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# SMART NANOCARRIERS FOR TARGETED TREATMENT OF RHEUMATOID ARTHRITIS: CURRENT PROGRESS AND CLINICAL TRANSLATION

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## ABSTRACT

Rheumatoid arthritis is a chronic, systemic autoimmune disease in which sustained synovial inflammation drives progressive cartilage and bone destruction. The conventional pharmacological armamentarium, from methotrexate and glucocorticoids to biological and targeted synthetic disease-modifying agents, controls the disease in many patients but does so at the cost of systemic exposure, dose-limiting toxicity, and incomplete penetration of drug into the inflamed joint. Nanocarriers reframe this problem as one of delivery rather than of pharmacology. By exploiting the leaky, angiogenic vasculature of the inflamed synovium and the surface receptors of activated synovial macrophages, engineered nanoparticles concentrate a payload where the disease is active while sparing healthy tissue. This review synthesises the current evidence on smart nanocarriers for rheumatoid arthritis, defined as systems that combine joint-selective targeting with a microenvironment-triggered release that answers to the acidic, oxidative, and enzymatically active conditions of the arthritic joint. The major platforms are examined in turn: liposomes, polymeric nanoparticles and micelles, dendrimers, inorganic and hybrid particles, and the cell-membrane biomimetic carriers that now define the frontier of the field. The passive and active mechanisms of joint targeting are set out, and the stimuli-responsive chemistries that convert a carrier into a smart one are compared. Across preclinical models the direction of the evidence is consistent: targeted and responsive nanocarriers lower the effective dose, raise joint drug concentration, and reduce systemic toxicity relative to free drug. Yet the translational record remains thin, with few candidates advancing to controlled trials. The barriers to translation, from manufacturing reproducibility to the absence of validated imaging biomarkers, are analysed, and a set of concrete priorities is proposed to move the field from elegant preclinical demonstration to a licensed nanomedicine for rheumatoid arthritis.

**Keywords:** rheumatoid arthritis; nanocarrier; targeted drug delivery; stimuli-responsive nanoparticle; liposome; methotrexate; macrophage targeting; clinical translation.

## 1. Introduction

Rheumatoid arthritis affects between roughly 0.5% and 1% of the adult population worldwide and remains one of the most common causes of preventable disability in working-age adults [1]. The disease is characterised by a self-perpetuating inflammation of the synovial membrane, in which activated macrophages, fibroblast-like synoviocytes, T and B lymphocytes, and a dense cytokine network drive the formation of an invasive tissue called pannus that erodes cartilage and subchondral bone [2]. The therapeutic goal has shifted over two decades from symptom relief toward sustained clinical remission, a goal made realistic by methotrexate as the anchor drug and by the biological and targeted synthetic agents that block tumour necrosis factor, interleukin-6, and the Janus kinases [3,4]. These advances are real, but they have not dissolved the central pharmacological tension of the disease.

That tension is one of exposure. Rheumatoid arthritis is systemic, yet its damage is focal, concentrated in the joints. A drug given orally or by injection distributes throughout the body to reach a target that occupies a small fraction of that volume, so the dose required to achieve a therapeutic synovial concentration also exposes the liver, marrow, gut, and other tissues to the same agent. Methotrexate carries hepatotoxicity and myelosuppression, long-term glucocorticoids bring metabolic and skeletal harm, and the biologics raise the risk of serious infection. Each of these liabilities is, in part, a delivery problem rather than an intrinsic property of the molecule. A drug that could be steered to the inflamed joint and released only there would widen the therapeutic window of agents the field already trusts.

Nanocarriers offer a route to exactly this kind of steering. A nanoparticle in the size range of tens to low hundreds of nanometres behaves in the circulation quite unlike a small molecule: it circulates longer, extravasates preferentially where the vasculature is leaky, and can be decorated with ligands that bind receptors enriched on the cells that sustain the disease [5]. The concept was proven first in oncology, where the enhanced permeability and retention effect and the approval of liposomal and other nanomedicines established that particle-based delivery could change a drug's biodistribution in patients [6,7]. Rheumatoid arthritis presents an analogous, and in several respects more tractable, opportunity, because the inflamed synovium shares the leaky, angiogenic vasculature of a tumour without the same barriers of high interstitial pressure and dense stroma.

This review takes as its subject the smart nanocarrier, by which is meant a system that does two things at once. It targets the arthritic joint, passively through the biology of inflammation or actively through a surface ligand, and it releases its payload in response to a signal specific to the diseased microenvironment, whether that signal is a low pH, a burst of reactive oxygen species, or the activity of a matrix metalloproteinase. The argument advanced here is that the combination of targeting and triggered release, rather than either

alone, is what distinguishes the current generation of carriers from the passively circulating liposomes of two decades ago, and that this combination is now mature in the laboratory while remaining almost untested in the clinic. The sections that follow set out the disease rationale, the mechanisms of joint targeting, the major carrier platforms and the chemistries that make them responsive, and finally the state of clinical translation and the specific work needed to close the gap between the two.

