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Perspective

Targeting macrophages in OA nanomedicine: Therapeutic opportunity or delivery delusion? A pragmatic reappraisal

Qing Yao[a,b,#], *Beilin Fu*[a,#], *Longfa Kou*[a,*]

[a] *Wenzhou Municipal Key Laboratory of Pediatric Pharmacy, Department of Pharmacy, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China*

[b] *School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, China*

1. Introduction

Osteoarthritis (OA), traditionally viewed as a mechanical and degenerative condition, increasingly involves chronic, low-grade inflammation. Among implicated immune cells, activated macrophages are key drivers of synovitis and cartilage degradation [1], spurring interest in therapies that selectively modulate macrophage activity within the joint while sparing other resident cells. Consequently, many nanoparticle formulations add surface ligands to promote receptor-mediated macrophage uptake for intra-articular delivery. Yet a central question remains: do these nanoparticles truly achieve receptor-specific delivery toward macrophages, or are they internalized because macrophages are inherently phagocytic and positioned at inflamed sites? When "active targeting" is asserted without verification, interpretation can drift from biology and hinder rational design. Resident synovial and infiltrating monocyte-derived macrophages also differ in markers and behavior, further affecting targeting and its interpretation [2]. This editorial reappraises macrophage "targeting" in OA and advocates a pragmatic, validation-first approach before claiming specificity.

2. Why macrophages matter in OA: Biology and accessibility?

Persistent inflammation contributes to OA progression and severity. Within joints, macrophages sustain pro-inflammatory responses and are enriched in the synovial lining and infrapatellar fat pad, with abundance varying between human OA and common animal models [3]. Across activation states, M1-like cells release pro-inflammatory cytokines and matrix-degrading enzymes contributing to cartilage destruction and pain, whereas M2-like cells support tissue repair and inflammation resolution. This plasticity makes macrophages both key disease mediators and therapeutic targets.

Preclinical studies suggest that modulating macrophage behavior like through depletion, phenotype polarization, or inhibition of pro-inflammatory subsets, can reduce synovitis and preserve cartilage [4]. These findings have motivated macrophage-targeted delivery of anti-inflammatory agents, gene modulators and signaling inhibitors. From a delivery perspective, macrophages are more accessible than many other joint-resident cells because the synovial lining is vascularized and contiguous with the joint cavity. Unlike

* Corresponding author.
E-mail address: klfpharm@163.com (L. Kou).

# These authors contributed equally.

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chondrocytes, which are embedded deep within the dense, avascular cartilage matrix, synovial macrophages reside closer to the joint cavity and are directly exposed to intra-articularly administered nanoparticles. Their phagocytic capacity further favors particulate uptake, especially in inflamed joints. Accordingly, the rationale for macrophage targeting in OA is strong, their biological role, physical accessibility, and phagocytic capacity. The key question is whether ligand decoration adds specificity beyond residence-driven exposure and innate scavenging.

3. Illusion of active targeting in OA nanomedicine

Many OA macrophage-targeting strategies use surface ligands to drive receptor-mediated uptake, yet such specificity is rarely validated in OA models. Common ligands include hyaluronic acid (HA, CD44), folate acid (folate receptor), and antibodies against macrophage markers (e.g., CD163). However, CD44 is also expressed on fibroblast-like synoviocytes, dendritic cells and chondrocytes, especially under inflammatory conditions. Moreover, receptor levels vary with tissue, disease state, and model. A TRPV1-targeted nanomedicine intended to engage both macrophages and chondrocytes based on the shared overexpression further illustrates how cellular selectivity can be blurred [5].

In many studies, targeting claims rely on indirect indicators (e.g., higher cellular uptake, stronger joint-level signal, or therapeutic effects) without proof of macrophage-specific delivery. Increased macrophage uptake after nanoparticle treatments is often taken as ligand-dependent macrophage targeting, yet it does not exclude contributions from other cell types. Fluorescent or radiolabeled synovial signals are often assumed to prove *in vivo* macrophage uptake, but cell-level colocalization with macrophage markers and/or matched non-targeted controls is frequently lacking. Moreover, a ligand may improve joint retention or efficacy through matrix adhesion or prolonged residence rather than increased macrophage uptake. For HA-modified systems, abundant native HA in synovial fluid may saturate CD44 or otherwise interfere with HA-CD44 interactions, yet this factor is rarely controlled. By contrast, folate-receptor-β tracers (e.g., $^{[18F]}$fluoro PEG folate PET tracer) used to image activated synovial macrophages in inflammatory arthritis demonstrate *in vivo* ligand competition and ex vivo colocalization, offering a methodological benchmark readily applicable to OA [6].

Critically, few studies conduct the experiments needed to substantiate active targeting. These include (i) *in vivo* receptor blocking with excess free ligand or a blocking antibody to abolish any ligand advantage; (ii) cellular-level confirmation from treated joints by flow cytometry or by high-resolution immunofluorescence; and (iii) loss-of-function tests using macrophage depletion/attenuation models such as clodronate liposomes or CSF1R inhibition. Apparent nanoparticle accumulation in OA may therefore reflect nonspecific localization rather than true cellular targeting. The extent of putative receptor-mediated uptake also depends on model factors (e.g., receptor abundance, local opsonization/phagocytic state) and formulation factors (e.g., PEGylation/other surface chemistry, ligand density). Head-to-head comparisons with ligand-free controls are essential to quantify the ligand contribution and distinguish it from innate phagocytosis/opsonization.

