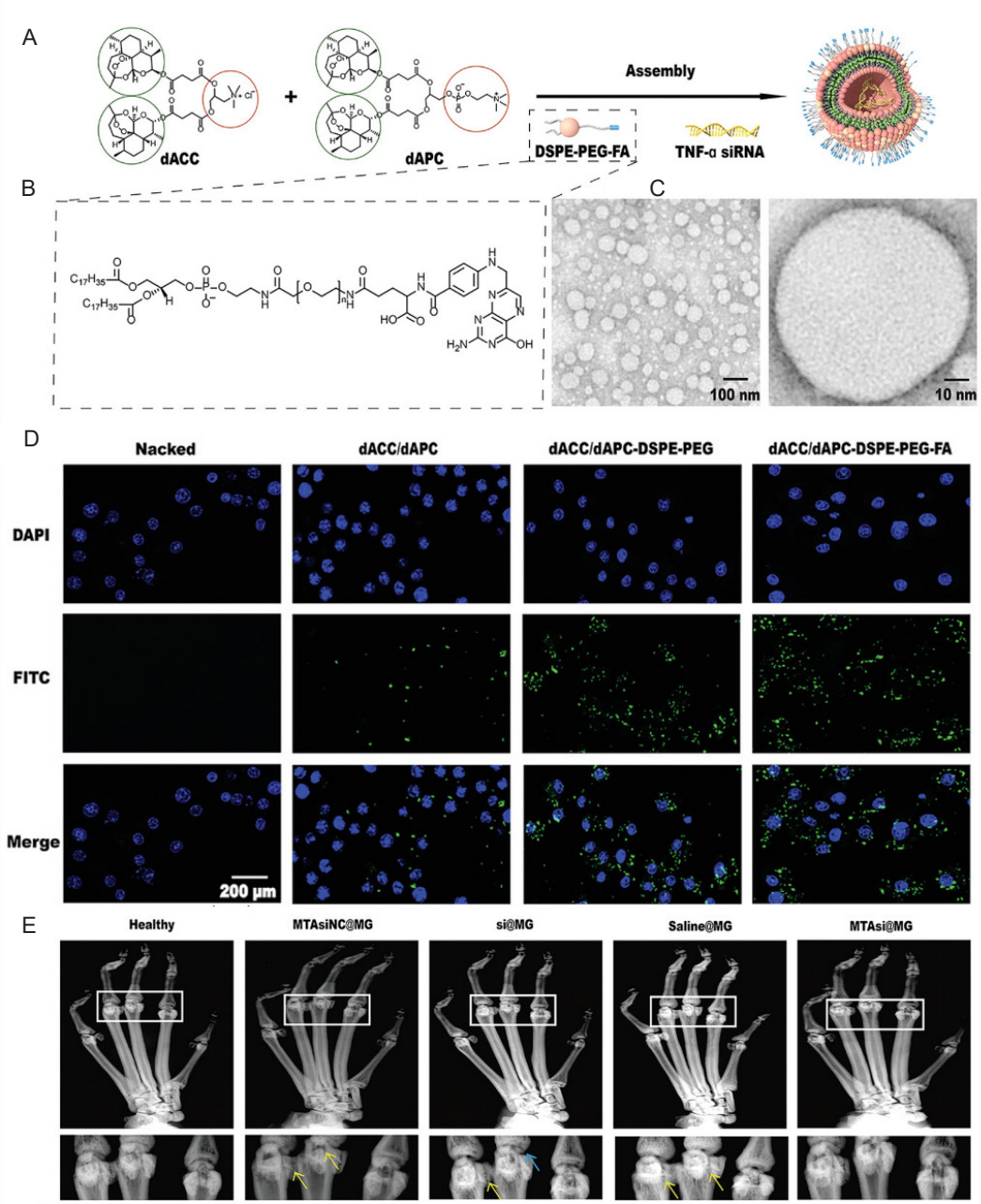

Figure 4. (A) Lipoplex was constructed by dAPC, dACC, and DSPE-PEG-FA, and then loaded with TNF-α siRNA. (B) Chemical structure of DSPE-PEG-FA. (C) TEM images of the lipoplex from the overall view (left) and the local view (right). Scale bars: 100 nm (left), 10 nm (right). (D) LSCM images to analyze the uptake efficacy of transfection. Scale bar: 200 μm. (E) Representative X-ray images in horizontal plane of the metatarsophalangeal joint of different treatments. Arrow represents significant bone erosion in the area. Reprinted from Li et al.[70] Copyright 2022 Wiley-VCH GmbH. ART: artesunate; dACC: dimeric ART-choline conjugate; dAPC: dimeric ART-phospholipid conjugate; DSPE-PEG-FA: phospholipid-polyethylene glycol-folic acid; LSCM: laser scanning confocal microscopy; siRNA: small interfering RNA; TEM: transmission electron microscope; TNF-α: tumour necrosis factor-α.

Nanoparticle systems, particularly those based on polymers, are increasingly utilised as drug delivery systems in RA therapy.[80] Many researchers have used poly(lactic-co-glycolic acid) nanoparticles to increase circulation time and regulate the release rate of encapsulated drugs. It has been observed that when injected intravenously into arthritic rats and mice, the poly(lactic-co-glycolic acid) betamethasone system is more effective than free glucocorticoids in reducing inflammation.[81] In another approach, Gandhi et al.[81] fabricated poly(lactic-co-glycolic acid) nanoparticles with gold and MTX as core components and coupled with anti-CD64 antibody on their surface. The results indicated that these antibody-coupled nanoparticles displayed good stability and homogeneity. Animals treated with antibody-coupled nanoparticles showed significant improvement in clinical indicators and arthritis scores compared to non-coupled nanoparticles and free drugs. This approach enhances therapeutic efficacy while limiting dose-related side effects.