## 2. The arthritic joint as a delivery target

A nanocarrier strategy is only as good as its reading of the target tissue, so the relevant features of rheumatoid pathophysiology deserve to be stated precisely. In the healthy joint the synovial lining is a thin layer, one or two cells deep, composed of macrophage-like and fibroblast-like synoviocytes. In rheumatoid arthritis this lining thickens into a hyperplastic, immune-cell-rich mass. Fibroblast-like synoviocytes lose their normal contact inhibition and adopt an aggressive, tumour-like phenotype, resisting apoptosis and secreting matrix metalloproteinases that degrade the surrounding cartilage [2,8]. Synovial macrophages, polarised toward the pro-inflammatory M1 state, pour out tumour necrosis factor, interleukin-1, and interleukin-6, and these cytokines feed forward through the nuclear factor kappa B and Janus kinase-signal transducer and activator of transcription pathways to sustain the inflammatory loop [4].

Three consequences of this biology matter for delivery, and they are summarised in Figure 1. The first is vascular. The expanding pannus is metabolically demanding and drives angiogenesis, and the new vessels are structurally immature, with wide interendothelial gaps and a discontinuous basement membrane. This leakiness is the anatomical basis for passive nanoparticle accumulation. The second is cellular. Activated synovial macrophages overexpress a set of surface markers, notably folate receptor beta, the hyaluronan receptor CD44, and scavenger and mannose receptors, that are largely absent or quiescent on their resting counterparts elsewhere in the body [5]. These markers are the handles that active targeting grasps. The third is chemical. The inflamed synovium is acidotic, with a reported extracellular pH that can fall toward 6.6, it is rich in reactive oxygen species generated by infiltrating phagocytes, and it carries high local concentrations of matrix metalloproteinases [9]. Each of these deviations from healthy tissue is a signal that a responsive carrier can be engineered to detect.

