Biomaterials Translational

Advanced nanoparticles in osteoarthritis treatment

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ABSTRACT

Osteoarthritis (OA) is the most prevalent degenerative joint disorder, affecting hundreds of millions of people globally. Current clinical approaches are confined to providing only symptomatic relief. Research over the past two decades has established that OA is not merely a process of wear and tear of the articular cartilage but involves abnormal remodelling of all joint tissues. Although many new mechanisms of disease have been identified in the past several decades, the efficient and sustainable delivery of drugs targeting these mechanisms in joint tissues remains a major challenge. Nanoparticles recently emerged as favoured delivery vehicles in OA treatment, offering extended drug retention, enhanced drug targeting, and improved drug stability and solubility. In this review, we consider OA as a disease affecting the entire joint and initially explore the pathophysiology of OA across multiple joint tissues, including the articular cartilage, synovium, fat pad, bone, and meniscus. We then classify nanoparticles based on their composition and structure, such as lipids, polymers, inorganic materials, peptides/proteins, and extracellular vesicles. We summarise the recent advances in their use for treatment and diagnosis of OA. Finally, we discuss the current challenges and future directions in this field. In conclusion, nanoparticle-based nanosystems are promising carriers that advance OA treatment and diagnosis.

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Introduction

Osteoarthritis (OA) is a persistent degenerative joint disease characterised by symptoms such as joint pain, stiffness, tenderness, swelling, and the formation of bone spurs. It commonly affects load-bearing joints like the knees and hips. OA is the world's most prevalent joint disorder and a leading cause of pain and disability, particularly among the elderly, impacting over 500 million people globally.[1, 2] It is also among the most costly health conditions, consuming up to 2.5% of the gross national product in countries with established market economies and incurring an average cost between $700–$15,600 per person with OA.[3] Thus, this condition significantly diminishes the quality of life for patients and imposes a substantial socio-economic burden on society.

Generally, two main types of OA can be distinguished based on the underlying causes. Post-traumatic OA (PTOA) arises after joint injuries, such as tears of the anterior cruciate ligament (ACL) tears, meniscal tears, patellar dislocations, or direct impacts on the cartilage. This type accounts for about 12% of all symptomatic OA cases and contributes to most OA occurrences among young healthy adults.[4, 5] On the other hand, age stands as the principal risk factor for the development of OA in predisposed joints. Age-related OA (idiopathic OA) is another major type of OA and is influenced by other risk factors including, but not limited to, obesity, gender, physical activity, diet, and genetic factors.[6] Irrespective of the OA type, the disease typically progresses through three stages. Initially, patients may experience mild pain and stiffness in the joints, but early-stage OA is often under-recognised and poorly

diagnosed, making early intervention challenging. In the middle stage, patients experience joint space narrowing, the formation of osteophytes, and apparent cartilage degradation, although clinical management mainly aims at pain relief and inflammation reduction. As OA advances to the late stage with a high disability rate, surgical intervention is often inevitable for the patients.[7]

Despite the pressing need, disease-modifying OA drugs (DMOADs) have yet to be introduced into clinical practice. The last twenty years has witnessed the significant progress in understanding the mechanisms underlying OA, and numerous potential drug targets have been identified. Nevertheless, the translation of these discoveries into effective treatments remains challenging, partly because of the absence of efficient drug delivery systems that can target joint tissues specifically and locally while minimising offsite effects. Because of the unique anatomical features of joints, nanoparticles (NPs) recently emerged as the most promising drug delivery system for OA treatment. The concept of nanotechnology, which involves manipulating materials at nanoscale dimensions to create remarkably varied and new properties, was first introduced by physicist Richard Feynman in 1959 and has since revolutionised medical research, particularly in the areas of treatment and diagnosis.[8-10] In this review, we begin by introducing the pathogenesis of OA with an emphasis on each type of joint tissue, followed by an overview of the current treatment options available for OA patients. We then highlight recent advances in the development of NP-based methods for OA drug delivery and OA diagnosis. Finally, we discuss the future prospects and challenges of applying nanomedicine in the field of OA.

Joint Structure and Osteoarthritis Pathogenesis

Joint is a complex organ. As a typical example, the knee joint comprises several key components: articular cartilage, which covers the ends of the femur and tibia at the load-bearing points; the subchondral bone, located beneath the articular cartilage; the synovium, which lines the inner surface of the joint capsule; the meniscus, acting as a cushion between the cartilage of the femur and tibia; the infrapatellar and posterior fat pads, which occupy the extracapsular spaces; and the ligaments, which provide connection between the femur and tibia (**Figure 1A**). While OA is predominantly marked by the degeneration of articular cartilage, it affects all other joint tissues as well. The progression of OA is characterised by various pathological manifestations, depending on the stage of the disease, including cartilage degradation, synovitis, subchondral bone sclerosis, osteophyte formation, and fat pad fibrosis.[11] In PTOA, injuries to meniscus or ACL are the primary causes for cartilage degeneration. The interaction between different types of tissues within the joint is crucial not only for the maintenance of joint health but also for the progression of OA. This interplay underscores the importance of addressing OA as a whole-joint disease.

Articular cartilage

The articular cartilage is a hyaline connective tissue that plays a vital role in enabling smooth and pain-free joint movement. Its extracellular matrix (ECM) is an interlocking network, consisting predominantly of 70–80% water, alongside 4–7% proteoglycans, and 15–22% collagens, with type II collagen being the most prevalent form.[12] Chondrocytes, the sole cell type within the articular cartilage, constitute less than 10% of the tissue's dry weight yet play a significant role in tissue turnover.[13] They contribute to cartilage homogeneous by secreting all ECM macromolecules and ECM degrading enzymes, such as the matrix metallopeptidase (MMP) family, and aggrecanases like the a disintegrin and a metalloproteinase with thrombospondin motifs (ADAMTS) family.[14]

In a healthy state, articular cartilage primarily functions as a load-bearing and lubricating site. It is structurally segmented into four distinct layers: the superficial zone, the middle zone, the deep zone, and the calcified zone (**Figure 1B**). The superficial zone at the cartilage surface featured two to three layers of disk-shaped small chondrocytes with horizontally arranged collagen fibrils. These cells typically align parallel to the cartilage surface and are the primary producers of the proteoglycan lubricant, proteoglycan 4 (lubricin).[15] Recent research also indicates that this zone may host cartilage-derived stem/progenitor cells.[16] In the middle or transitional zone, the chondrocytes are spherical and embedded within a matrix of diagonally aligned collagen fibres. The deep or radial zone contains enlarged chondrocytes arranged in columns perpendicular to the tissue surface, with radially oriented collagen fibrils. The calcified zone, demarcated from the deep zone by the tidemark, comprises hypertrophic chondrocytes and perpendicularly arranged collagen fibrils.[17] The variation in cell orientation and collagen alignment across these layers enables the articular cartilage to efficiently disperse loads and facilitate smooth joint movements.

