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Cartilage-targeted drug delivery in osteoarthritis: Redefining local therapy with intelligent hydrogel microspheres

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Osteoarthritis (OA) is a chronic degenerative joint disease characterized by articular cartilage degradation, osteophyte formation, subchondral bone remodeling, and synovial inflammation, often accompanied by restricted joint mobility, pain, and functional impairment.[1] OA has become one of the leading causes of disability in individuals over the age of 65. According to updated data from the World Health Organization (WHO), OA affects approximately 528 million individuals worldwide, with an estimated 344 million people at high risk of severe disability requiring medical intervention. Due to the unique anatomical structure of joints—naturally devoid of blood vessels, nerves, and lymphatics—systemically administered drugs face substantial challenges in achieving targeted accumulation, maintaining therapeutic concentrations, and providing sustained treatment at the joint site.[2] As a result, intra-articular injection has been developed as a strategy to efficiently deliver lubricants or anti-inflammatory agents (such as hyaluronic acid and steroid) directly into the joint space for effective OA management. Owing to their excellent drug-loading capacity and injectability, hydrogel microspheres (HMs) have emerged as a research hotspot in OA therapy and can be fabricated using techniques such as microfluidics, emulsification, electrospray, and lithography (Figure 1).

In a recent study published by Lu et al. in *The Innovation*, the authors designed an advanced nano–micron combined HM-based drug delivery system (DDS), inspired by the concept of the Trojan horse.[3] This DDS is capable of achieving three key therapeutic functions—stimuli-responsive drug release, chondrocyte-specific penetration, and lysosomal escape—through a single intra-articular injection, significantly delaying chondrocyte senescence. Specifically, the researchers utilized amino-modified mesoporous silica nanoparticles (MSNs) as a "Trojan horse" vehicle, loaded with the bioactive marine polysaccharide fucoidan and covalently conjugated with a cartilage-targeting peptide (WYRGRL), thereby enabling precise recognition of cartilage extracellular matrix components. These functionalized nanoparticles were subsequently encapsulated within a composite HM sensitive to the osteoarthritic joint microenvironment, facilitating charge neutralization, enhanced tissue penetration, and spatiotemporally controlled release across the joint cavity, cartilage matrix, and intracellular compartments. This innovative DDS systematically establishes a hierarchical targeting cascade—comprising tissue-specific targeting, cell membrane penetration, lysosomal escape, and cytoplasmic drug release—for the effective intra-articular delivery of fucoidan to osteoarthritic cartilage. Upon precise entry into chondrocytes, fucoidan modulates mitochondrial homeostasis by finely balancing SIRT3-mediated apoptosis and mitophagy. This dual regulatory action enhances mitochondrial energy metabolism, alleviates the cellular energy crisis, and optimizes mitochondrial oxidative phosphorylation, which significantly boosts ATP production in chondrocytes. Furthermore, fucoidan promotes the activation of PINK1-PRKN mitophagy pathway, thereby eliminating damaged mitochondria and maintaining mitochondrial integrity. This combined effect not only downregulates senescence-associated markers such as P16 and P21, but also upregulates pro-survival factors and inhibits inflammation, interrupting the vicious cycle of inflammation driven by the senescence-associated secretory phenotype (SASP). Consequently, the system improves mitochondrial function, delays chondrocyte senescence, and ultimately exerts a protective effect on cartilage integrity by enhancing cellular energy availability and mitigating mitochondrial dysfunction.

Of note, the DDS developed by Lu et al.,[3] inspired by the "Trojan horse" concept, fundamentally represents a nano–micron combined strategy. This approach cleverly integrates multiple critical components, including microenvironment responsiveness, targeted recognition, barrier penetration, intracellular delivery, and prolonged intra-articular retention. Such a strategy not only enables precise localization and stepwise release of therapeutics at OA lesions but also enhances tissue penetration and intracellular delivery efficiency within cartilage. Importantly, it significantly extends drug residence time within the joint cavity, thereby improving therapeutic outcomes—an essential consideration for achieving effective OA treatment. Due to the robust immune surveillance of the human body and the rapid clearance mechanisms of the synovial membrane, intra-articularly injected hyaluronic acid (HA) typically remains in the joint cavity for no more than three days in clinical practice. Remarkably, in this study, the release duration of fucoidan was extended to 28 days. This observation aligns with previous findings from other nano–micron combined DDSs and underscores the immense potential of such systems for achieving long-acting, sustained intra-articular drug delivery.