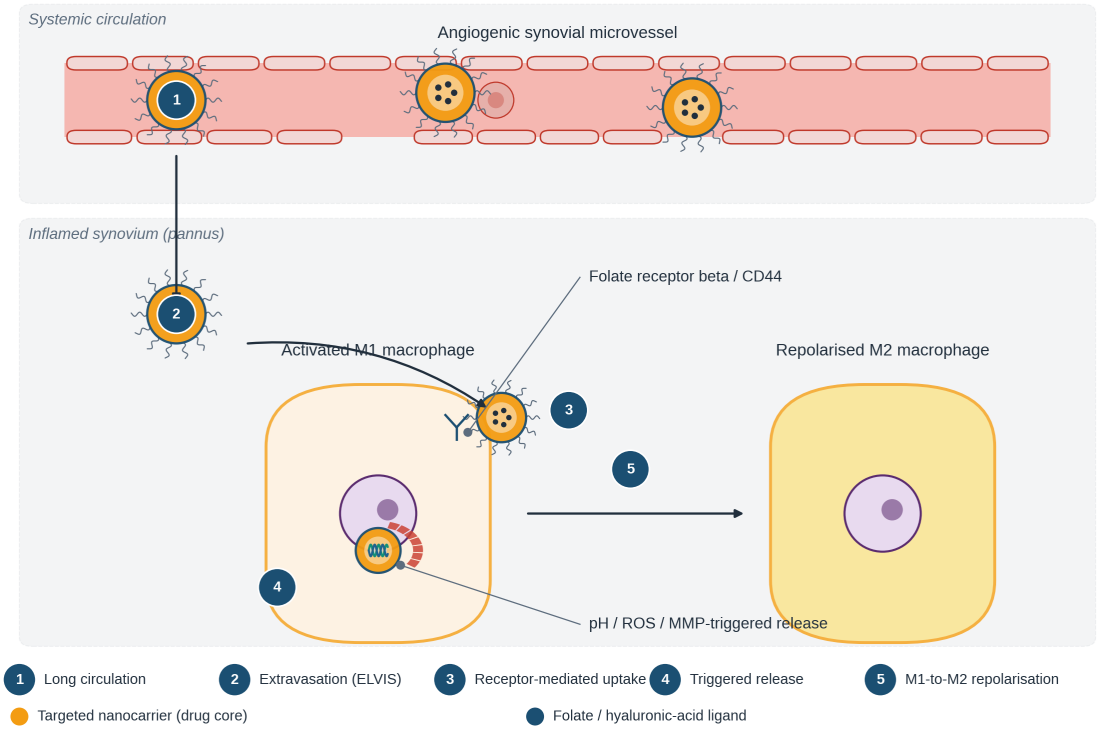


***Figure 1. Mechanisms by which a smart nanocarrier targets the rheumatoid joint. Long-circulating, ligand-decorated nanocarriers (1) persist in the systemic circulation, then (2) extravasate through the wide interendothelial gaps of the angiogenic synovial microvessel and are retained in the inflamed synovium, the passive process termed ELVIS (extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration). Surface folate or hyaluronic-acid ligands engage folate receptor beta or CD44 on activated M1 macrophages, driving (3) receptor-mediated uptake. Within the acidic, oxidative, protease-rich cell the carrier undergoes (4) release of its drug triggered by low pH, reactive oxygen species (ROS), or matrix metalloproteinases (MMPs), which (5) can repolarise the macrophage from the pro-inflammatory M1 toward the reparative M2 phenotype. Schematic, not drawn to scale.***

Two qualifications temper this otherwise favourable picture, and both bear directly on delivery. The first is heterogeneity. Rheumatoid arthritis is not a single uniform lesion but a disease that differs between patients in its dominant cellular infiltrate and its degree of vascular proliferation, and that fluctuates within a patient between flare and remission [8]. The leaky vasculature on which passive targeting depends is therefore not a fixed property but a variable one, strongest where inflammation is most active, which means a delivery strategy tuned to florid synovitis may underperform in the smouldering disease that much long-term treatment addresses. The second qualification is that the same receptors and chemical cues that mark the joint are not entirely absent elsewhere. Folate receptor beta appears on activated macrophages at other sites of inflammation, and reactive oxygen species and low pH accompany inflammation generally, so no single signal is perfectly specific to the arthritic joint. This is the reason, developed in Section 5, that the most convincing carriers combine two or more cues rather than relying on any one.

Taken together these features make the rheumatoid joint an unusually favourable target

for smart delivery. It advertises its location through a leaky vasculature, it labels its key effector cells with distinctive receptors, and it maintains a chemical environment that differs sharply from that of the tissues a drug must be protected from. The design problem for a nanocarrier is therefore well defined: reach the joint, bind the right cell, and release the drug only under conditions found nowhere else, and do so robustly across the variable states the disease presents. The remainder of this review examines how far each of these requirements has been met.

## 3. Mechanisms of joint targeting

### *3.1 Passive accumulation and the ELVIS effect*

The first way a nanocarrier reaches the inflamed joint requires no ligand at all. It relies on the same physics that underlies the enhanced permeability and retention effect in tumours, first articulated for macromolecular therapeutics in the 1980s and 1990s [6,10]. In the arthritic context this passive mechanism has been given its own name, ELVIS, for extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration [5]. The two halves of the acronym describe a two-step capture. Circulating nanoparticles first escape the bloodstream through the enlarged gaps between endothelial cells of the angiogenic synovial vasculature, and enter the interstitium of the inflamed tissue. They are then retained there, taken up and sequestered by the abundant activated phagocytes of the pannus, because the inflamed joint lacks the efficient lymphatic clearance that would otherwise flush the extravasated material away.

The practical consequence is that a long-circulating particle of appropriate size will accumulate in the arthritic joint simply by virtue of the disease biology. Size is the governing variable. Particles that are too small are cleared renally or diffuse back out of the tissue, while particles that are too large are removed by the mononuclear phagocyte system before they can reach the joint. A careful study of nanoparticle biodistribution in chronic inflammation found that although the smallest particles achieved the highest absolute accumulation, particles in the intermediate range of roughly 100 to 200 nanometres gave the most favourable ratio of inflamed to healthy tissue, the selectivity that actually matters for a targeted therapy [11]. Surface chemistry is the second lever. Grafting polyethylene glycol onto the particle surface suppresses opsonisation and prolongs circulation, which raises the fraction of the injected dose that survives long enough to find the leaky vasculature [9].

Passive targeting is powerful but blunt. It concentrates a carrier in inflamed tissue in general rather than in a chosen cell, and its magnitude varies with the intensity of inflammation, which fluctuates over the course of the disease. For these reasons the field has increasingly layered active targeting on top of the passive baseline, using ELVIS to deliver the particle to the neighbourhood and a surface ligand to direct it to the right door.