At the onset of OA, the articular cartilage is one of the first to react even before significant macroscopic alterations in joint histology become apparent. Abnormal mechanical loading, sensed by chondrocyte mechanosensors, leads to a decrease in glycosaminoglycan (GAG) content and an increase in cell apoptosis within the cartilage, initiating tissue degeneration (**Figure 1B**).[18] As OA advances, chondrocytes begin to secrete enzymes that degrade the ECM, undermining the mechanical integrity and homeostasis of the articular cartilage. In response to this degradation, chondrocytes attempt to repair the loss of ECM by enhancing their proliferation, clustering together, and becoming hypertrophic.[19] As an avascular and non-innervated tissue, articular cartilage's capacity for regeneration is inherently limited, challenging the restoration of balance between anabolic and catabolic processes. Current DMOAD discovery is primarily aimed at identifying compounds that can either stimulate the anabolic activities of chondrocytes or inhibit their catabolic functions. Growth factors are considered promising agents because they can support

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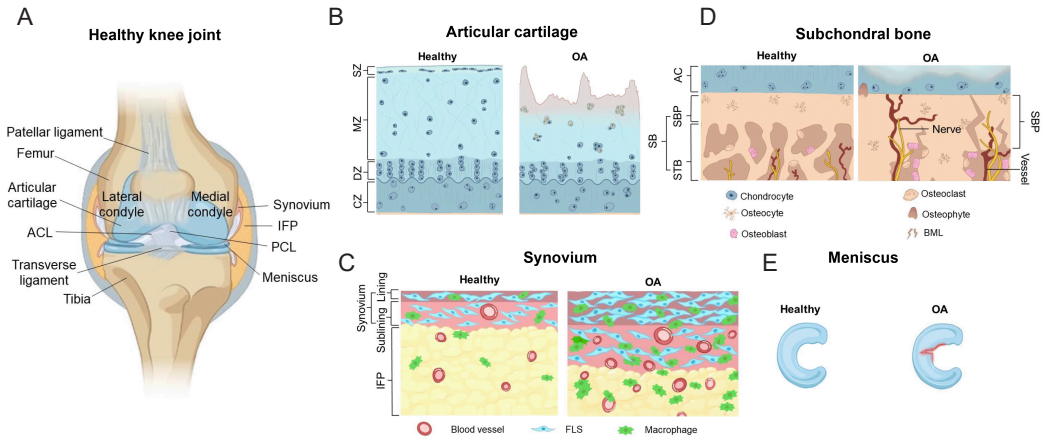

Figure 1. Anatomy of a knee joint in healthy and OA conditions. (A) Schematic illustration of knee joint anatomy. (B) Comparison between healthy and OA articular cartilage. With the onset of OA, the cartilage experiences various alterations such as extracellular matrix degradation, surface erosion, and chondrocyte clustering. (C) Comparison between healthy and OA synovium. In OA, the synovium thickens due to the proliferation of synoviocytes. Additionally, OA synovium is characterised by macrophage infiltration and the invasion of blood vessels. (D) Comparison between healthy and OA subchondral bone. As OA progresses, changes in the subchondral bone include sclerosis and increased remodelling of the trabecular bone. Furthermore, the subchondral bone in OA may exhibit bone marrow lesions, osteophyte formation, and increased innervation. (E) Comparison between healthy and OA meniscus. Damage to the meniscus plays a crucial role in the initiation and progression of OA. Created with BioRender.com and Procreate. AC: articular cartilage; ACL: anterior cruciate ligament; BML: bone marrow lesion; CZ: calcified zone; DZ: deep zone; FLS: fibroblast-like synoviocyte; IFP: infrapatellar fat pad; MZ: middle zone; OA: osteoarthritis; PCL: posterior cruciate ligament; SB: subchondral bone; SBP: subchondral bone plate; STB: subchondral trabecular bone; SZ: superficial zone.

chondrocyte proliferation, survival, and matrix production. The most well-studied ones are insulin-like growth factors (IGFs),[20-22] fibroblast growth factors,[23-26] transforming growth factor (TGF) β,[27, 28] bone morphogenetic proteins,[29-31] platelet-derived growth factor,[32-34] and epidermal growth factor family member TGFα.[35-38] Some of these, such as IGF and TGFα, have been conjugated to cartilage-penetrating NPs, showing encouraging results in OA treatments.[37, 39-41]

Synovium

The synovium, encompassing the synovial membrane and the synovial fluid within, plays a crucial role in joint health. In healthy joints, synovial membrane is a thin, highly vascularised connective tissue divided into a lining layer (intima) and a sublining layer (subintima). It contains two major cell types: type A synoviocytes (macrophages), and type B synoviocytes (fibroblasts, also known as fibroblast-like synoviocytes or FLSs) (**Figure 1C**). Macrophages play a key role in joint inflammation.[42] FLSs, the most prevalent cell type in the synovial membrane, are responsible for synthesising collagen, hyaluronic acid (HA), and lubricin, crucial components for maintaining the synovial fluid's volume and composition.[43] Recent single-cell RNA sequencing studies have unveiled considerable heterogeneity among macrophages and FLSs within the synovium.[44-47] In addition, the sublining layer is rich in lymphatics and capillaries, essential for the exchange of substances between the joint and the rest of the body, with the lymphatic system playing a key role in clearing NPs from the joint, complemented by macrophage phagocytosis.[48]

Synovitis, a hallmark of OA, is characterised by FLS proliferation, lining layer hyperplasia, and immune cell infiltration (**Figure 1C**). The thickening of the synovial membrane is closely linked with OA progression and associated joint pain.[49-51] Interactions between the inflamed synovium and cartilage significantly contribute to the heightened catabolic activity in chondrocytes. During OA, FLSs produce MMP-3, vascular endothelial growth factor, interleukin (IL)-6, and tissue inhibitors of MMPs which activate macrophages to release IL-1β, IL-6, tumour necrosis factor (TNF)α, and other pro-inflammatory mediators.[50] These cytokines then prompt chondrocytes to produce elevated levels of MMPs and ADAMTSs, leading to accelerated ECM breakdown and further stimulating a feedback loop that exacerbates the inflammation and cartilage degradation.[52]

Given the synovium's central role in OA inflammation and cartilage deterioration, targeting synovitis presents a novel therapeutic avenue for OA treatment. The clinical application of local and systemic nonsteroidal anti-inflammatory drugs and corticosteroids has been effective in modulating synovial inflammation. Additionally, certain chondroprotective medications, like chondroitin sulfate and HA, have demonstrated capabilities in reducing macrophage infiltration and attenuating synovitis in the OA synovium.[53] Current research efforts in synovium-targeted therapies primarily aim to mitigate reactive oxygen species (ROS) stress and modulate macrophage polarisation. For example, NPs containing superoxide dismutase (SOD) have been observed to accumulate in the synovium and significantly

alleviate oxidative stress in a mouse OA model.[54] Furthermore, strategies like knocking down phosphoglycerate mutase 5 (PGAM5) or activating transient receptor potential vanilloid-1 (TRPV1) in macrophages block OA progression.[55, 56] Despite these advances, significant challenges remain in identifying the pathogenic pathways of OA synovitis and in the development of NP-based DMOADs.