In addition to prolonged intra-articular retention, enhancing the precision of drug targeting toward diseased cartilage tissue and cells is also essential for achieving optimal therapeutic outcomes in OA. In recent years, researchers have explored various strategies to achieve targeted delivery to cartilage (Figure 1). For instance, in a study published in *Science Advances*, Lei et al. developed a HM system encapsulating rapamycin (RAPA)-loaded liposomes.[4] This system not only provided self-renewable hydration lubrication but also released positively charged cationic liposomes that electrostatically targeted the negatively charged cartilage matrix. The released RAPA, an autophagy activator, then promoted cellular homeostasis by enhancing autophagy, thereby slowing OA progression. Similarly, in a study reported by Liu et al. in *Biomaterials*, HMs carrying HA-modified selenium nanoparticles were shown to adhere specifically to damaged cartilage via Schiff base bonding with the extracellular cartilage matrix.[5] Moreover, the released selenium nanoparticles were further targeted to OA chondrocytes via receptor–ligand interactions between HA and CD44, which is highly expressed on OA chondrocyte membranes. The targeted delivery of selenium helped construct a multifaceted antioxidant defense system, alleviating oxidative stress and restoring mitochondrial function, ultimately attenuating OA progression. In the present study, Lu et al. designed a hierarchical DDS that enables stepwise targeting of fucoidan. The HMs, serving as the "bus," rapidly degrade in the OA joint microenvironment in response to elevated collagenase activity, thereby releasing the "passengers"—fucoidan-loaded MSNs. These nanoparticles are guided to the cartilage matrix via the cartilage-targeting peptide WYRGRL. Once internalized by chondrocytes, the nanoparticles escape the lysosomal compartment through the proton sponge effect and subsequently release fucoidan into the cytoplasm. This stepwise targeting strategy enables synchronized regulation of metabolic remodeling and senescence suppres-