### *3.2 Active targeting through surface ligands*

Active targeting exploits the receptors that activated synovial cells display in excess. The most widely used handle is folate receptor beta, which is strongly upregulated on activated but not resting macrophages, which makes it close to an ideal marker for the effector cells of rheumatoid inflammation. Folate-decorated carriers of almost every class have been shown to bind these cells selectively and to enter them by receptor-mediated endocytosis. An early and influential demonstration used a folate-targeted dendrimer nanoparticle carrying methotrexate, which reduced arthritis severity in a rat model as effectively as a substantially larger dose of the free drug. This established that receptor targeting could translate into a genuine dose advantage rather than merely a change in biodistribution [12]. The same principle has since been applied to liposomes, polymeric micelles, and metal-organic frameworks, discussed in the platform sections below.

The hyaluronan receptor CD44 offers a second route, engaged by coating particles with hyaluronic acid, a natural ligand that is both the targeting moiety and a biocompatible, biodegradable surface. Because CD44 is overexpressed on activated macrophages and fibroblast-like synoviocytes alike, hyaluronic-acid-based carriers can address both of the principal effector populations of the pannus, and such carriers have been engineered to release their payload selectively in the inflamed microenvironment while homing to M1 macrophages [5,13]. Beyond these two dominant strategies, carriers have been directed with peptides recognising inflamed endothelium, with antibodies and antibody fragments against cytokines or cell-surface markers, and with small molecules binding scavenger and mannose receptors. The general lesson from this body of work is that the arthritic joint presents several usable molecular addresses, that folate receptor beta and CD44 are the best validated, and that active targeting reliably improves cellular uptake and joint retention over passive accumulation alone, though it adds manufacturing complexity that bears directly on translation.

## 4. Smart nanocarrier platforms

The distinction between a carrier and a smart carrier lies in what happens after the particle arrives. This section surveys the principal platforms, noting for each how targeting and, where present, triggered release have been engineered. Table 1 summarises representative studies across the platforms, and Table 2 sets the platforms against one another by their principal strengths and limitations.

### *4.1 Liposomes*

Liposomes are the most clinically mature nanocarrier and the natural starting point. These bilayer vesicles encapsulate hydrophilic drugs in their aqueous core and lipophilic drugs in the membrane, they are biocompatible and biodegradable, and their surface accepts both polyethylene glycol for stealth and ligands for targeting [9]. The foundational proof of concept in rheumatoid arthritis came from long-circulating liposomal glucocorticoids. A single intravenous

dose of polyethylene-glycol liposomal prednisolone phosphate produced complete and durable remission of experimental arthritis in rats, an effect far exceeding that of the same dose of free glucocorticoid and attributable to the sustained, joint-concentrated exposure the liposome provided [14]. This result reframed the glucocorticoid, a drug limited in chronic use by systemic toxicity, as a candidate for safe intermittent high-dose therapy when packaged appropriately.

Subsequent work has made liposomes both targeted and responsive. A folate-decorated, reactive-oxygen-species-responsive liposome carrying methotrexate combined active macrophage targeting with triggered release: encapsulated catalase decomposed the elevated hydrogen peroxide of the inflamed cell into oxygen, destabilising the vesicle and releasing methotrexate specifically where the oxidative signal was strongest, which raised methotrexate accumulation in inflamed joints while limiting organ exposure [15]. Folate-conjugated double liposomes co-loading prednisolone and methotrexate achieved joint targeting superior to unconjugated or single liposomes and delivered two mechanistically complementary drugs from one particle [16]. More recent designs have moved toward immunological reprogramming, using a folate liposome to co-deliver methotrexate with small interfering RNA against the nuclear factor kappa B subunit RELA, which drove synovial macrophages from the pro-inflammatory M1 state toward the reparative M2 phenotype and produced synergistic anti-arthritic effects in cells and in arthritic rats [17]. The trajectory of liposome research thus runs from passive depot, to targeted depot, to a multifunctional particle that both delivers a drug and reshapes the immune microenvironment.

### *4.2 Polymeric nanoparticles and micelles*

Polymeric carriers trade the liposome's clinical familiarity for greater control over degradation rate and release kinetics. Nanoparticles of poly(lactic-co-glycolic acid) and related biodegradable polymers can be tuned to release their payload over days to weeks, and amphiphilic block copolymers self-assemble into micelles that solubilise poorly water-soluble drugs in their hydrophobic core. As with liposomes, the surface can carry folate or hyaluronic acid for active targeting [5]. The appeal of the polymeric platform is that the same chemistry that forms the particle can be made stimuli-responsive, by incorporating acid-labile or oxidation-sensitive linkages into the polymer backbone so that the carrier itself dissolves in the diseased microenvironment [18].