Subchondral bone

Subchondral bone is the bone tissue situated below the calcified zone of articular cartilage. Anatomically, it is divided into two parts: the subchondral bone plate, a cortical bone layer beneath the calcified cartilage, and the subchondral trabecular bone, a spongy bone structure that is subject to ongoing bone remodelling (**Figure 1D**).[57] This remodelling is regulated by two primary cell types: osteoblasts, which are responsible for forming new bone, and osteoclasts, which resorb older bone. Relatively balanced activities of these cells maintain the health and functionality of the subchondral bone, thereby providing necessary mechanical support. The subchondral bone dynamically adjusts its turnover rate in response to changes in mechanical load.[58]

During OA progression, subchondral bone undergoes several pathological changes. One of the most notable changes in advanced OA is subchondral bone sclerosis, particularly the thickening of the subchondral bone plate (**Figure 1D**).[57, 59] The remodelling rate in the subchondral trabecular bone accelerates under OA conditions, leading to undermineralised subchondral trabecular bone and reduced mechanical integrity.[60-63] Additionally, bone marrow lesions or bone marrow oedema, characterised by localised fat necrosis, bone marrow fibrosis, and heightened bone remodelling, can result in microfractures within the subchondral trabecular bone.[64] In later stages of OA, subchondral bone cysts or intra-osseous lesions may develop due to bone marrow lesions and subsequent abnormal bone resorption. The crosstalk between the subchondral bone and articular cartilage is also crucial. In a healthy joint, the subchondral bone plate includes canals allowing for nutrient and molecular exchange with the cartilage. However, in OA, enhanced bone remodelling and vascularisation lead to the abnormal invasion of blood vessels and nerves into the cartilage, contributing to joint pain and facilitating the transport of inflammatory factors, which exacerbate the condition (**Figure 1D**).[57, 58, 65] Given the important roles of subchondral bone in OA development, therapeutic strategies addressing dysregulated remodelling, abnormal angiogenesis, and excessive innervation are being actively explored to counteract OA progression.

Meniscus

In healthy individuals, the meniscus is responsible for shock absorbance, tension resistance and lubrication, contributing significantly to the mechanical stress distribution across the knee joint and ensuring the integrity and stability of the joint during movement (**Figure 1E**). The meniscus primarily comprises two cell types, which are distributed differently: fibroblasts are predominantly found in the outer region, whereas the inner and middle regions are composed mainly of fibrochondrocytes. The inner and middle sections of the meniscus, in contrast to the outer portion, have a scant blood supply and few nerves, resulting in very limited intrinsic repair capabilities.[66, 67]

Meniscal injury is an important early event in the initiation of PTOA, which also exacerbates meniscal damage, accelerating the overall disease progression. Changes in biological pathways caused by abnormal mechanical loading contribute to meniscal degradation in OA. For example, increased abnormal compressive stress can elevate IL-1 and nitric oxide levels in meniscal cells, which subsequently promotes tissue degeneration.[68] A multicenter OA study also found that meniscal subluxation/extrusion is linked with other joint tissue damage, such as tibiofemoral cartilage loss, subchondral bone marrow lesion, and synovitis, which are all risk factors of OA.[69] While surgical interventions such as conservative partial meniscectomy can alleviate immediate symptoms, they do not necessarily slow the progression of PTOA and may even hasten it. Despite the importance of meniscus in OA, currently few menisci targeting DMOAD are under studied.

Others

As the largest intra-articular adipose tissue, the infrapatellar fat pad (IFP), is located between patellar tendon, femoral condyle, and tibial plateau, highly vascularised, and lined with the synovial membrane. Characterised as a white adipose tissue, it comprises lobules divided by connective tissue septa, with adipocytes being the predominant cell type. Additionally, the IFP contains a significant number of fibroblasts, which contribute to ECM production, and various immune cells, such as leukocytes, macrophages, and lymphocytes.[70, 71] Therefore, it is not only a shock absorbent that protects the joint from mechanical damages, but also an endocrine tissue that regulates joint homeostasis and inflammation.[70] Research indicates that the volume of the IFP is closely related to the progression of OA and joint pain. An increased IFP surface area has been associated with reduced joint damage in OA.[71, 72] While the full range of IFP functions remains to be elucidated, it is clear that it plays a significant role in OA pathogenesis.

Ligament rupture and laxity affect joint stability and accelerate the progression of OA. The enthesis, where the ligament attaches to the bone, is vital for the biomechanical functionality of the knee joint and is implicated in early OA stages.[73] For instance, degeneration in the posterior cruciate ligament and its synovial-enthesial complex in OA has been evidenced by neovascularisation, enthesis chondrocyte clustering, and collagen matrix fissuring.[74] Additionally, meniscal enthesis also undergoes structural changes during OA development.[75] While research into the signalling pathways driving intra-articular ligament degeneration is sparse, certain factors, such as Mohawk, Sry-type HMG box 9, and TGFβ1, are suspected to play roles.[76-78] Given that articular cartilage has minimal innervation, the joint ligaments, which contain pain receptors, are also likely contributors to OA pain.[79, 80]

Osteoarthritis Diagnosis and Treatment

The articular cartilage loses its regenerative ability rapidly upon OA initiation, making joint repair increasingly challenging in the disease's middle or late stages. Consequently, a segment of research has focused on developing diagnostic tools for early intervention in OA. Radiography, including X-ray imaging, stands as the most commonly utilised image-based diagnostic method for OA, offering a cost-effective and straightforward means to detect cysts, osteophytes, and other ossified structures in OA. However, radiography falls short in capturing the full spectrum of pathological changes across all joint tissues.[81] Magnetic resonance imaging, while expensive, has been long favoured in the clinic. It can illustrate morphological changes in the cartilage, synovium, ligaments, menisci, and bone marrow, enabling the detection of early OA signs that radiography cannot identify.[82] Ultrasound imaging presents a less expensive alternative with higher resolution and is being investigated for its potential as a diagnostic tool for OA.[83] Arthroscopy, due to its invasiveness, is rarely used solely for diagnostic purposes in clinical settings. However, it is recommended for patients with focal cartilage lesions, serving both diagnostic and therapeutic purposes.[84]

Currently, there are four major types of OA treatment: non-pharmacological, pharmacological, biological, and surgical (**Table 1**).[85-97] For patients in the early stages of OA, who primarily experience mild pain and stiffness, the standard treatment options are nonsteroidal anti-inflammatory drugs and analgesics that target pain and inflammation.[98] Glucocorticoids, such as trenbolone acetate, betamethasone sodium phosphate, and dexamethasone (DEX), are commonly used.[88-90] Additionally, Diclofenac, a cyclooxygenase-2 inhibitor, is a U.S. Food and Drug Administration (FDA)-approved drug for OA patients to relieve pain and suppress inflammation.[91] At this stage, the therapeutic approach primarily focuses on mitigating pain rather than promoting regeneration or repairing tissue.