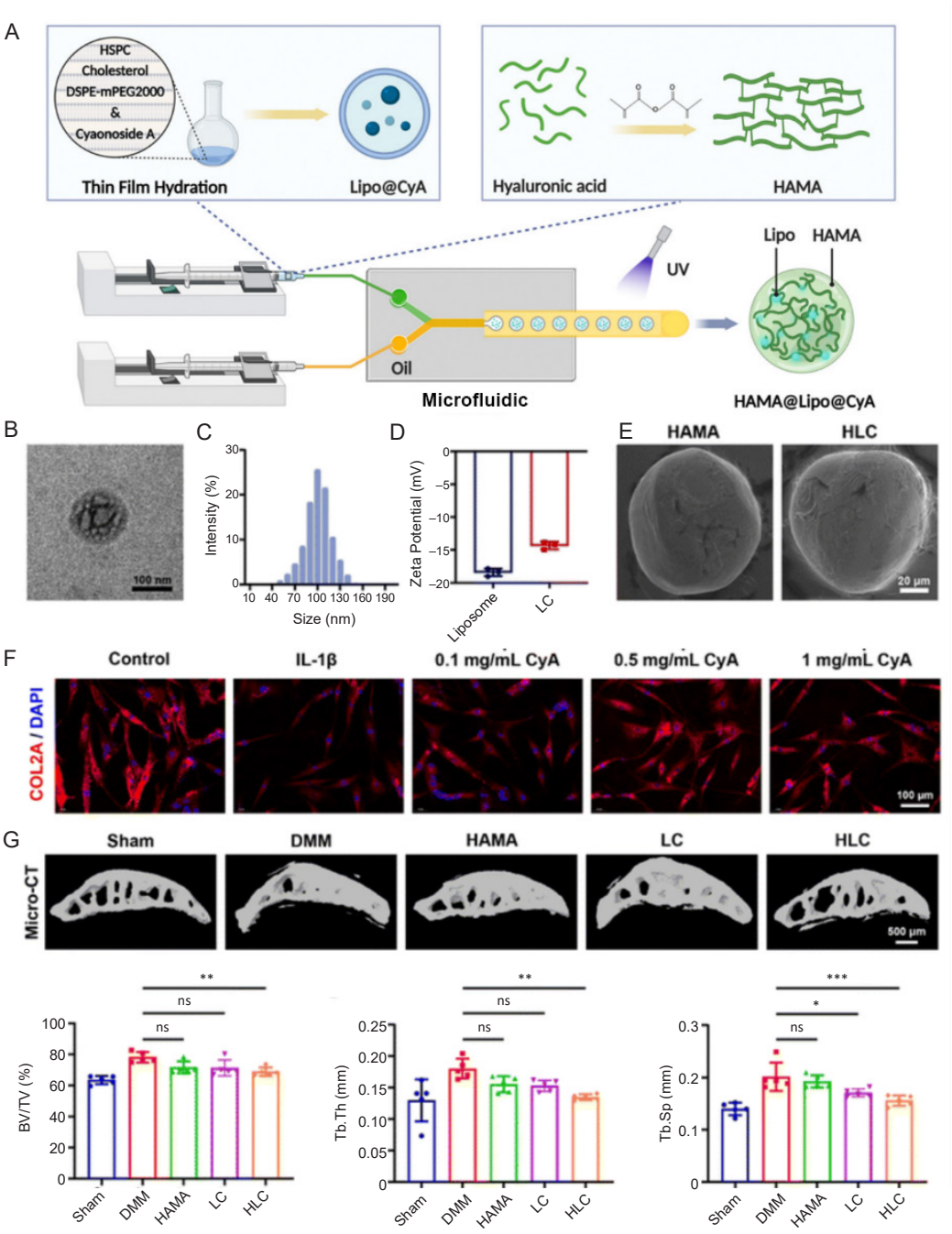

Figure 5. (A) Schematic illustration of the design of drug-loaded composite hydrogel microspheres HLC. (B) Representative TEM image of Lipo@CyA. (C) Particle size analysis of Lipo@CyA. (D) Zeta potential assay of Lipo@CyA. (E) Representative SEM images of the HAMA and HLC microspheres. (F) Representative immunocytofluorescence images of COL2A in human chondrocytes. (G) 3D reconstructed images of subchondral bone in different groups and quantitative analysis of BV/TV, Tb.Th, and Tb.Sp. Reprinted from An et al.[74] BV/TV: bone volume fraction; CT: computed tomography; CyA: cyaonoside A; DAPI: 4′,6-diamidino-2-phenylindole; HAMA: hyaluronic acid methacryloyl; HLC: HAMA@Lipo@CyA; IL-1β: interleukin-1 beta; LC: Lipo@CyA; Lipo: liposomes; ns: no statistical difference; SEM: scanning electron microscope; Tb.Sp: trabecular separation; Tb.Th: trabecular thickness; TEM: transmission electron microscope; UV: ultraviolet.

Another study developed Janus mesenchymal stem cell-hitchhiked melanin nanoparticles (MSC^{FM}) for RA therapy, where half of the mesenchymal stem cells were perseved to migrate chemotactically towards the RA inflammation site, where they effectively balanced the Th17/Treg equilibrium (**Figure 6**). The other half were coupled with iron-enriched melanin nanoparticles, which were deployed to neutralise free radicals, thus preserving the stability of the Th17/Treg balance. *In vivo* results indicated that intravenously injected MSC^{FM} could target the RA site of collagen-induced arthritis mouse model and alleviate RA progression.[82]

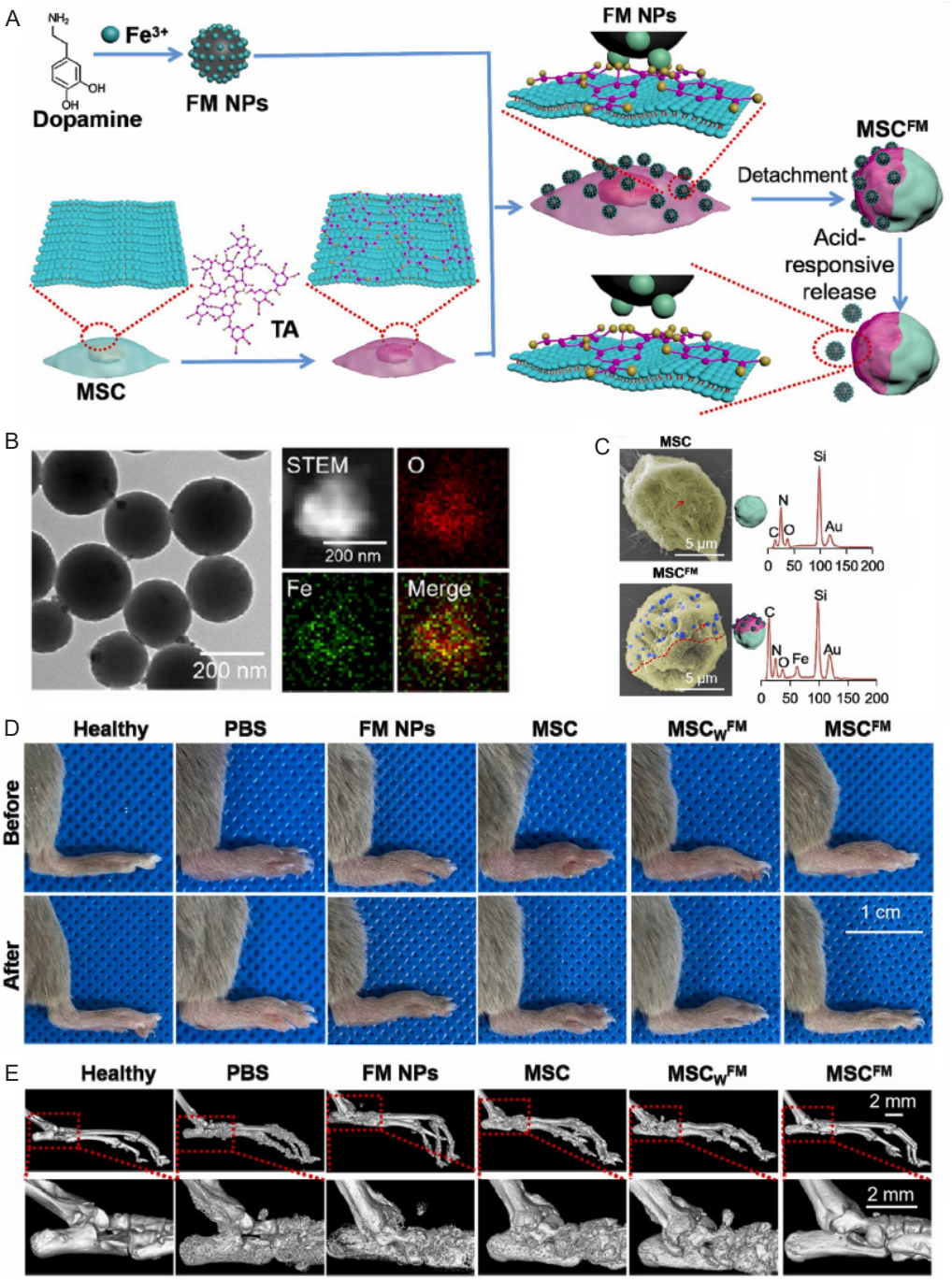

Figure 6. (A) Schematic illustration for MSC^{FM} preparation. (B) TEM of FM NPs. Scale bars: 200 nm. (C) SEM images coupled with EDS spectroscopy of MSC and MSC^{FM}. The cells (yellow) and FM NPs (blue) were painted with pseudocolours. Scale bars: 5 μm. (D) The hind paws images of different treated mice after 16 days of treatments. Scale bar: 1 cm. (E) The micro-CT images of mouse hind paws after the treatments. Scale bars: 2 mm. Reprinted from Han et al.[82] Copyright 2024 Elsevier Ltd. CT: computed tomography; EDS: energy-dispersive X-ray spectroscopy; FM NPs: half hitchhiked the iron-doped melanin nanoparticles; FM: (Fe^{3+})-doped melanin; MSC: mesenchymal stem cell; MSC^{FM}: Janus mesenchymal stem cell-loaded melanin nanoparticles; MSC_W^{FM}: MSC-hitchhiked melanin nanoparticles; PBS: phosphate buffered saline; STEM: scanning transmission electron microscopy; TA: tannic acid; TEM: transmission electron microscope.