4. Scavenging, not targeting: Macrophages' innate uptake as delivery engine

The effectiveness of macrophage-targeted systems may arise less from ligand-receptor recognition and more from macrophage biology. As professional phagocytes, macrophages internalize particulates, especially under inflammatory conditions and regardless of surface modifications. Their role in clearing apoptotic cells, pathogens, debris and foreign matter means high intracellular signal can be expected. In human OA, *in vivo* imaging has provided evidence that synovial inflammation increases macrophage activation, amplifying apparent uptake [7]. Outside the joint, liver Kupffer cells dominate nanoparticle clearance, illustrating that in macrophage-rich tissues, passive phagocytic mechanisms often override surface modifications [8].

This innate scavenging tendency can easily be misinterpreted as active targeting when controls are insufficient. Ligand-modified nanoparticles may show modest uptake gains versus unmodified controls, yet this can reflect incremental enhancement of a nonspecific process. Without receptor-blocking, cell-level colocalization, or depletion models, such interpretations remain speculative. Moreover, macrophage uptake is highly sensitive to nanoparticle physicochemical parameters, such as size, surface charge, rigidity, and hydrophilicity. As a practical starting point, sizes around 50–150 nm often balance diffusion with uptake, while mildly positive and moderately rigid, roughly spherical particles are more readily internalized than negatively charged, softer, or irregularly shaped counterparts [9]. Report hydrodynamic size and zeta potential in synovial fluid or a synovial-mimicking buffer so that measurements reflect intra-articular conditions. In this context, features intended to promote "active targeting" may inadvertently improve passive recognition instead. For example, HA coatings can improve colloidal stability, tissue retention and diffusion, increasing joint-level accumulation that is not necessarily CD44-mediated. Indeed, even "stealth" nanoparticles, like PEG-modified nanoparticles, have shown macrophage internalization and anti-inflammatory efficacy in OA models [10], plausibly through improved residence and transport rather than receptor-specific routing. These observations argue that ligand-based cellular targeting is not a prerequisite for macrophage engagement; instead, PEGylation and related surface engineering should be framed as a tunable trade-off between residence and cell association.

5. Rethinking passive clearance as a design principle, not a limitation

If macrophages internalize intra-articular nanoparticles, it is more rational to embrace and refine biology than to rely on invalidated ligands. The question is therefore not how

to "actively target" macrophages, but how to exploit innate scavenging for therapeutic gain.

Designing for passive uptake does not abandon precision. Rather, it redefines it around controllable physicochemical determinants. Tuning size, charge density, surface chemistry, and colloidal stability can promote macrophage uptake without uncertain ligand-receptor claims. Spherical nanoparticles are generally more readily phagocytosed than nonspherical ones. Surface chemistry is equally important. For example, pre-coating nanoparticles with opsonins (e.g., IgG) may increase their recognition by Fc receptors on macrophages, mimicking natural clearance rather than bypassing it. Kou et al. increased macrophage engulfment of bilirubin nanoparticles via IgG incubation in a rat OA model [11], although dose-ranging should consider immunogenicity and complement activation. Likewise, apoptotic cell–inspired 'eat-me' signals such as phosphatidylserine can promote engulfment [12], but may also bias efferocytosis-associated immune programs and thus warrant monitoring. Another practical strategy is minimalist surface modification: zwitterionic coatings (e.g., PMPC) can enhance joint residence and thereby improve overall access to macrophages, without adding complex ligands. Ultimately, ligand-free designs should be evaluated head-to-head against ligand-decorated counterparts using matched controls, particularly to test whether prolonged residence can offset any reduction in per-cell uptake.

Passive strategies also offer translational advantages, including simpler manufacturing and fewer of receptor heterogeneity or ligand-associated immunogenicity. This is reflected in intra-articular liposomal dexamethasone formulations: TLC599 (phase III; pain/function benefits through 12–24 weeks in randomized studies) and Lipotalon® (clinically used in Germany), both achieving efficacy without active-targeting ligands [13]. Together, these experiences support a pragmatic view: in OA, reliable joint residence and biologically aligned macrophage engagement may be more actionable than receptor-specific targeting designs.

6. Conclusion

Macrophages remain a compelling target for intra-articular nanomedicine in OA, but "active targeting" should be claimed only with mechanistic proof. Much of the apparent uptake reflects intra-articular residence and innate scavenging rather than ligand-specific routing. A pragmatic approach is to optimize joint residence and baseline macrophage engagement first, and then test whether a ligand adds value. Before claiming "targeting", studies should demonstrate (i) *in vivo* loss of advantage under receptor competition/blocking, (ii) cell-level colocalization in treated joints, and (iii) loss of function via macrophage depletion or attenuation. Looking ahead, we emphasize implementation: conduct head-to-head ligand-modified versus ligand-free comparisons; use joint-mimetic assays to quantify retention, diffusion, and stability in synovial-relevant media; report key physicochemical parameters under intra-articular conditions; pre-specify immunogenicity/efferocytosis readouts when employing opsonins or phosphatidylserine; and routinely report negative as well as positive controls to reduce bias.

Conflicts of interest

The authors declares no conflict of interest.

CRediT authorship contribution statement

Qing Yao: Conceptualization, Writing – original draft. **Beilin Fu:** Writing – original draft. **Longfa Kou:** Conceptualization, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2026.101127.

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