A representative example of the platform's versatility is a hybrid micelle built from a methotrexate-conjugated polymer that also carried a microRNA. The methotrexate was chemically bound to the polymer rather than merely entrapped, giving controlled release, while the co-loaded microRNA-124 addressed bone protection, so a single folate-targeted micelle attacked both the inflammatory and the erosive arms of the disease and induced remission more completely than either agent alone [19]. Polymeric systems have proven

especially suited to co-delivery of this kind, where a small-molecule drug and a nucleic acid with different physicochemical demands must travel together, and to the incorporation of the responsive linkages examined in Section 5.

### *4.3 Dendrimers*

Dendrimers are precisely branched, monodisperse macromolecules whose numerous surface groups can be functionalised at defined stoichiometry, which gives an unusually exact control over the number of drug and targeting molecules per carrier. This precision made them the vehicle for one of the earliest convincing demonstrations of active targeting in arthritis, the folate-conjugated methotrexate dendrimer already noted, which matched the efficacy of a much larger free-drug dose in inflammatory arthritis [12]. The strength of the dendrimer, its defined surface chemistry, is also the origin of its principal limitation, since the cationic surface groups of some dendrimer families carry a risk of concentration-dependent toxicity that must be mitigated by careful surface capping. Dendrimers have consequently remained more a tool for mechanistic proof than a mainstream translational platform, but they retain value where exact control of ligand density is the scientific question.

### *4.4 Inorganic and hybrid nanoparticles*

Inorganic and hybrid particles add functions that organic carriers cannot easily provide, in particular intrinsic catalytic or imaging activity. Gold nanoparticles are biocompatible, readily conjugated, and carry a modest intrinsic anti-inflammatory activity of their own. Methotrexate-conjugated gold nanoparticles reduced arthritic and vascular inflammatory markers in adjuvant-induced arthritis more effectively than free methotrexate, with the added benefit of improving the rheumatoid vascular dysfunction that contributes to the cardiovascular burden of the disease [20]. Metal-based particles can also act on the microenvironment directly. A manganese dioxide carrier delivering methotrexate did more than release its cargo: the manganese dioxide scavenged reactive oxygen species and catalysed the decomposition of hydrogen peroxide into oxygen, relieving the local oxidative stress and hypoxia while responding to the acidic pH of the joint to release the drug, so that the carrier and its payload acted in concert on the inflamed tissue [21]. Metal-organic frameworks, hybrid crystalline materials of metal nodes and organic linkers, offer very high drug-loading capacity and pH-responsive disassembly, and have been used as a methotrexate reservoir within biomimetic particles as described below [22]. Solid lipid nanoparticles occupy a middle ground between the liposome and the polymeric particle, which combines a solid lipid matrix with good tolerability; a rhein and methotrexate co-decorated solid lipid nanoparticle slowed adjuvant arthritis by pushing synovial cells into endoplasmic-reticulum-stress apoptosis [23].

### *4.5 Cell-membrane biomimetic nanocarriers*

The most active frontier of the field wraps a synthetic core in a membrane harvested from a living cell, so that the particle inherits the surface

identity of that cell. This biomimetic camouflage confers two advantages at once: the membrane's own proteins evade immune clearance and, because leukocytes home naturally to inflammation, they direct the particle to the joint by a biological route that no synthetic ligand fully reproduces [24]. Macrophage-membrane-coated particles have been used to reprogramme synovial macrophages toward the anti-inflammatory M2 phenotype, which lowered joint inflammation and cartilage destruction; the coating both targeted the tissue and acted as a decoy that soaked up inflammatory cytokines [25]. Neutrophil-membrane-coated carriers exploit the neutrophil's own inflammation-homing machinery; a peptide-anchored neutrophil-membrane nanodrug carrying celastrol combined membrane-mediated joint targeting with a peptide directing it to scavenger-receptor-bearing macrophages, achieving high joint accumulation, M1-to-M2 repolarisation, and a marked reduction in the hepatotoxicity that limits free celastrol [26].

Vesicle-derived coatings extend the same logic. Exosome-based biomimetic particles, built from macrophage-derived exosomes surface-modified with folate, delivered dexamethasone to folate-receptor-bearing macrophages in inflamed joints with superior cytokine suppression and cartilage preservation compared with conventional formulations [27]. Microvesicle-camouflaged particles have been used to cloak a methotrexate-loaded metal-organic framework, giving the high loading of the framework, the pH-responsive release of its structure, and the targeting and stealth of the natural membrane in a single construct [22]. The biomimetic approach, and the broader class of natural biological carriers, is attractive precisely because it substitutes evolved biological targeting for engineered chemistry, which improves biocompatibility and specificity; its cost is a manufacturing process built on harvested cellular material, a point that returns forcefully in the discussion of translation [24,28].