Wu et al.[83] have developed an intra-articular mesoporous silica nanosystem (MSN-TP@PDA-GlcN) with anti-inflammatory properties and joint-protectivecapabilities. The nanosystem was engineered by embedding triptolide (TP) in mesoporous silica nanoparticles and coated with pH-sensitive dopamine (PDA), to which glucosamine (GlcN) was attached. This anti-inflammatory and joint-protective nano-delivery system showed promising efficacy against RA. TMSN-TP@PDA-GlcN was stable and exhibited sustained drug release in acidic environment. It also effectively repaired joint destruction *in vivo* without causing any tissue toxicity.

Among various surface modification techniques, the cell-membrane mimicking strategy has displayed significant promise in enhancing the performance of nanoparticle-based drug delivery systems.[84] By incorporating a wealth of biocompatible proteins on their surface, nanoparticles disguised with cell membranes can efficiently bypass the immune system. This allows for increased drug concentration in the targeted joints, thereby improving the precision of drug delivery and ensuring a highly focused accumulation at the site of interest. Hao et al.[85] developed three biomimetic nanoparticles derived from different cells for dual targeting of inflammatory sites and M1 macrophages. The results showed that the nanoparticles had a large accumulation at inflammatory sites in M1 macrophages and had a high internalisation efficiency. After loading MTX, the nanoparticles markedly suppressed the proliferation of stimulated macrophages and curbed the release of inflammatory cytokines. Within a murine model of arthritis induced by adjuvant, the nanoparticles efficiently lessened inflammatory macrophage counts, pro-inflammatory cytokine output, and the degradation of cartilaginous and osseous structures.

Liposomes, which are spherical vesicles consisting of one or more concentric bilayer phospholipid layers, are a versatile nanodrug delivery system.[86, 87] Liposomes offer a variety of advantages, including good biocompatibility, self-assembly ability, drug encapsulation, and modification of drug biological properties.[88, 89] Fu et al.[90] designed a multifunctional liposome system (MPM nanoparticle were coated with temperature-sensitive liposomes, MPM@Lipo), which integrates chemotherapy, photothermal therapy, and oxygenation strategies (**Figure 7**). This approach aims to eliminate excessively proliferating inflammatory cells and enhance the oxygen-starved conditions typically found in the joints for the treatment of RA. The findings demonstrated that MPM@Lipo effectively neutralised reactive oxygen species and alleviated joint hypoxia, promoting the shift of M1 macrophages to the M2 phenotype. Moreover, MPM@Lipo localised to inflamed joints, curbed inflammatory mediator synthesis, and safeguarded cartilage *in vivo*. Furthermore, upon laser exposure, MPM@Lipo increased temperature, effectively eradicating excessive inflammatory cells and boosting the generation of MTX and oxygen, leading to a superior therapeutic outcome for RA.

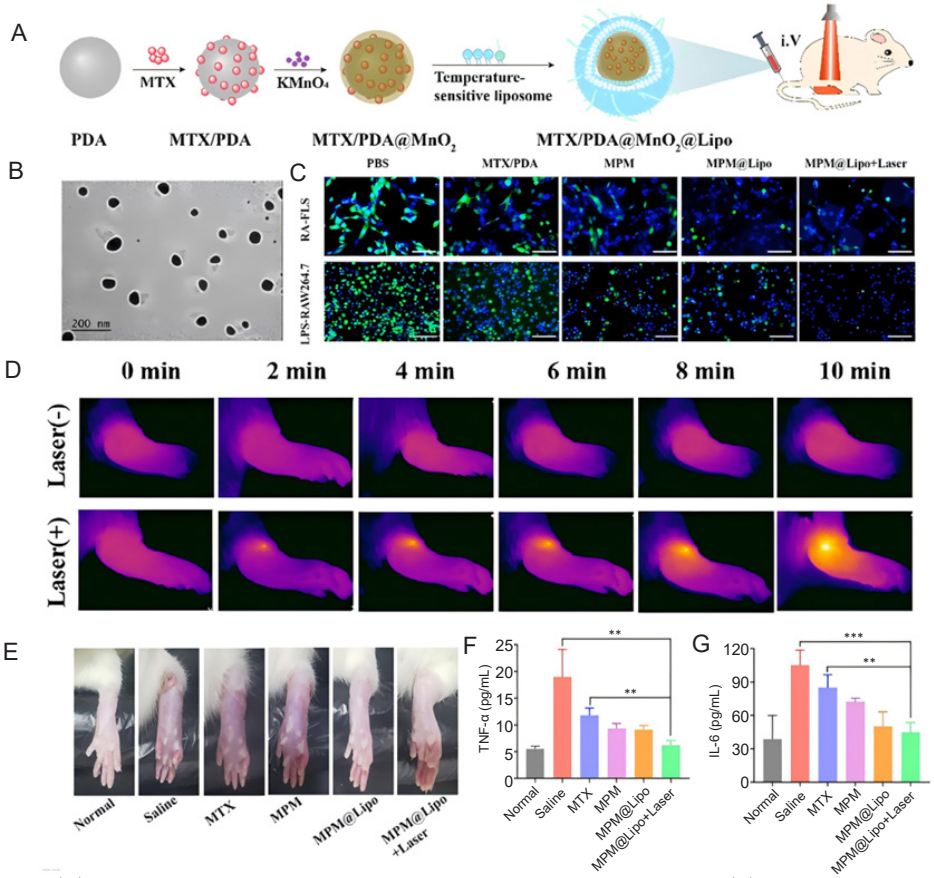

Figure 7. (A) Schematic diagram of the MPM@Lipo construction mechanism. (B) Representative TEM images of MPM@Lipo. Scale bar: 200 nm. (C) The intracellular ROS levels in RA-FLSs cells and LPS-activated RAW264.7 cells were observed by fluorescence microscopy. Scale bar: 100 μm. (D) Photothermal images of the ankle of AIA rats in MPM@Lipo group under laser irritation. (E) Representative photograph of right hind limbs after treatment. (F, G) The levels of TNF-α (F) and IL-6 (G) in different groups were measured by ELISA. Data are expressed as mean ± SD (n = 6). $^{**}P < 0.01$, $^{***}P < 0.001$. Reprinted from Fu et al.[90] AIA: adjuvant-induced arthritis; ELISA: enzyme-linked immunosorbent assays; i.V: injection; IL-6: interleukin-6; LPS: lipopolysaccharide; MPM: MTX/PDA@MnO_2; MPM@Lipo: MTX/PDA@MnO_2@Lipo; MTX/PDA@MnO_2: a MnO_2 layer was formed on the PDA nanoparticle; MTX/PDA@MnO_2@Lipo: MPM nanoparticle were coated with temperature-sensitive liposomes; MTX: methotrexate; PDA: polydopamine; RA-FLSs: rheumatoid arthritis-fibroblast-like synoviocyte; ROS: reactive oxygen species; TEM: transmission electron microscope; TNF-α: tumour necrosis factor-α.