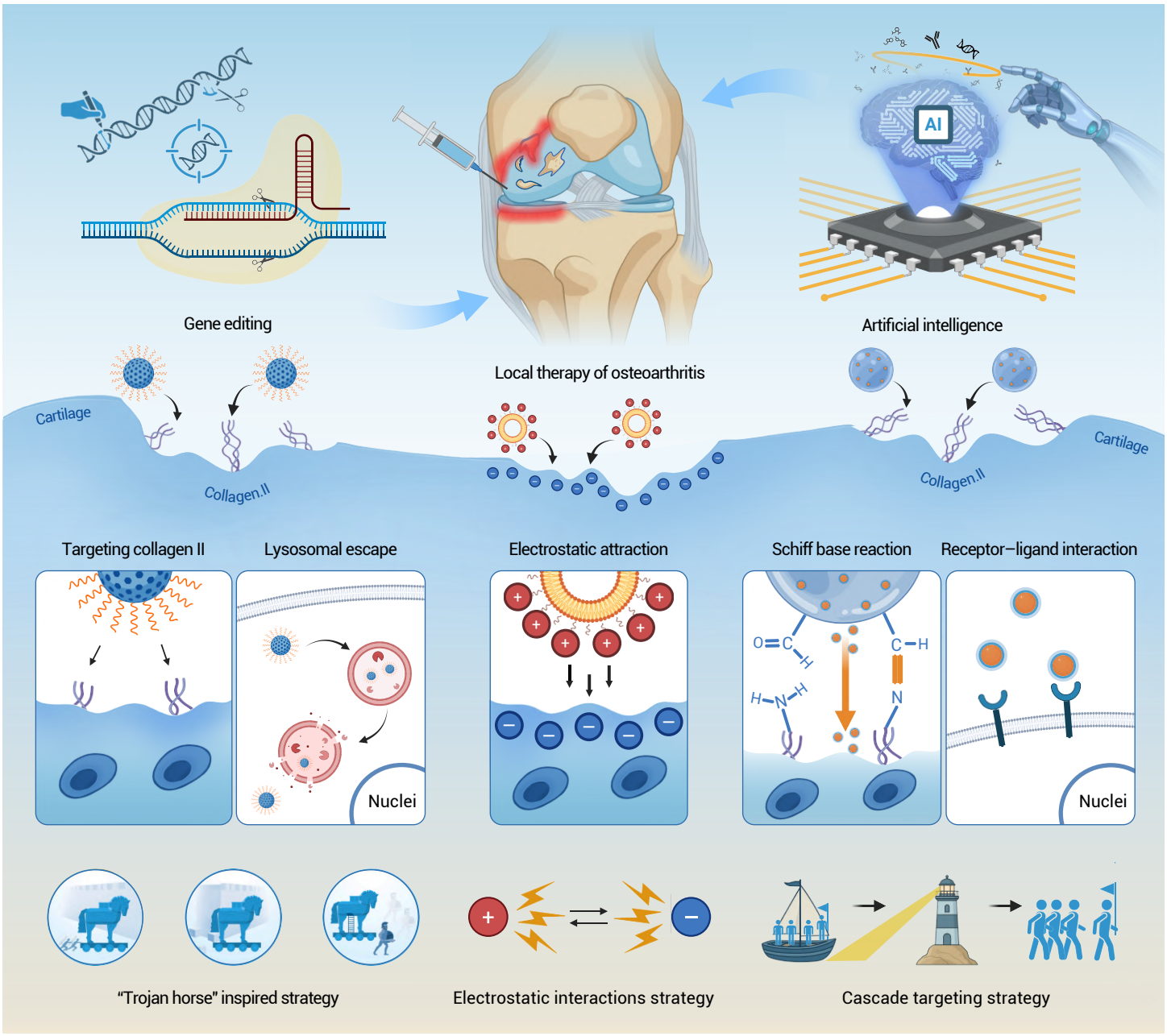

Figure 1. Cartilage-targeted drug delivery in osteoarthritis – common strategies based on nano-micron combined hydrogel microspheres.

sion in chondrocytes, contributing to sustained cartilage protection.

Although this strategy has achieved significant breakthroughs in mechanistic exploration and in vivo validation, several important issues remain to be addressed in future studies. First, the long-term safety and in vivo metabolic fate of the system require further investigation, particularly concerning the immunotolerance of the nanoparticle carriers and polysaccharide-based bioactive agents, with preclinical studies in large animal models (such as pigs, goat, or monkeys) or non-animal alternatives like organ-on-a-chip technology being essential for evaluating these aspects before clinical translation. Second, the pharmacokinetic characteristics and structural heterogeneity of fucoidan itself, and their impact on therapeutic efficacy, warrant systematic evaluation. Third, the applicability and differential responses of this DDS across various OA subtypes—such as obesity-associated OA or inflammatory OA—have yet to be validated in clinical settings. Based on the pathological differences between OA subtypes, future DDS designs may need to be tailored to specific subtypes, such as optimizing targeting ligands or adjusting stimuli responsiveness, to better accommodate the distinct microenvironment of each subtype. Fourth, whether this composite platform can be synergistically combined with stem cell therapies or biomechanical stimulation (e.g., joint mobilization) to further enhance cartilage repair remains an exciting and unexplored avenue. While stem cell therapy provides necessary cell sources and biomechanical stimulation activates repair mechanisms, challenges like delivery timing and compatibility with stem cells need to be addressed before attempt for optimal results. Fifth, the clinical translation of this complex therapeutic system faces challenges related to manufacturing processes, regulatory approval, and long-term safety, all of which need to be thoroughly addressed in future research. Moreover, it is worth highlighting that this study exemplifies a highly integrated cross-disciplinary approach, bridging smart materials, targeted nanomedicine, and bioenergetic metabolic intervention. It represents a paradigm of "interdisciplinary innovation driven by disease-centric needs". In this process, integrating emerging technologies such as artificial intelligence and gene editing holds the potential to further enhance the personalization and precision of OA treatment. If further extended to other degenerative soft tissue disorders—such as intervertebral disc degeneration or tendinopathy—this platform holds significant translational potential and could open new therapeutic frontiers.

This study conducted by Lu and colleagues presents a sophisticated, Trojan horse-inspired nano–micron combined HM system that achieves multi-level precision therapy for osteoarthritis, encompassing microenvironment-responsive release, cartilage-specific targeting, intracellular delivery, and organelle-level regulation. This work not only offers a novel and integrated therapeutic paradigm for OA—combining targeted drug delivery with bioenergetic modulation—but also exemplifies a powerful "cross-disciplinary + disease-oriented" research model.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.