Table 1. Summary of currently available OA therapies

Type of treatment	Example	Pros	Cons	Reference
Non-pharmacological	Exercise, therapeutic ultrasound, phototherapy, thermotherapy, electrical stimulation, acupuncture	Analgesia, joint function restoration, wide access, recommended to all patients	Long-term treatment, large variation in therapeutic effects	85, 86
Pharmacologic	NSAIDs (e.g., glucocorticoids, COX-2 inhibitors), Chondroprotective drugs (e.g., chondroitin sulfate, HA)	Affordable, analgesia, anti-inflammation, wide access, effective on most OA patients	Side-effects on brain, gastrointestinal and cardiovascular systems, little pro-regenerative and disease-modifying effects	87-92
Biological	Platelet-rich plasma, MSC-based therapy	Providing necessary factors to aid cartilage regeneration, improve OA injury and patient's life quality	Complex manufacture, expensive, fibrocartilage formation, more effective in symptom relief than regeneration	93, 94
Surgical	Microfracture, autologous graft, partial/total knee arthroplasty	Effective end-stage OA therapies, necessary for late-OA patients to reduce pain, prevent disability and improve life quality	Invasive, costly, some require re-surgeries	95-97

Note: COX-2: cyclooxygenase-2; HA: hyaluronic acid; MSC: mesenchymal stem cell; NSAIDs: nonsteroidal anti-inflammatory drugs; OA: osteoarthritis.

For individuals with middle-stage OA, characterised by narrowed joint spaces and evident cartilage erosion, more pharmacologic and biological interventions are required to halt the disease progression. Chondroprotective drugs, such as chondroitin sulfate and HA, have demonstrated effectiveness in alleviating OA symptoms.[92, 99, 100] Biological strategies for OA management include regenerative therapies. Platelet-rich plasma, for instance, can supply essential growth factors to aid in the joint's recovery process.[93] Another promising approach involves intra-articular injections of autologous mesenchymal stem cells (MSCs). As the only cell-based treatment approved by the FDA for OA, autologous MSC therapy typically involves harvesting MSCs from the patient's bone marrow or adipose tissue, followed by *in vitro* expansion and re-implantation into the affected osteochondral area.[94] However, regenerative treatments for OA face several hurdles, including technical complexity, unstable chondrocyte-like phenotype, and donor site limitation.[101]

Surgical interventions become the primary recommendation for patients with advanced OA when non-surgical management methods no longer yield effective results. Beginning with less invasive procedures, perforation and microfracture are employed to stimulate the migration of self-derived bone marrow MSCs to the cartilage defect sites to promote regeneration. Additionally, autologous chondrocytes or osteochondral grafts are utilised for cartilage restoration.[95, 96, 102] Partial knee arthroplasty targets the removal of inflamed and damaged tissue, which can escalate to total knee arthroplasty in the end stages of OA.[97] Despite the clinical successes of surgical approaches, they are often invasive, costly, and might necessitate subsequent surgeries.

There is a notable gap in the current spectrum of OA therapies: the lack of straightforward, effective drugs to directly address and alter the OA pathological mechanisms to halt or even reverse its progression. Although substantial research efforts have been made and many new DMOAD candidates have been identified, their transition to clinically approved OA treatments faces significant challenges: structural and compositional changes of joint tissues would interfere with the fate of injected drugs, making targeted treatments more difficult to be achieved. Moreover, the retention of injected substances within the whole joint is influenced by OA progression, as the mechanisms for molecular clearance may evolve with the disease.[103, 104]

These obstacles underscore the need for a 'drug protector' that can enhance drug bioavailability by minimising clearance by macrophages and drainage through capillaries while also improving the drug's biodistribution by facilitating targeted delivery. In this context, NPs, with their highly customisable size, large surface area, and surface properties, have emerged as promising candidates to address these challenges, positioning themselves as potential key players in the future of OA therapy.

The Application of Nanoparticles in Osteoarthritis Treatments

Overview of therapeutic nanoparticles

Intra-articular injection is routinely used for the delivery of drugs in OA treatment because it increases the bioavailability of therapeutic agents at the affected site while reducing systemic exposure and potential side effects (**Figure 2**). However, the primary limitation of this traditional drug administration approach is rapid clearance of the drug from the synovial fluid. Small molecule drugs (i.e., those below 10 kDa) typically undergo clearance through a combination of fenestrated and non-fenestrated capillaries, whereas larger macromolecules, like proteins, are cleared via lymphatic pathways in the synovium.[48, 103, 105, 106] Furthermore, changes in joint tissue structure and composition, along with influxes of immune cells (such as macrophages and lymphocytes), fibrosis, oedema, and the inflamed joint milieu, can all impact the distribution and retention of administered drugs.[103] Lastly, the penetration of many promising OA therapeutics into the deep cartilage is hindered by the dense, avascular nature of cartilage tissue. Hence, targeted drug delivery systems that deliver the therapeutic agent to the site of interest are typically favoured to reduce off-target toxicity and improve treatment efficacy.

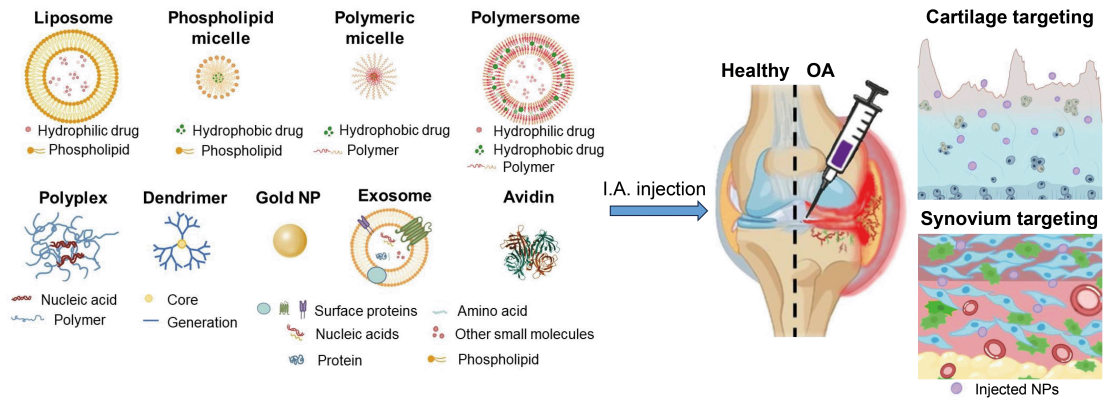

Figure 2. Schematic diagrams of commonly used NPs and I.A. injection. Commonly used NPs for OA treatments including liposome, phospholipid micelle, polymeric micelle, polymersome, polyplex, dendrimer, gold NPs and exosome. Administered through I.A. injection, the NP primarily enhances OA diagnosis/treatment by targeting the articular cartilage and/or synovium. Created with BioRender.com, Procreate, Microsoft PowerPoint and Protein Data Bank (PDB ID: 2AVI). I.A.: intra-articular; OA: osteoarthritis; NP: nanoparticle.