In another study, Guo et al.[91] prepared a multifunctional microenvironmentally responsive liposome. In this system, TP was encapsulated within a bilayer structure resembling a biofilm. The targeting moiety is mannose-coupled 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000, and PVGLIG, an enzyme-responsive peptide, serves as a linker arm connecting to 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy (polyethylene glycol)-5000. This arrangement creates a hydrophilic membrane on the liposome's exterior, enhancing its dwell time in circulation and preventing the interaction of targeting elements with macrophages in healthy tissues. This strategy minimises drug deposition in non-target areas, thus diminishing both therapeutic inefficacy and adverse side effects. Additionally, these liposomes have been shown to curb osteoclast development and the emission of inflammatory mediators, including cytokines, reactive oxygen species, and matrix metalloproteinases, as demonstrated through both *in vivo* and *in vitro* assessments. This approach combines anti-inflammatory and osteoprotective effects and provides a novel approach for comprehensive RA therapy (**Figure 8**).[92]

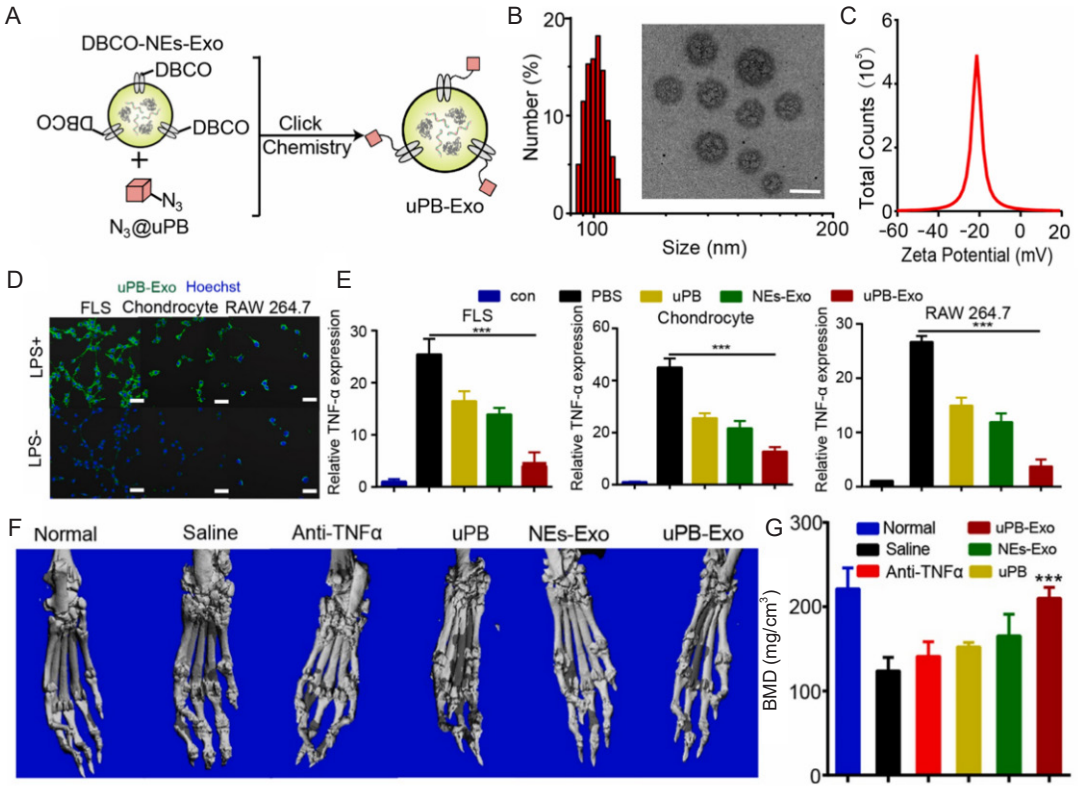

Figure 8. (A) Schematic representation of uPB-Exo designed for selectively suppressing inflammatory stress in RA joints. (B) Hydrodynamic size of uPB-Exo measured by DLS. The insert image indicated the transmission electron microscopy images of uPB-Exo. Scale bar: 100 nm. (C) The zeta potential of uPB-Exo measured by DLS. (D) Confocal microscopic images of activated FLS, chondrocytes, and RAW264.7 cells incubated with DiO labeled uPB-Exo. Scale bars: 20 μm. (E) The relative expression of TNF-α in activated FLS, chondrocyte, RAW264.7 cells incubated with activated uPB-Exo, NEs-Exo and uPB. Cells treated with PBS were used as control. (F) Representative micro-CT images of ankle joints from mice with different treatments. (G) Quantitative micro-CT analysis of bone mineral density. Data are expressed as mean ± SD. ***$P < 0.001$. Reprinted from Zhang et al.[92] con: control; DBCO: dibenzylcyclootyne; DiO: 3,3′-dioctadecyloxacarbocyanine perchlorate; DLS: dynamic light scattering; FLS: fibroblast like synoviocytes; LPS: lipopolysaccharide; NEs-Exo: neutrophils-derived exosomes; PBS: phosphate buffered saline; RA: rheumatoid arthritis; TNF-α: tumour necrosis factor-α; uPB: sub-5 nm ultrasmall PBNPs; uPB-Exo: functionalized NEs-Exo with sub-5 nm ultrasmall PBNPs.

Exosomes, which are nanoscale vesicles originating from endosomes, play a pivotal role in intercellular communication. These natural nanoparticles, released by a variety of cells, are seen as promising vehicles for drug delivery and therapeutic interventions due to their material properties.[93] They have minimal immunogenicity and toxicity, high biocompatibility, excellent circulatory stability, and excellent biological barrier permeability, making them superior to conventional carriers. Thus, exosomes are considered ideal drug delivery carriers and have potential as drug delivery systems.[94-96] Su et al.[97] found that mesenchymal stem cell-derived exosomes were involved in intercellular transfer of long non-coding RNA heart and neural crest derivatives expressed 2-antisense RNA 1 and inhibited the activation of RA-fibroblast-like synoviocyte via the miR-143-3p/tumour necrosis factor alpha-inducible protein 3/NF-κB pathway, which provided new insights into the pathogenesis and treatment of RA. Different sources of exosomes also have different roles and functions for the treatment of RA, making exosomes a valid future therapeutic target.[98]

Overall, nanoparticles can increase the circulation time and prolong the drug release with better therapeutic effect compared to free drug.[79, 99] It can be used as a solution to the limitations of *in vivo* methods for the effective delivery of small interfering RNAs, microRNAs, and other biomolecules associated with gene therapy. Moreover, the enhanced drug-targeting capability enables them to accumulate in the joint inflammation site, which can lead to improved distribution of the drug within the affected tissues, a reduction in side effects, and ultimately, an enhanced therapeutic outcome.[100] Specifically, local injection of this carrier system reduces degenerative lesions in RA.[101] However, it is associated with various limitations as these are more expensive, more difficult to produce, reduced ability to adjust dosage, highly complex technology requiring manufacturing skills, and stability of dosage forms that are difficult to maintain.[102]

Conclusions and Future Perspectives

In conclusion, the review has underscored the significant strides made in the development of injectable drug delivery systems for RA, particularly focusing on hydrogels, microspheres, and nanoparticles. Compared to conventional treatments, these systems offer advantages such as sustained release, targeted delivery, reduced side effects, and improved patient compliance. The potential for personalised medicine, enhanced by precision delivery systems, is particularly noteworthy, offering a tailored approach to managing RA that considers individual patient needs.

Despite the progress, the delivery of therapeutic agents for the treatment of RA is still being explored and facing a variety of challenges, including biocompatibility, long-term safety, scalability, and regulatory approval processes. Further research and development are essential to overcome the current limitations of injectable drug delivery systems for RA. Future studies should focus on optimising the design of these systems to enhance their efficacy, safety, and biocompatibility. Additionally, by addressing current challenges and embracing novel opportunities, researchers and clinicians can work together to usher in a new era of personalised and targeted therapies that have the potential to revolutionise patient care in the field of rheumatology.

Author contributions

PZ and KC conceptualised and designed the review; YL and QD drafted the manuscript; JH checked and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflicts of interest statement

The authors declare no conflict of interest.