***Table 1. Representative smart nanocarrier studies for rheumatoid arthritis, grouped by platform. AIA, adjuvant-induced arthritis; CIA, collagen-induced arthritis; MTX, methotrexate; ROS, reactive oxygen species; siRNA, small interfering RNA; SR-B1, scavenger receptor class B type 1.***

| Carrier platform | Payload | Targeting / trigger | Model | Principal finding | Ref |
|---|---|---|---|---|---|
| Long-circulating liposome | Prednisolone phosphate | Passive (PEG, ELVIS) | Rat experimental arthritis | Single dose produced complete, durable remission exceeding free drug | [14] |
| ROS-responsive folate liposome | Methotrexate | Folate receptor beta; H2O2 or catalase trigger | CIA | Raised joint MTX accumulation while limiting organ exposure | [15] |
| Folate double liposome | Prednisolone and MTX | Folate receptor beta | Arthritic rodent | Joint targeting superior to single or unconjugated liposomes | [16] |

| | | | | | |
|---|---|---|---|---|---|
| Folate liposome | MTX and RELA siRNA | Folate receptor beta | RAW264.7 cells; arthritic rats | M1-to-M2 repolarisation with synergistic anti-arthritic effect | [17] |
| Hybrid polymeric micelle | MTX (conjugated) and miR-124 | Folate receptor | Arthritic rodent | Anti-inflammatory and bone-protective; remission beyond either agent alone | [19] |
| PAMAM dendrimer | Methotrexate | Folate | Rat inflammatory arthritis | Efficacy matching a much larger free-MTX dose | [12] |
| Gold nanoparticle | MTX (conjugated) | Conjugate; passive | AIA | Reduced arthritic and vascular inflammation versus free MTX | [20] |
| pH-responsive manganese dioxide particle | Methotrexate | pH trigger; ROS scavenging and O2 generation | CIA mice | Greatest fall in joint scores and cytokines with cartilage protection | [21] |
| Microvesicle-cloaked metal-organic framework | Methotrexate | Folate; pH-responsive; membrane stealth | CIA rats | Long circulation, best joint targeting, reduced hepatotoxicity | [22] |
| Solid lipid nanoparticle | Rhein and MTX | Passive | AIA | Slowed arthritis via endoplasmic-reticulum-stress apoptosis | [23] |
| Macrophage-membrane biomimetic particle | Anti-inflammatory agent | Membrane homing; cytokine decoy | Arthritic rodent | M2 repolarisation with reduced inflammation and cartilage damage | [25] |
| Neutrophil-membrane biomimetic particle | Celastrol | Membrane homing plus SR-B1 peptide | CIA mice | High joint accumulation, M1-to-M2 shift, reduced hepatotoxicity | [26] |
| Macrophage-exosome biomimetic particle | Dexamethasone | Folate | Inflamed joints | Superior cytokine suppression and cartilage preservation | [27] |
| Transformable self-assembly nanoplatform | Anti-inflammatory agent | Microenvironment-driven assembly | RA model | Formed a vascular barrier and remodelled the joint microenvironment | [29] |

*Table 2. Comparison of the principal smart nanocarrier platforms by their main strengths and limitations for rheumatoid arthritis delivery [5,9,24].*

| Platform | Principal strengths | Principal limitations |
|---|---|---|
| Liposomes | Clinically mature and biocompatible; versatile drug loading; readily PEGylated and ligand-decorated | Physical and chemical stability; potential drug leakage; cost of targeted, controlled manufacture |
| Polymeric nanoparticles and micelles | Tunable release kinetics; straightforward stimuli-responsive chemistry; suited to co-delivery | Possible polymer or degradant toxicity; burst release; scale-up reproducibility |
| Dendrimers | Exact drug and ligand stoichiometry; monodisperse | Cationic-surface toxicity; cost; limited payload capacity |
| Inorganic and hybrid (gold, manganese dioxide, framework) | Intrinsic catalytic or imaging function; high loading; theranostic potential | Long-term biopersistence and clearance; regulatory novelty |
| Solid lipid nanoparticles | Good tolerability with physiological lipids; scalable | Limited drug loading; drug expulsion on storage |
| Cell-membrane biomimetic | Innate inflammation homing; immune evasion; high specificity | Very difficult to manufacture reproducibly at scale; source-material variability |

## 5. Making the carrier smart: stimuli-responsive release

Targeting delivers a particle to the joint, but a carrier that leaks its drug throughout the circulation before it arrives, or that holds the drug locked once it has arrived, wastes the advantage that targeting won. The defining feature of a smart nanocarrier is therefore a release that is switched by the diseased microenvironment itself. The three chemical abnormalities of the inflamed synovium introduced in Section 2, low pH, high reactive oxygen species, and elevated matrix metalloproteinase activity, each provide such a switch, and the most sophisticated carriers now respond to more than one.