NPs represent a broad category of substances defined by their nanoscale dimensions. NP-based drug delivery system has been extensively exploited in cancer treatment due to their small size and large surface area, which endow NPs with distinctive physical and chemical characteristics.[107] In clinical applications, NPs can modify the pharmacokinetic behaviour of drugs, reduce off-target toxicity, and improve the therapeutic effects by offering improved pharmacokinetics, biodistribution, and solubility compared to the free drugs. An example of such a formulation is the mRNA-lipid NP vaccine for coronavirus disease 2019 (COVID-19), where lipid NPs shield the mRNA from degradation and boost its intracellular delivery and endosomal escape.[108] There is increasing interest in developing NP-based delivery systems for OA. Subsequent sections will discuss the latest advances in NP designs, including lipid-based, polymer-based, inorganic, as well as novel platforms like avidin, exosomes, and hybrid systems, which could potentially accelerate their clinical adoption for OA treatment.

Lipid-based nanoparticles

Liposomes

Liposomes are self-assembling spherical vesicles comprised of one or more phospholipid bilayers encircling an aqueous core (**Figure 2**).[109] They are among the most extensively studied drug delivery systems, renowned for their capacity to encapsulate both hydrophobic and hydrophilic substances within their phospholipid layers and aqueous interiors, as well as their favourable safety profiles (**Table 2**).[110-121] For example, Doxil®, a liposome-based formulation, is the first nanodrug approved by FDA.[122]

Table 2. The pros and cons of commonly used nanoparticles

Nanoparticle	Pros	Cons	Reference
Liposomes	Increased drug therapeutic efficiency, increased drug stability, low toxicity, tunability, biocompatibility	Low solubility, high cost, leakage/ fusion, short half-life	110
Micelles	Small sizes, simple preparation, high encapsulation capacity, increased water solubility	Fast clearance, stability concern, limited drug loading, critical micelle concentration	111-113
Polymersomes	Chemical versatility, increased stability than liposomes, flexible cargo capacity, prolonged half-life	Inferior biocompatibility/ biodegradability, low permeability, disintergration	114, 115
Polyplexes	Tunability, protect nucleic acids from degeneration, high water solubility	Toxicity, biodegradability concern, low transfection efficiency	116
Dendrimers	Increased drug solubility, tunability, covalently binding cargo, increased drug exposure time/efficiency	High cost, toxicity, scalability, stability	113
Gold nanoparticles	Uniformity, tunability, increased surface area, enhanced loading capacity	Toxicity	117, 118
Avidin	High biotin affinity, preferable versatility, non-toxicity, electronic interaction	Immunogenicity, toxicity, denaturation concerns	119
Exosomes	Versatility, biocompatibility, improved targeting	Scalability, heterogeneity, the lack of standard administrative protocol	120, 121

In 2020, Corciulo et al.[123] used liposomes to carry either adenosine or a selective A2A receptor agonist, CGS21680. Adenosine, serving as a crucial autocrine factor, acts on the A2A receptor to mitigate the expression of genes regulating chondrocyte hypertrophy, catabolism, and apoptosis. Genome-wide analysis of chondrocytes from the treated obesity-related OA mice or PTOA rats revealed that the liposomal formulations carrying adenosine or CGS21680 curtailed cartilage degradation by downregulating matrix-degrading genes and upregulating those involved in cell proliferation. Similarly, Dravid et al.[124] encapsulated Resolvin D1 within liposomes to modulate inflammation in OA joints. Resolvin D1, prone to rapid clearance or inactivation in the inflammatory joint environment, achieved prolonged joint retention and efficacy at reduced dosages when delivered via liposomes. In obesity-related OA mouse model, Resolvin D1 within liposome administration resulted in lower Osteoarthritis Research Society International (OARSI) scores and diminished cartilage damage, alongside an increase in anti-inflammatory M2 macrophages relative to pro-inflammatory M1 macrophages in the treated groups. In 2023, Zhong et al.[125] developed a meloxicam and calcium acetate-loaded liposome to improve the water solubility of meloxicam, a lipophilic anti-inflammatory drug for temporomandibular joint OA. In a rat model of unilateral anterior crossbite, intra-articular injection of this liposomal concoction improved lubrication in the temporomandibular joint and reduced levels of inflammatory markers, such as prostaglandin E2.

Phospholipid micelles

Phospholipid micelles, nanoscale spheres formed from phospholipids, possess a hydrophobic core surrounded by a hydrophilic shell (**Figure 2**). While liposomes can encapsulate both hydrophobic and hydrophilic drugs, phospholipid micelles are predominantly employed to deliver hydrophobic agents (**Table 2**).[126]

Although polymers are commonly used to create micelles for OA treatment, lipids are also favourable for micelle production. For example, poly(ethylene glycol) (PEG)-distearoylphosphatidylethanolamine is recognised for its high biocompatibility and has received FDA approval, making it a valuable component in developing lipid micelles aimed at OA therapy.[127] In 2021, Wei et al.[128] developed micelles loaded with secretory phospholipase A2 inhibitor using a PEG-distearoylphosphatidylethanolamine-based formulation. Their research demonstrated that these secretory phospholipase A2 inhibitor-loaded micelles reduced MMP-13 and ADAMTS5 expression while increasing aggrecan and collagen type II alpha 1 (COL2A1) levels in treated mouse femoral head explants under IL-1β-induced inflammation. The chondroprotective effect of the secretory phospholipase A2 inhibitor micelles was further validated in both destabilisation of the medial meniscus (DMM) mice and load-induced mouse models of PTOA.

Polymer-based nanoparticles

Polymeric micelles

Polymeric micelles are nanoscopic NPs formed through the self-assembly of amphiphilic block copolymers (**Figure 2**). They offer several advantages over phospholipid micelles, such as enhanced stability, a reduced critical micelle concentration, and the capacity to encapsulate substantial amounts of hydrophobic drugs[129, 130] (**Table 2**). The majority of these micelles are synthesised from diblock copolymers, with PEG often serving as the hydrophilic segment, exemplified by poly(caprolactone)-b-PEG micelles. Typically, the size of these micelles is under 20 nm.[129]

In 2021, Wei et al.[41] pioneered the development of TGFα-conjugated polymeric micelles via a copper-free click chemistry method. Their study highlighted that the overactivation of epidermal growth factor receptor could significantly promote the proliferation and viability of chondroprogenitors, resulting in larger articular cartilage in adolescent conditional overexpression mice. TGFα, as a ligand of epidermal growth factor receptor, thus exhibited considerable promise for

OA therapy. Yet, the quick elimination of this small protein from the synovial fluid following intra-articular injection represented a major obstacle for its therapeutic application. To overcome this, TGFα was introduced onto poly(caprolactone)-b-PEG-based micelles, which markedly slowed OA progression in DMM mice relative to those receiving only free TGFα. Additionally, Kang et al.[131] designed acrylate-based micelles for the controlled release of curcumin, a potent anti-inflammatory and anti-ROS agent. Using a monosodium iodoacetate (MIA)-induced mouse OA model, curcumin-loaded micelles substantially decreased IL-1β and TNFα levels and preserved joint structure and integrity, maintaining proteoglycan, aggrecan, and collagen levels comparable to those in the sham-treated group.