1. Conforti, A.; Di Cola, I.; Pavlych, V.; Ruscitti, P.; Berardicurti, O.; Ursini, F.; Giacomelli, R.; Cipriani, P. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. *Autoimmun Rev.* **2021,** *20,* 102735.
2. Nemtsova, M. V.; Zaletaev, D. V.; Bure, I. V.; Mikhaylenko, D. S.; Kuznetsova, E. B.; Alekseeva, E. A.; Beloukhova, M. I.; Deviatkin, A. A.; Lukashev, A. N.; Zamyatnin, A. A., Jr. Epigenetic changes in the pathogenesis of rheumatoid arthritis. *Front Genet.* **2019,** *10,* 570.
3. Ciofoaia, E. I.; Pillarisetty, A.; Constantinescu, F. Health disparities in rheumatoid arthritis. *Ther Adv Musculoskelet Dis.* **2022,** *14,* 1759720x221137127.
4. Weyand, C. M.; Goronzy, J. J. The immunology of rheumatoid arthritis. *Nat Immunol.* **2021,** *22,* 10-18.
5. Porchas-Quijada, M.; Reyes-Castillo, Z.; Muñoz-Valle, J. F.; Durán-Barragán, S.; Aguilera-Cervantes, V.; López-Espinoza, A.; Vázquez-Del Mercado, M.; Navarro-Meza, M.; López-Uriarte, P. IgG anti-ghrelin immune complexes are increased in rheumatoid arthritis patients under biologic therapy and are related to clinical and metabolic markers. *Front Endocrinol (Lausanne).* **2019,** *10,* 252.
6. Nygaard, G.; Firestein, G. S. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. *Nat Rev Rheumatol.* **2020,** *16,* 316-333.
7. Wu, Z.; Ma, D.; Yang, H.; Gao, J.; Zhang, G.; Xu, K.; Zhang, L. Fibroblast-like synoviocytes in rheumatoid arthritis: Surface markers and phenotypes. *Int Immunopharmacol.* **2021,** *93,* 107392.
8. Hannemann, N.; Apparailly, F.; Courties, G. Synovial macrophages: from ordinary eaters to extraordinary multitaskers. *Trends Immunol.* **2021,** *42,* 368-371.
9. Croia, C.; Bursi, R.; Sutera, D.; Petrelli, F.; Alunno, A.; Puxeddu, I. One year in review 2019: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol.* **2019,** *37,* 347-357.
10. Scherer, H. U.; Häupl, T.; Burmester, G. R. The etiology of rheumatoid arthritis. *J Autoimmun.* **2020,** *110,* 102400.
11. Fraenkel, L.; Bathon, J. M.; England, B. R.; St Clair, E. W.; Arayssi, T.; Carandang, K.; Deane, K. D.; Genovese, M.; Huston, K. K.; Kerr, G.; Kremer, J.; Nakamura, M. C.; Russell, L. A.; Singh, J. A.; Smith, B. J.; Sparks, J. A.; Venkatachalam, S.; Weinblatt, M. E.; Al-Gibbawi, M.; Baker, J. F.; Barbour, K. E.; Barton, J. L.; Cappelli, L.; Chamseddine, F.; George, M.; Johnson, S. R.; Kahale, L.; Karam, B. S.; Khamis, A. M.; Navarro-Millán, I.; Mirza, R.; Schwab, P.; Singh, N.; Turgunbaev, M.; Turner, A. S.; Yaacoub, S.; Akl, E. A. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* **2021,** *73,* 924-939.
12. Rai, P. K.; Sharma, V.; Mukharjee, J.; Dhote, V. V. A brief review on inflammatory mediators and drug therapy for rheumatoid arthritis. *Trends Drug Deliv.* **2019,** *6,* 1-4.
13. Khalil, N. Y.; Aldosari, K. F. Meloxicam. *Profiles Drug Subst Excip Relat Methodol.* **2020,** *45,* 159-197.
14. Khan, S.; Andrews, K. L.; Chin-Dusting, J. P. F. Cyclo-oxygenase (COX) inhibitors and cardiovascular risk: are non-steroidal anti-inflammatory drugs really anti-inflammatory? *Int J Mol Sci.* **2019,** *20,* 4262.
15. Paglia, M. D. G.; Silva, M. T.; Lopes, L. C.; Barberato-Filho, S.; Mazzei, L. G.; Abe, F. C.; de Cássia Bergamaschi, C. Use of corticoids and non-