pH-responsive designs are the most developed, because the drop in extracellular pH toward 6.6 in the inflamed joint, and the still lower pH of the endosome after cellular uptake, is a reliable and well-characterised signal [18]. Carriers built with acid-labile bonds, or with polymers that swell or dissolve as they are protonated, remain intact in the neutral bloodstream and disassemble on reaching the acidic target. The manganese dioxide methotrexate carrier discussed above is a clear example, and it couples pH-triggered drug release to the simultaneous correction of oxidative stress [21]. Reactive-oxygen-species-responsive systems exploit the oxidative burst of activated phagocytes, incorporating thioether, selenium, or peroxalate groups that are cleaved by hydrogen peroxide, or, as in the catalase-loaded folate liposome, they use the oxidative signal to generate a gas that physically disrupts the carrier [15]. The appeal of an oxidation-triggered system is that it responds to a hallmark of active inflammation, so drug release tracks disease activity. Matrix-metalloproteinase-responsive carriers use a peptide linker that these enzymes cleave, so that release is gated by the very proteases that drive cartilage destruction, which ties the therapeutic action to the pathological one.

The strongest current designs combine triggers, on the reasoning that no single microenvironmental signal is perfectly specific to the joint. Dual pH and reactive-oxygen-species responsive nanoparticles release their payload only where both conditions are met, which sharpens the discrimination between diseased and healthy tissue. The field is now moving beyond triggered release toward carriers that transform in situ: a microenvironment-driven transformable nanoplatform has been shown to self-assemble on arrival into a structure that both forms a physical barrier over the inflamed synovial vasculature and delivers an anti-inflammatory payload, and it achieves a spatiotemporal remodelling of the joint microenvironment that a simple release event cannot [29]. This progression, from a carrier that opens in response to the environment, to one that reshapes the environment, marks the current leading edge of what smart means in this context. The most advanced carriers also act therapeutically through their own structure rather than serving as inert packaging, as when a manganese or metal-based framework scavenges reactive oxygen species while releasing its drug [21,22], a convergence of carrier and drug that blurs the old distinction between the two.

## 6. Clinical translation: progress and barriers

The preclinical case for smart nanocarriers in rheumatoid arthritis is, on the evidence assembled above, consistent and strong. Across platforms and across targeting strategies the same pattern recurs: a targeted, responsive carrier concentrates drug in the joint, lowers the dose needed for efficacy, and reduces the systemic toxicity that limits the free agent. The direction of the evidence is not in serious doubt. What is missing is the confirmation of that promise in patients, and here the record is sparse.

The reference point is oncology, where nanomedicine has a licensed presence. Liposomal doxorubicin demonstrated that a nanoparticle could change a drug's biodistribution and toxicity profile in patients and win approval, and it remains the archetype for what the field aspires to [7]. Yet the broader clinical record of nanomedicine, catalogued in successive surveys of approved and trialled products, shows how few candidates cross from preclinical success to the clinic, and how many of those that do offer a better safety profile rather than a decisive efficacy gain [30]. Rheumatoid arthritis has followed this cautious pattern. Liposomal glucocorticoids, the most translationally advanced concept, reached early-phase clinical evaluation on the strength of the complete remission seen in animal models [9,14], but no smart nanocarrier has yet secured approval for the disease, and the pipeline of controlled trials remains thin relative to the volume of preclinical publication [31].

Several barriers explain this gap, and they are worth naming precisely because generic calls for more research do not address them. The first is manufacturing. The multifunctional carriers that perform best in the laboratory, particularly the cell-membrane biomimetic systems built from harvested cellular material, are the hardest to

produce reproducibly and at scale under the quality standards a medicine requires [24,32]. A particle that must carry a defined drug load, a defined ligand density, and a natural membrane of consistent composition presents a formidable chemistry, manufacturing, and controls problem, and complexity that is a virtue in a proof of concept becomes a liability in a product. The second barrier is the predictive weakness of the animal models. Collagen-induced and adjuvant-induced arthritis in rodents reproduce features of the human disease but not its chronicity or heterogeneity, and the leaky vasculature that drives passive targeting varies between models, between joints, and over the course of disease in ways that make the human ELVIS effect uncertain in magnitude [5,11]. The third is the absence of a companion diagnostic. If passive and active targeting depend on the state of a patient's synovial vasculature and receptor expression, then selecting the patients most likely to benefit, and confirming that a carrier has reached its target, will require validated imaging or biomarker tools that the field has not yet built. A fourth barrier is regulatory and economic: nanomedicines face a demanding and still-evolving approval pathway, and the cost of manufacturing a complex targeted carrier must be justified against effective and increasingly inexpensive existing therapies, including biosimilars.