Polymeric micelles can be tailored for targeted delivery to specific joint tissues (**Table 3**).[132-139] For instance, a PEG-based nanoprobe was modified with a cartilage-targeting peptide (DWRVIIPPRPSA) and a ROS-responsive thioketal linker (TKCP), enabling the controlled release of DEX in response to ROS levels in chondrocytes.[132] DEX-TKCP micelles markedly reduced the expression levels of MMP-13, IL-6, and MMP-3, while enhancing the expression of Col2a1, compared to both the control and non-functionalised NPs. Additionally, the therapeutic effectiveness was assessed in MIA-induced OA mice, revealing that DEX-TKCP micelles demonstrated specific cartilage targeting and protective effects, along with extended retention in the joint. In 2020, Urich et al.[133] engineered a polymeric micelle using polyethylene oxide and polypropylene oxide to transport recombinant adeno-associated viral vectors carrying the cartilage-associated Sox9 gene that crucial for chondrogenesis. These NPs were designed to specifically target chondrocytes, aiming to shield them from IL-1β-induced apoptosis and degeneration by overexpressing Sox9, thus potentially restoring metabolic balance in osteoarthritic conditions.[133]

Table 3. Examples of targeted drug delivery of nanomedicines for OA treatment

NP	Cargo	Target	OA model	Major finding	Reference
DWRVIIPPRPSA-modified polymeric micelles	DEX	Articular cartilage	MIA mice	Inhibit the degradation of COLII, superior cartilage targeting property, prolonged retention time	132
Polymeric micelles	rAAV Sox9	Chondrocytes	Human chondrocytes	Sustained Sox9 expression, increased COLII deposition	133
Polyplex	IL-1Rα mRNA	IL-1β in cartilage and synovium	MIA rats	Less loss of cartilage matrix, reduced pain, cartilage loss, and inflammation	134
Polyplex	Periostin-siRNA	Chondrocytes	DMM mice	Reduce OARSI score and subchondral bone sclerosis	135
PEG-PAMAM dendrimer	Kartogenin	MSCs	Papain rats	Increased chondrogenic markers, distinct chondrogenic properties in treated BMSCs	136
PLGA-based PNPs	p66shc siRNA	Chondrocytes	MIA rats	Attenuated ROS, inhibited cartilage damage and inflammation, reduced pain	137
PLGA-based PNPs	p47phox siRNA	Chondrocytes	MIA rats	Attenuated ROS, inhibited cartilage damage and inflammation, reduced pain	138
Hemoglobin-PNPs	Notch-siRNA	Pro-inflammatory macrophage	Papain mice	Reduced pro-inflammatory cytokines and cartilage erosion	139
	ssDNA		Human blood		
Multi-arm Avidin	DEX	Articular cartilage	Bovine cartilage explant	Full penetration of cartilage, increased retention *in vivo*, sustained drug release	140
Chondrocyte affinity peptide-exosomes	CRISPR/Cas9 plasmid	Chondrocytes	DMM rats	Decreased COLII degradation and OARSI score, improved penetration and retention	141
Exosomes	miR-9-5p	MSCs	ACLT rats	Decreased inflammatory factors, improved Mankin score and favoured joint histology	142

Note: ACLT: anterior cruciate ligament transection; AuNP: gold NP; BMSC: bone marrow-derived MSC; COLII: type II collagen; CRISPR/Cas9: clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9; DEX: dexamethasone; DMM: destabilisation of the medial meniscus; IL-1Rα: interleukin-1 receptor antagonist; IL-1β: interleukin-1β; MIA: monosodium iodoacetate; MSC: mesenchymal stem cell; NP: nanoparticle; OA: osteoarthritis; OARSI: osteoarthritis research society international; PAMAM: polyamidoamine; PEG: poly(ethylene glycol); PLGA: poly(lactic-co-glycolic acid); PNP: polymer-based nanoparticle; rAAV: recombinant adeno-associated viral; ROS: reactive oxygen species; siRNA: small interfering RNA; Sox9: SRY-box transcription factor 9; ssDNA: single-stranded DNA.

Polymersomes

Polymersomes are vesicles self-assembled from amphiphilic block copolymers, featuring an aqueous interior surrounded by a hydrophobic membrane (**Figure 2**). Their distinct architecture enables them to serve as versatile carriers for both hydrophilic and hydrophobic drugs.[143] Compared with liposomes, polymersomes typically exhibit greater stability and reduced membrane permeability. Their durability and extensive tunability allow for biological functionalisation (targeting with surface-bound ligands), physical modification (creating responsiveness to pH, light, or temperature), and structural alterations (designing porous or hybrid NPs) (**Table 2**). [144-146]

Various manufacturing techniques, such as thin film hydration, electroformation, and double emulsion, are employed to produce polymersomes.[145] While the application of polymersomes in cancer therapy has been extensively explored,[144] their use in OA treatment is less documented. A recent study by Gui et al.[54] highlighted the potential of polymersomes in OA management by encapsulating SOD within porous polymersomes. This design enables the penetration of ROS into the core and access SOD, yielding an effective antioxidant effects. The SOD-loaded polymersomes demonstrated extended retention in mouse joints, predominantly accumulating in the synovium rather than in the articular cartilage. Subsequent *ex vivo* and *in vivo* evaluations indicated that these SOD-containing polymersomes mitigated oxidative damage and slowed down the progression of OA, as evidenced in a DMM mouse model. These findings underscore the potential of polymersomes as innovative drug delivery systems for OA therapy, suggesting a promising avenue for future research and application.

Polyplexes

To mitigate the undesirable immunological responses elicited by viral-based gene delivery systems, polyplexes have been developed as nanoscale carriers that encapsulate nucleic acids.[147] Typically ranging from 30 to 200 nm in diameter, polyplexes are formed through electrostatic interactions between cationic polymers and negatively charged nucleic acids (**Figure 2**). These non-viral vectors offer enhanced pharmaceutical control, improved safety profiles, and greater scalability in production compared to conventional viral vectors (**Table 2**).[148]

Most polyplexes are designed for targeted gene therapies in the realm of OA (**Table 3**). In 2022, Deng et al.[134] designed a PEGylated polyplex micelle to deliver mRNA that encodes the IL-1 receptor antagonist. This agent competes with IL-1β for IL-1 receptor 1 binding without triggering the receptor's activation. Using a MIA-induced rat OA model, the study demonstrated that the polyplexes curtail the degradation of the cartilage matrix, reduce chondrocyte clustering, and mitigate subchondral bone erosion. Furthermore, they modulated OA-induced inflammation by down-regulating the expression level of IL-6, a proinflammatory cytokine. In 2021, Duan et al.[135] delivered Periostin-siRNA using peptide-nucleotide polyplexes to treat PTOA in mice. Periostin, a matricellular protein, has been observed to elevate during OA progression. In a DMM mouse OA model, Periostin siRNA treatment was shown to decrease MMP-13 expression and significantly lower the OARSI score compared to controls, pointing towards an effective reduction in cartilage degradation. However, no differences were observed in synovitis, suggesting that Periostin primarily influences on cartilage rather than the synovial membrane.