steroidal anti-inflammatories in the treatment of rheumatoid arthritis: Systematic review and network meta-analysis. *PLoS One.* **2021,** *16,* e0248866.
16. Xie, P.; Xue, W.; Qi, W.; Li, Y.; Yang, L.; Yang, Z.; Shi, A. Safety, tolerability, and pharmacokinetics of ibuprofenamine hydrochloride spray (NSAIDs), a new drug for rheumatoid arthritis and osteoarthritis, in healthy Chinese subjects. *Drug Des Devel Ther.* **2021,** *15,* 629-638.
17. Bahap-Kara, M.; Sariyildiz, E.; Yardimci, G. K.; Karadag, O.; Bayraktar-Ekincioglu, A. Addressing glucocorticoid-related problems with the clinical pharmacist collaboration in rheumatology practice: a prospective follow-up study. *Rheumatol Ther.* **2024,** *11,* 1043-1055.
18. Xu, W.; Ye, J.; Cao, Z.; Zhao, Y.; Zhu, Y.; Li, L. Glucocorticoids in lung cancer: Navigating the balance between immunosuppression and therapeutic efficacy. *Heliyon.* **2024,** *10,* e32357.
19. Song, S.; Wang, Y.; Fang, Y.; Teng, F.; Yue, T.; Chen, L.; Wan, X.; Hong, R.; Xue, M. Glucocorticoids promote joint microenvironment alteration of GABBR1 expression associated with mitigating rheumatoid arthritis. *Cell Mol Biol (Noisy-le-grand).* **2024,** *70,* 73-77.
20. Hua, C.; Buttgereit, F.; Combe, B. Glucocorticoids in rheumatoid arthritis: current status and future studies. *RMD Open.* **2020,** *6,* e000536.
21. Coburn, B. W.; Baker, J. F.; Hsu, J. Y.; Wu, Q.; Xie, F.; Curtis, J. R.; George, M. D. Association of cardiovascular outcomes with low-dose glucocorticoid prescription in patients with rheumatoid arthritis. *Arthritis Rheumatol.* **2024,** *76,* 1585-1593.
22. Smolen, J. S.; Landewé, R. B. M.; Bergstra, S. A.; Kerschbaumer, A.; Sepriano, A.; Aletaha, D.; Caporali, R.; Edwards, C. J.; Hyrich, K. L.; Pope, J. E.; de Souza, S.; Stamm, T. A.; Takeuchi, T.; Verschueren, P.; Winthrop, K. L.; Balsa, A.; Bathon, J. M.; Buch, M. H.; Burmester, G. R.; Buttgereit, F.; Cardiel, M. H.; Chatzidionysiou, K.; Codreanu, C.; Cutolo, M.; den Broeder, A. A.; El Aoufy, K.; Finckh, A.; Fonseca, J. E.; Gottenberg, J. E.; Haavardsholm, E. A.; Iagnocco, A.; Lauper, K.; Li, Z.; McInnes, I. B.; Mysler, E. F.; Nash, P.; Poor, G.; Ristic, G. G.; Rivellese, F.; Rubbert-Roth, A.; Schulze-Koops, H.; Stoilov, N.; Strangfeld, A.; van der Helm-van Mil, A.; van Duuren, E.; Vliet Vlieland, T. P. M.; Westhovens, R.; van der Heijde, D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis.* **2023,** *82,* 3-18.
23. Alfaro-Lara, R.; Espinosa-Ortega, H. F.; Arce-Salinas, C. A. Systematic review and meta-analysis of the efficacy and safety of leflunomide and methotrexate in the treatment of rheumatoid arthritis. *Reumatol Clin (Engl Ed).* **2019,** *15,* 133-139.
24. Fleischmann, R.; Takeuchi, T.; Schiff, M.; Schlichting, D.; Xie, L.; Issa, M.; Stoykov, I.; Lisse, J.; Martinez-Osuna, P.; Rooney, T.; Zerbini, C. A. F. Efficacy and safety of long-term baricitinib with and without methotrexate for the treatment of rheumatoid arthritis: experience with baricitinib monotherapy continuation or after switching from methotrexate monotherapy or baricitinib plus methotrexate. *Arthritis Care Res (Hoboken).* **2020,** *72,* 1112-1121.
25. Radu, A. F.; Bungau, S. G. Management of rheumatoid arthritis: an overview. *Cells.* **2021,** *10,* 2857.
26. García-González, C. M.; Baker, J. Treatment of early rheumatoid arthritis: Methotrexate and beyond. *Curr Opin Pharmacol.* **2022,** *64,* 102227.
27. Patra, S.; Choudhury, T. P.; Barman, S. The journey of methotrexate and potential alternative pharmacotherapies for rheumatoid arthritis. *Curr Drug Res Rev.* **2024.** doi: 10.2174/0125899775258634231226052204.
28. Dickson, K. S.; Regan, A.; Wemyss, C.; Paley, M.; Siddiqui, A. A call for guidance on the treatment of patients taking disease-modifying anti-rheumatic drugs (DMARDs). *Br J Oral Maxillofac Surg.* **2024,** *62,* 389-390.
29. Cronstein, B. N.; Aune, T. M. Methotrexate and its mechanisms of action in inflammatory arthritis. *Nat Rev Rheumatol.* **2020,** *16,* 145-154.
30. Wang, Z.; Huang, J.; Xie, D.; He, D.; Lu, A.; Liang, C. Toward overcoming treatment failure in rheumatoid arthritis. *Front Immunol.* **2021,** *12,* 755844.
31. Hamed, K. M.; Dighriri, I. M.; Baomar, A. F.; Alharthy, B. T.; Alenazi, F. E.; Alali, G. H.; Alenazy, R. H.; Alhumaidi, N. T.; Alhulayfi, D. H.; Alotaibi, Y. B.; Alhumaidan, S. S.; Alhaddad, Z. A.; Humadi, A. A.; Alzahrani, S. A.; Alobaid, R. H. Overview of methotrexate toxicity: a comprehensive literature review. *Cureus.* **2022,** *14,* e29518.
32. Bellinvia, S.; Cummings, J. R. F.; Ardern-Jones, M. R.; Edwards, C. J. Adalimumab biosimilars in europe: an overview of the clinical evidence. *Biodrugs.* **2019,** *33,* 241-253.
33. Subedi, S.; Gong, Y.; Chen, Y.; Shi, Y. Infliximab and biosimilar infliximab in psoriasis: efficacy, loss of efficacy, and adverse events. *Drug Des Devel Ther.* **2019,** *13,* 2491-2502.
34. Atiqi, S.; Hooijberg, F.; Loeff, F. C.; Rispens, T.; Wolbink, G. J. Immunogenicity of TNF-Inhibitors. *Front Immunol.* **2020,** *11,* 312.
35. Rai, V.; Patel, N.; Mammen, S. R.; Chaudhary, S. M.; Arshad, S.; Munazzam, S. W. Futuristic novel therapeutic approaches in the treatment of rheumatoid arthritis. *Cureus.* **2023,** *15,* e49738.
36. Kubo, S.; Nakayamada, S.; Tanaka, Y. Baricitinib for the treatment of rheumatoid arthritis and systemic lupus erythematosus: a 2019 update. *Expert Rev Clin Immunol.* **2019,** *15,* 693-700.
37. Song, P.; Cui, Z.; Hu, L. Applications and prospects of intra-articular drug delivery system in arthritis therapeutics. *J Control Release.* **2022,** *352,* 946-960.
38. de la Torre-Aboki, J.; Uson, J.; Pitsillidou, I.; Vardanyan, V.; Nikiphorou, E.; Rodriguez-Garcia, S. C.; Castellanos-Moreira, R.; Pandit, H.; O'Neill, T. W.; Doherty, M.; Boesen, M.; Möller, I.; Terslev, L.; D'Agostino, M. A.; Kampen, W. U.; Berenbaum, F.; Naredo, E.; Carmona, L. Intra-articular therapies: patient preferences and professional practices in European countries. *Rheumatol Int.* **2022,** *42,* 869-878.
39. Gardner, J. E.; Williams, C. W.; Bowers, R. L. Subchondral versus intra-articular orthobiologic injections for the treatment of knee osteoarthritis: a review. *Regen Med.* **2022,** *17,* 389-400.
40. Ma, L.; Zheng, X.; Lin, R.; Sun, A. R.; Song, J.; Ye, Z.; Liang, D.; Zhang, M.; Tian, J.; Zhou, X.; Cui, L.; Liu, Y.; Liu, Y. Knee osteoarthritis therapy: recent advances in intra-articular drug delivery systems. *Drug Des Devel Ther.* **2022,** *16,* 1311-1347.
41. Kolasinski, S. L.; Neogi, T.; Hochberg, M. C.; Oatis, C.; Guyatt, G.; Block, J.; Callahan, L.; Copenhaver, C.; Dodge, C.; Felson, D.; Gellar, K.; Harvey, W. F.; Hawker, G.; Herzig, E.; Kwoh, C. K.; Nelson, A. E.; Samuels, J.; Scanzello, C.; White, D.; Wise, B.; Altman, R. D.; DiRenzo, D.; Fontanarosa, J.; Giradi, G.; Ishimori, M.; Misra, D.; Shah, A. A.; Shmagel, A. K.; Thoma, L. M.; Turgunbaev, M.; Turner, A. S.; Reston, J. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken).* **2020,** *72,* 149-162.
42. Mordin, M.; Parrish, W.; Masaquel, C.; Bisson, B.; Copley-Merriman, C. Intra-articular hyaluronic acid for osteoarthritis of the knee in the united states: a systematic review of economic evaluations. *Clin Med Insights Arthritis Musculoskelet Disord.* **2021,** *14,* 11795441211047284.