The liposomal glucocorticoid experience is instructive because it is the one concept that travelled furthest, and its trajectory maps the gap in miniature. The complete remission achieved in animal models with a single dose of long-circulating liposomal prednisolone phosphate was striking enough to justify clinical evaluation, and formulations of this type advanced into early-phase human study [9,14]. That they have not since become a standard therapy, despite an unambiguous preclinical signal and a drug already in wide clinical use, illustrates that a strong animal result is a necessary but far from sufficient condition for a nanomedicine. The reasons are the ordinary ones of drug development, the need for a controlled demonstration of benefit over the free drug in patients, a manufacturing process that meets regulatory standards at commercial scale, and a commercial case that holds against inexpensive incumbents, and they apply with greater force to the more elaborate targeted and responsive carriers that dominate the current literature. A realistic reading of the field is that its most complex constructs are furthest from the clinic precisely because their sophistication multiplies each of these hurdles.

None of these barriers is insurmountable, and none negates the preclinical case. But they explain why a field so productive in the laboratory has been so quiet in the clinic, and they define what the next phase of work must deliver.

## 7. Challenges and future directions

The path from the current state of the art to a licensed nanomedicine for rheumatoid arthritis runs through a small number of specific problems, and progress will come from

confronting them directly rather than from further variations on the carriers already demonstrated.

The first priority is to align carrier design with manufacturability from the outset. The most translationally credible near-term candidates are likely to be the simpler ones, a well-characterised targeted liposome or polymeric particle carrying an established drug, rather than the most elaborate biomimetic constructs, because these can be made reproducibly and evaluated against a clear regulatory precedent. The biomimetic systems that dominate the recent literature will need parallel investment in scalable, standardised production of their cellular components before their preclinical superiority can be tested in patients [24]. Designing for the factory, not only for the animal model, is the single change most likely to move the field.

The second priority is to develop the imaging and biomarker tools that would make targeted delivery a stratified therapy. Because the benefit of a nanocarrier depends on the very disease features that vary between patients, the joint's vascular leakiness and its receptor expression, a theranostic approach that images carrier accumulation before committing a patient to treatment would convert an uncertain average benefit into a predictable individual one. This is both a scientific opportunity and, given the regulatory weight now placed on companion diagnostics, a translational necessity.

The third priority is to exploit the shift, visible across the recent literature, from carriers that deliver a conventional drug to carriers that reprogramme the disease. The most striking recent results come from systems that repolarise synovial macrophages from the M1 to the M2 phenotype, that silence inflammatory drivers with nucleic acids, or that transform in situ to remodel the joint microenvironment [17,25,29]. Delivery of small interfering RNA and other nucleic acids, in particular, is a natural fit for nanocarriers, since these molecules cannot reach their intracellular targets without protection, and the emergence of nucleic-acid nanomedicine as a validated modality in other diseases gives this direction a credibility it lacked a decade ago [33]. The convergence of a delivery technology with an immunomodulatory payload, rather than the packaging of an old drug in a new particle, is where the largest gains are likely to lie.

Finally, the field would benefit from standardising how carriers are compared. The preclinical literature reports joint accumulation, dose reduction, and toxicity sparing in incompatible units across incompatible models, which makes it difficult to judge one platform against another or to build the cumulative evidence base that a translational decision requires. Common models, common endpoints, and transparent reporting of both the successes and the failures would let the field learn faster from its own large output.

## 8. Conclusion

Smart nanocarriers address a problem that the pharmacology of rheumatoid arthritis has not solved: how to bring an effective drug to the inflamed joint without exposing the whole body

to its harm. The biology of the disease is unusually cooperative, offering a leaky vasculature for passive capture, distinctive receptors for active targeting, and a chemically abnormal microenvironment for triggered release, and the laboratory has exploited all three with growing sophistication, moving from passive liposomal depots to targeted, responsive, and now microenvironment-transforming carriers that both deliver a drug and reshape the immune landscape of the joint. The weight of preclinical evidence consistently supports lower effective doses, higher joint drug concentrations, and reduced systemic toxicity relative to free drug. The decisive gap is translational, not conceptual: manufacturing complexity, imperfect animal models, and the absence of companion diagnostics have kept a productive science largely out of the clinic. The most important single takeaway is that the field's future progress depends less on inventing new carriers than on designing the credible ones for manufacture, patient selection, and the immunomodulatory payloads that play to the technology's true strength.

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