Dendrimers

Dendrimers are tree-like nanoscale carriers constructed from highly branched polymer units.[149] The charge of a dendrimer is predominantly determined by its surface groups, which can be anionic, cationic, or neutral. The size of dendrimer is determined by its generation level,[150] thus allowing precise control over its size, surface charge, and shape through the selection of chemical components and the generation number (**Table 2**). [151]

Polyamidoamine dendrimers stand out as particularly prominent in OA research (**Figure 2**). Geiger et al.[39] developed an IGF-1-conjugated polyamidoamine dendrimer, modifying its surface with PEG to regulate surface charge. This dendrimer was capable of penetrating bovine cartilage to a depth comparable to human cartilage thickness within two days and demonstrated retention in rat knees for up to 30 days. In an ACL transection (ACLT) rat model of OA, a single injection of these IGF-1-dendrimers significantly reduced cartilage degeneration by 60% and osteophyte formation by 80% compared to untreated controls. In 2017, Hu et al.[136] developed MSC-targeted polyamidoamine-PEG dendrimers to deliver kartogenin, aiming to enhance chondrogenic differentiation in MSCs (**Table 3**). The kargogenin-conjugated dendrimers improved the expression of chondrogenic markers such as aggrecan and Sox9 in bone marrow-derived MSCs (BMSCs), showing superior chondrogenic properties compared to those treated with kartogenin alone. Given the ongoing discovery of new pathological pathways associated with OA, dendrimers' versatile functionalisation and targeting capabilities hold promise for the future of OA management and treatment.

Gold NPs

Gold NPs (AuNPs) have been synthesised in various shapes such as nanospheres, nanorods, nanosheets, and nanocages, exploiting their distinct optical properties for applications in biosensing and bioimaging.[152] The high surface-to-volume ratio, adjustable surface chemistry, size tunability, and multi-functionalisation capabilities enable AuNPs as highly efficient drug carriers (**Table 2**). Typically ranging from 0.5 to 25 nm, the size of AuNPs can be tailored for specific research purposes, with several synthetic methods available for their production (**Figure 2**). [153-155]

AuNPs combined with other biomaterials have demonstrated significant potential in OA treatment. Snider et al.[156] designed a porcine diaphragm ECM embedded with AuNPs, curcumin , and HA, which showed promise in reducing cellular oxidative stress and apoptosis in IL-1β-stimulated chondrocytes. In a related study, Filho et al.[157] observed that HA combined with AuNPs substantially reduced pro-inflammatory cytokines and oxidative stress markers in a DMM rat model of OA. Further, Sarkar et al.[158] fabricated a hybrid system by integrating

dipalmitoyl phosphatidylcholine liposomes with AuNPs for delivering fish oil proteins (FP-AuNP-DPPC), demonstrating its efficacy in modulating oxidative stress in an OA context by down-regulating the expression of prooxidant markers, while up-regulating the levels of antioxidant markers. In addition, FP-GNP-DPPC reduced the secretion of serum apoptotic marker nuclear factor-kappa B (NF-κB) and restored the level of catalase, an oxidoreductase. In a recent study, Pitou et al.[159] designed a single-strand DNA (Aptamers)-modified AuNPs to identify OA-related miRNA therapeutic targets. Their research unveiled the potential of miRNA-93 as a novel therapeutic and diagnostic target in OA, showcasing the versatility of AuNPs in gene therapy vectors for OA management.

Avidin

Avidin is a small, cationic glycoprotein isolated from egg white, renowned for its high affinity for biotin (**Figure 2**).[160] Studies have demonstrated that avidin penetrates cartilage more effectively than similarly sized neutral NPs, likely due to its mild electrostatic interactions with the anionic GAGs present in cartilage. This property underscores avidin's viability as a delivery vector for cartilage-targeting therapeutics (**Table 2**).[161]

The adaptability of avidin's chemical and physical properties attributes allows it to transport a variety of drugs. In 2020, He et al.[140] designed multi-arm Avidin NPs, which provided multiple active sites for drug conjugation, facilitating deep penetration into the cartilage (**Table 3**). Using DEX as a model medicine, these avidin NPs demonstrated a controlled and extended release over 2 weeks. Remarkably, a single low dose of the DEX-conjugated avidin NPs significantly suppressed the IL-1α-induced GAG loss, cell death, and inflammatory response in calf explants more effectively than free DEX. Kartogenin, a hydrophobic chondroprotective drug, often shows suboptimal retention and penetration in OA-affected joints when administered directly. The same research group showed that the Avidin-kartogenin NPs modified with 8-arm PEGs rapidly infiltrate into cartilage and achieve prolonged drug release.[162] Using calf knee cartilage explants, a single administration of avidin-kartogenin substantially diminished GAG loss, cell death, and inflammatory response. Collectively, these findings suggest avidin as a promising nanocarrier for drug delivery in OA therapy, offering exceptional biocompatibility and an enhanced penetration profile, which could potentially improve therapeutic outcomes in OA treatment.

Exosomes

Exosomes, which are extracellular vesicles originating from endosomes, typically range from 30 to 150 nm in diameter (**Figure 2**).[163] They are capable of transporting a variety of cargoes, including nucleic acids, proteins, and bioactive lipids. However, their significant heterogeneity in size, content, and source presents challenges for large-scale production (**Table 2**).

Exosomes are usually harvested from MSCs and chondrocytes for OA treatment. Liang et al.[141] developed a chondrocyte-targeting exosome system to carry clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) plasmids for MMP-13 knockdown (**Table 3**). This hybrid exosome approach successfully inhibited the degradation of type II collagen in chondrocytes treated with IL-1β. In DMM rats, this engineered exosome mitigated the degradation of key ECM proteins, including aggrecan and type II collagen. In 2021, Zhou et al.[164] derived exosomes from human BMSCs for anti-inflammatory treatment of OA. These BMSC-derived exosomes were effective in downregulating pro-inflammatory genes such as IL-6 and NF-κB, which were upregulated by IL-1β stimulation, and in restoring the expression of the anti-inflammatory gene TGFβ, which was suppressed by IL-1β. Additionally, Jin et al.[142] highlighted the therapeutic potential of BMSC-derived exosomes enriched with microRNA-9-5p (miR-9-5p) (**Table 3**). Their study revealed that the miR-9-5p-laden exosomes targeted the gene syndecan-1, resulting in decreased inflammatory mediators and markers of oxidative stress injury. Treatment with these exosomes in an ACLT-induced rat OA model led to a healthier joint structure, reduced MMP-13 expression, elevated SOD levels, and diminished inflammatory cell infiltration. These studies underscore the promising utility of exosomes as vehicles for delivering therapeutic agents in OA, potentially mitigating inflammation, oxidative stress, and tissue degradation associated with the disease.