43. Guarise, C.; Tessari, M.; Pavan, M.; Pluda, S.; Di Lucia, A.; Barbera, C.; Galesso, D. Hydrophobic derivatives of sulfated hyaluronic acid as drug delivery systems for multi-target intra-articular treatment of post-traumatic osteoarthritis. *J Pharm Sci.* **2022,** *111,* 2505-2513.
44. Marinho, A.; Nunes, C.; Reis, S. Hyaluronic acid: a key ingredient in the therapy of inflammation. *Biomolecules.* **2021,** *11,* 1518.
45. Le Merdy, M.; Mullin, J.; Lukacova, V. Development of PBPK model for intra-articular injection in human: methotrexate solution and rheumatoid arthritis case study. *J Pharmacokinet Pharmacodyn.* **2021,** *48,* 909-922.
46. Salaffi, F.; Di Carlo, M.; Farah, S.; Carotti, M. Adherence to subcutaneous anti-TNFα agents in patients with rheumatoid arthritis is largely influenced by pain and skin sensations at the injection site. *Int J Rheum Dis.* **2020,** *23,* 480-487.
47. Bullock, J.; Rizvi, S. A. A.; Saleh, A. M.; Ahmed, S. S.; Do, D. P.; Ansari, R. A.; Ahmed, J. Rheumatoid arthritis: a brief overview of the treatment. *Med Princ Pract.* **2018,** *27,* 501-507.
48. Dwivedi, S.; Testa, E. J.; Modest, J. M.; Ibrahim, Z.; Gil, J. A. Surgical management of rheumatoid arthritis of the hand. *R I Med J (2013).* **2020,** *103,* 32-36.
49. Liu, G.; Zhou, Y.; Xu, Z.; Bao, Z.; Zheng, L.; Wu, J. Janus hydrogel with dual antibacterial and angiogenesis functions for enhanced diabetic wound healing. *Chin Chem Lett.* **2023,** *34,* 107705.
50. Zhang, Z.; Hao, Z.; Xian, C.; Zhang, J.; Wu, J. Triple functional magnesium ascorbyl phosphate encapsulated hydrogel: A cosmetic ingredient promotes bone repair via anti-oxidation, calcium uptake and blood vessel remodeling. *Chem Eng J.* **2023,** *472,* 145061.
51. Chapa-Villarreal, F. A.; Stephens, M.; Pavlicin, R.; Beussman, M.; Peppas, N. A. Therapeutic delivery systems for rheumatoid arthritis based on hydrogel carriers. *Adv Drug Deliv Rev.* **2024,** *208,* 115300.
52. Zewail, M.; Nafee, N.; Helmy, M. W.; Boraie, N. Synergistic and receptor-mediated targeting of arthritic joints via intra-articular injectable smart hydrogels containing leflunomide-loaded lipid nanocarriers. *Drug Deliv Transl Res.* **2021,** *11,* 2496-2519.
53. Bernhard, S.; Tibbitt, M. W. Supramolecular engineering of hydrogels for drug delivery. *Adv Drug Deliv Rev.* **2021,** *171,* 240-256.
54. Wu, Y.; Ge, Y.; Wang, Z.; Zhu, Y.; Tian, T.; Wei, J.; Jin, Y.; Zhao, Y.; Jia, Q.; Wu, J.; Ge, L. Synovium microenvironment-responsive injectable hydrogel inducing modulation of macrophages and elimination of synovial fibroblasts for enhanced treatment of rheumatoid arthritis. *J Nanobiotechnology.* **2024,** *22,* 188.
55. Liu, X.; Zhang, Q.; Cao, Y.; Hussain, Z.; Xu, M.; Liu, Y.; Ullah, I.; Lu, Z.; Osaka, A.; Lin, J.; Pei, R. An injectable hydrogel composing anti-inflammatory and osteogenic therapy toward bone erosions microenvironment remodeling in rheumatoid arthritis. *Adv Healthc Mater.* **2024,** *13,* e2304668.
56. Wu, H.; Wang, K.; Wang, H.; Chen, F.; Huang, W.; Chen, Y.; Chen, J.; Tao, J.; Wen, X.; Xiong, S. Novel self-assembled tacrolimus nanoparticles cross-linking thermosensitive hydrogels for local rheumatoid arthritis therapy. *Colloids Surf B Biointerfaces.* **2017,** *149,* 97-104.
57. Wu, Y.; Wang, Z.; Ge, Y.; Zhu, Y.; Tian, T.; Wei, J.; Jin, Y.; Zhao, Y.; Jia, Q.; Wu, J.; Ge, L. Microenvironment responsive hydrogel exerting inhibition of cascade immune activation and elimination of synovial fibroblasts for rheumatoid arthritis therapy. *J Control Release.* **2024,** *370,* 747-762.
58. Geng, W.; Zhao, J.; Tao, B.; Yang, Y.; Duan, Q.; Gao, P.; He, T.; Liu, S.; Feng, Q.; Zhao, P.; Cai, K. Regulation of rheumatoid arthritis microenvironment via a self-healing injectable hydrogel for improved inflammation elimination and bone repair. *Bioact Mater.* **2024,** *36,* 287-300.
59. Wang, N.; Ma, J.; Song, W.; Zhao, C. An injectable hydrogel to disrupt neutrophil extracellular traps for treating rheumatoid arthritis. *Drug Deliv.* **2023,** *30,* 2173332.
60. Shah, D. K.; Ghosh, S.; More, N.; Choppadandi, M.; Sinha, M.; Srivalliputtur, S. B.; Velayutham, R.; Kapusetti, G. ECM-mimetic, NSAIDs loaded thermo-responsive, immunomodulatory hydrogel for rheumatoid arthritis treatment. *BMC Biotechnol.* **2024,** *24,* 26.
61. Yu, Z.; Xu, Q.; Dong, C.; Lee, S. S.; Gao, L.; Li, Y.; D'Ortenzio, M.; Wu, J. Self-assembling peptide nanofibrous hydrogel as a versatile drug delivery platform. *Curr Pharm Des.* **2015,** *21,* 4342-4354.
62. Yi, J.; Liu, Y.; Xie, H.; An, H.; Li, C.; Wang, X.; Chai, W. Hydrogels for the treatment of rheumatoid arthritis. *Front Bioeng Biotechnol.* **2022,** *10,* 1014543.
63. Wang, S.; Qiu, Y.; Qu, L.; Wang, Q.; Zhou, Q. Hydrogels for treatment of different degrees of osteoarthritis. *Front Bioeng Biotechnol.* **2022,** *10,* 858656.
64. Miao, K.; Zhou, Y.; He, X.; Xu, Y.; Zhang, X.; Zhao, H.; Zhou, X.; Gu, Q.; Yang, H.; Liu, X.; Huang, L.; Shi, Q. Microenvironment-responsive bilayer hydrogel microspheres with gelatin-shell for osteoarthritis treatment. *Int J Biol Macromol.* **2024,** *261,* 129862.
65. Liu, J.; Zhou, Z.; Hou, M.; Xia, X.; Liu, Y.; Zhao, Z.; Wu, Y.; Deng, Y.; Zhang, Y.; He, F.; Xu, Y.; Zhu, X. Capturing cerium ions via hydrogel microspheres promotes vascularization for bone regeneration. *Mater Today Bio.* **2024,** *25,* 100956.
66. Wei, L.; Pan, Q.; Teng, J.; Zhang, H.; Qin, N. Intra-articular administration of PLGA resveratrol sustained-release nanoparticles attenuates the development of rat osteoarthritis. *Mater Today Bio.* **2024,** *24,* 100884.
67. Rajesh, K.; Khatua, C.; Singh, P.; Roy, P.; Keshri, A. K.; Lahiri, D. Microsphere embedded hydroxyapatite coating on metallic implant for sustained drug release in orthopedic applications. *J Drug Deliv Sci Technol.* **2024,** *98,* 105840.
68. Xiao, P.; Han, X.; Huang, Y.; Yang, J.; Chen, L.; Cai, Z.; Hu, N.; Cui, W.; Huang, W. Reprogramming macrophages via immune cell mobilized hydrogel microspheres for osteoarthritis treatments. *Bioact Mater.* **2024,** *32,* 242-259.
69. Singh, R.; Jadhav, K.; Kamboj, R.; Malhotra, H.; Ray, E.; Jhilta, A.; Dhir, V.; Verma, R. K. Self-actuating inflammation responsive hydrogel microsphere formulation for controlled drug release in rheumatoid arthritis (RA): Animal trials and study in human fibroblast like synoviocytes (hFLS) of RA patients. *Biomater Adv.* **2024,** *160,* 213853.
70. Li, C.; Du, Y.; Lv, H.; Zhang, J.; Zhuang, P.; Yang, W.; Zhang, Y.; Wang, J.; Cui, W.; Chen, W. Injectable amphipathic artesunate prodrug-hydrogel microsphere as gene/drug nano-microplex for rheumatoid arthritis therapy. *Adv Funct Mater.* **2022,** *32,* 2206261.
71. Yao, Y.; Wei, G.; Ding, J.; Cui, W. Injectable hydrogel microspheres experimental research for the treatment of osteoarthritis. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi.* **2023,** *37,* 918-928.
72. Morici, L.; Gonzalez-Fernandez, P.; Jenni, S.; Porcello, A.; Allémann, E.; Jordan, O.; Rodríguez-Nogales, C. Nanocrystal-chitosan particles for intra-articular delivery of disease-modifying osteoarthritis drugs. *Int J Pharm.* **2024,** *651,* 123754.
73. Peng, X.; Dai, Z.; Zhang, Q.; Gao, S.; Li, N. Intelligent microsphere-gel structures: Pioneering multi-range temperature sensing technology. *Appl Mater Today.* **2024,** *38,* 102244.

74. An, X.; Zhou, F.; Li, G.; Wei, Y.; Huang, B.; Li, M.; Zhang, Q.; Xu, K.; Zhao, R. C.; Su, J. Cyaonoside A-loaded composite hydrogel microspheres to treat osteoarthritis by relieving chondrocyte inflammation. *J Mater Chem B.* **2024,** *12*, 4148-4161.
75. Butreddy, A.; Gaddam, R. P.; Kommineni, N.; Dudhipala, N.; Voshavar, C. PLGA/PLA-based long-acting injectable depot microspheres in clinical use: production and characterization overview for protein/peptide delivery. *Int J Mol Sci.* **2021,** *22*, 8884.
76. Liu, Y.; Cao, F.; Sun, B.; Bellanti, J. A.; Zheng, S. G. Magnetic nanoparticles: A new diagnostic and treatment platform for rheumatoid arthritis. *J Leukoc Biol.* **2021,** *109*, 415-424.
77. Wong, X. Y.; Sena-Torralba, A.; Álvarez-Diduk, R.; Muthoosamy, K.; Merkoçi, A. Nanomaterials for nanotheranostics: tuning their properties according to disease needs. *ACS Nano.* **2020,** *14*, 2585-2627.
78. Han, Y.; Huang, S. Nanomedicine is more than a supporting role in rheumatoid arthritis therapy. *J Control Release.* **2023,** *356*, 142-161.
79. Radu, A. F.; Bungau, S. G. Nanomedical approaches in the realm of rheumatoid arthritis. *Ageing Res Rev.* **2023,** *87*, 101927.
80. Geng, W.; Liu, X.; Tao, B.; He, Y.; Li, K.; Gao, P.; Feng, Q.; Zhao, P.; Luo, Z.; Cai, K. Nitric oxide scavenging and hydrogen sulfide production synergistically treat rheumatoid arthritis. *Adv Healthc Mater.* **2023,** *12*, e2202380.
81. Gandhi, S.; Shende, P. Anti-CD64 antibody-conjugated PLGA nanoparticles containing methotrexate and gold for theranostics application in rheumatoid arthritis. *AAPS PharmSciTech.* **2024,** *25*, 22.
82. Han, X.; Song, P.; Cai, R.; Zhu, H.; Yan, J.; Wang, X.; Wang, Y.; Kang, Y.; Ma, Y.; Wang, L.; Zhang, H. Construction of janus mesenchymal stem cell-hitchhiked melanin nanoparticles to modulate the Th17/Treg balance for rheumatoid arthritis therapy. *Nano Today.* **2024,** *57*, 102322.
83. Wu, Y. Z.; Chen, W. Y.; Zeng, Y.; Ji, Q. L.; Yang, Y.; Guo, X. L.; Wang, X. Inflammation-responsive mesoporous silica nanoparticles with synergistic anti-inflammatory and joint protection effects for rheumatoid arthritis treatment. *Pharm Res.* **2024,** *41*, 1493-1505.
84. Gan, J.; Huang, D.; Che, J.; Zhao, Y.; Sun, L. Biomimetic nanoparticles with cell-membrane camouflage for rheumatoid arthritis. *Matter.* **2024,** *7*, 794-825.
85. Hao, X.; Gai, W.; Zhang, Y.; Zhou, W.; Feng, Y. Biomimetic and inflammation-targeted nanoparticles for rheumatoid arthritis therapy via M1-macrophages apoptosis and polarization. *Mater Des.* **2024,** *239*, 112806.
86. Dhiman, N.; Sarvaiya, J.; Mohindroo, P. A drift on liposomes to proliposomes: recent advances and promising approaches. *J Liposome Res.* **2022,** *32*, 317-331.
87. Filipczak, N.; Pan, J.; Yalamarty, S. S. K.; Torchilin, V. P. Recent advancements in liposome technology. *Adv Drug Deliv Rev.* **2020,** *156*, 4-22.
88. Monteiro, N.; Martins, A.; Reis, R. L.; Neves, N. M. Liposomes in tissue engineering and regenerative medicine. *J R Soc Interface.* **2014,** *11*, 20140459.
89. Haider, M.; Abdin, S. M.; Kamal, L.; Orive, G. Nanostructured lipid carriers for delivery of chemotherapeutics: a review. *Pharmaceutics.* **2020,** *12*, 288.
90. Fu, X.; Song, Y.; Feng, X.; Liu, Z.; Gao, W.; Song, H.; Zhang, Q. Synergistic chemotherapy/PTT/oxygen enrichment by multifunctional liposomal polydopamine nanoparticles for rheumatoid arthritis treatment. *Asian J Pharm Sci.* **2024,** *19*, 100885.
91. Guo, R. B.; Kong, L.; Yu, Y.; Liu, Y.; Zhang, L.; Qu, X. W.; Li, S. T.; Yu, J. J.; Li, X. T.; Li, X. Y. Matrix metalloproteinase-sensitive size-shrinkable liposomes targeting activated macrophages for the treatment of rheumatoid arthritis. *Appl Mater Today.* **2024,** *38*, 102182.
92. Zhang, L.; Qin, Z.; Sun, H.; Chen, X.; Dong, J.; Shen, S.; Zheng, L.; Gu, N.; Jiang, Q. Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment. *Bioact Mater.* **2022,** *18*, 1-14.
93. Mondal, J.; Pillarisetti, S.; Junnuthula, V.; Saha, M.; Hwang, S. R.; Park, I. K.; Lee, Y. K. Hybrid exosomes, exosome-like nanovesicles and engineered exosomes for therapeutic applications. *J Control Release.* **2023,** *353*, 1127-1149.
94. Jiang, X.; Shi, L.; Feng, H.; Zhang, Y.; Dong, J.; Shen, Z. Engineered exosomes loaded with triptolide: an innovative approach to enhance therapeutic efficacy in rheumatoid arthritis. *Int Immunopharmacol.* **2024,** *129*, 111677.
95. Liu, H.; Li, R.; Liu, T.; Yang, L.; Yin, G.; Xie, Q. Immunomodulatory effects of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles in rheumatoid arthritis. *Front Immunol.* **2020,** *11*, 1912.
96. Wang, S.; Lei, B.; Zhang, E.; Gong, P.; Gu, J.; He, L.; Han, L.; Yuan, Z. Targeted therapy for inflammatory diseases with mesenchymal stem cells and their derived exosomes: from basic to clinics. *Int J Nanomedicine.* **2022,** *17*, 1757-1781.
97. Su, Y.; Liu, Y.; Ma, C.; Guan, C.; Ma, X.; Meng, S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. *J Orthop Surg Res.* **2021,** *16*, 116.
98. Zhang, S.; Duan, Z.; Liu, F.; Wu, Q.; Sun, X.; Ma, H. The impact of exosomes derived from distinct sources on rheumatoid arthritis. *Front Immunol.* **2023,** *14*, 1240747.
99. Xiao, S.; Tang, Y.; Lv, Z.; Lin, Y.; Chen, L. Nanomedicine - advantages for their use in rheumatoid arthritis theranostics. *J Control Release.* **2019,** *316*, 302-316.
100. Abdel-Hakem, N. E.; Talaat, R. M.; Samaka, R. M.; Bassyouniy, I. H.; El-Shahat, M.; Alkawareek, M. Y.; Alkilany, A. M. Therapeutic outcomes and biodistribution of gold nanoparticles in collagen-induced arthritis animal model. *J Drug Deliv Sci Technol.* **2022,** *67*, 102944.
101. Song, Y.; Su, Y.; Hussain, S. A.; Tang, C. Resveratrol and prednisolone loaded into human serum albumin nanoparticles for the alleviation of rheumatoid arthritis symptoms: an in vitro and in vivo study. *Mater Sci Poland.* **2024,** *42*, 16-25.
102. Ma, L.; Jiang, X.; Gao, J. Revolutionizing rheumatoid arthritis therapy: harnessing cytomembrane biomimetic nanoparticles for novel treatment strategies. *Drug Deliv Transl Res.* **2025,** *15*, 66-83.

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