Hybrid drug delivery systems

While NPs offer advantageous features for drug delivery, the field faces challenges like restricted drug loading capacity, premature burst release of drugs, and suboptimal *in vivo* retention.[165] Hydrogels, composed of three-dimensional crosslinked polymer networks, emerge as ideal matrices to host various NPs, enhancing the therapeutic outcomes by providing a stable reservoir for them. The combination of NPs with hydrogel (i.e., NP-hydrogel) can extend drug retention time and modulate drug release kinetics.[166, 167] Particularly, when amalgamated with liposomes, the liposome-hydrogel constructs can continually refresh their hydration layers, effectively preventing the surface erosion of the material.[168]

An exemplary implementation of such hybrid systems is the combination of injectable hydrogels with NPs. In 2022, Zhou et al.[169] developed a HA/platelet-rich plasma hydrogel integrated with bovine serum albumin-MnO_2 nanozymes. This innovative hybrid hydrogel demonstrated the ability to foster chondrocyte proliferation and mitigate severe oxidative stress *in vitro*. Furthermore, in a MIA-induced rat OA model, the nanozyme-enhanced hydrogel significantly mitigated the degeneration of the cartilage matrix, demonstrating the potential of NP-hydrogel systems in advancing OA therapeutics.

To mitigate the uneven injection forces associated with traditional injectable hydrogels, hydrogel microspheres (HMs) are emerging as a promising alternative for hybrid drug delivery systems in OA treatment. In 2022, Lei et al.[168] developed a self-renewable liposomes-HA HMs hybrid system for the delivery of rapamycin, an immunosuppressive drug and autography activator (**Figure 3**). This system demonstrated superior lubrication performance over HMs alone and also

enabled prolonged drug release—up to 28 days compared to just 14 days with liposomes alone. In ACLT OA rats, the rapamycin-liposome-HMs effectively mitigated joint damage by reducing osteophyte formation, narrowing joint space, and preventing the degradation of aggrecan and type II collagen. In the same year, Jin et al.[170] designed a GelMa HMs-liposome hybrid system modified with Arbutin for anti-inflammatory and antioxidant therapy. This system effectively reduced the inflammatory response in IL-1β-stimulated chondrocytes by blocking NF-κB signalling and alleviating oxidative stress through the activation of nuclear factor E2-related factor 2. The Arbutin-liposome-HMs also attenuated OA progression by diminishing inflammation and oxidative stress in the articular cartilage of DMM mice. Moreover, Yu et al.[166] designed ROS-responsive GelMa HMs encapsulating polymeric micelles for DEX delivery. The hybrid nanomedicine was further modified with a type II collagen-targeting peptide WYRGRL to improve cartilage targeting. The results indicated that the DEX-loaded micelle-HMs significantly promote chondrogenic differentiation and reduce the levels of pro-inflammatory cytokines such as IL-6 and TNFα. Overall, although their manufacturing processes can be more complex than those for conventional NPs, hybrid NP-hydrogel systems offer a promising and efficacious strategy to increase drug loading and retention, thereby enhancing therapeutic outcomes in OA treatment.

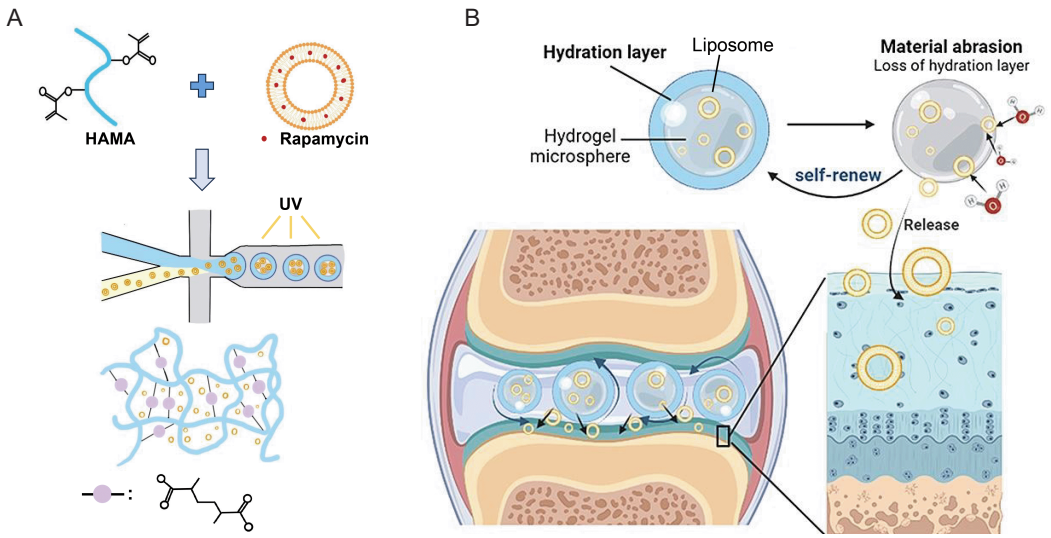

Figure 3. Schematic diagrams illustrating the hybrid liposome-HM system developed by Lei et al.[168] (A) Formation of liposome-HMs. Initial gel droplets containing HAMA and rapamycin-liposomes are generated using a microfluidic device. Subsequently, UV exposure crosslinks the mixture, resulting in the formation of liposome-HMs. (B) Operational mechanism of the liposome-HM: The microgel functions as a reservoir for liposomes, while the liposomes serve as a platform for drug delivery and aid in replenishing the hydration layer of the HM following material abrasion. Created with BioRender.com, Procreate and Microsoft PowerPoint. HAMA: methacrylated hyaluronic acid; HM: hydrogel microsphere; UV: ultraviolet.

Nanoparticles for Diagnosis

Beyond therapeutic interventions, NPs hold substantial promise for OA diagnosis, leveraging their distinctive optical properties and adaptability. AuNPs, in particular, have been extensively investigated for their diagnostic applications in OA. In 2021, Wang et al.[171] developed an AuNP for the immunodetection of type II collagen urinary C-terminal telopeptide fragment, a blood-based biomarker for OA. The system utilised an antibody conjugated to AuNPs, with detection achieved via the immobilised antibody-AuNP complex on an interdigitated electrode. Xu et al.[172] also developed gold nanoclusters coated with a peptide for the detection of proteins with unique sequences associated with OA. The design allowed these materials to interact with OA-specific proteins through electrostatic and hydrophobic interactions, leading to distinctive binding energies and fluorescence lifetimes. OA diagnosis is thereby feasible by identifying unique biomarker 'fingerprints', differentiating serum samples from severe OA patients from those of healthy individuals. In 2018, another diagnostic tool was developed based on a probe consisting of a fluorogenic peptide conjugated to an AuNP for the detection of ADAMTS-4.[173] Comparative tests using synovial fluid from both adult rabbits and human patients demonstrated the probe's ability to detect mild cartilage injuries with 83% sensitivity and 80% specificity. These advancements underscore the potential of NPs, particularly AuNPs, in revolutionising the early detection and diagnosis of OA, paving the way for timely and more effective treatment strategies.

NP-based imaging contrast agents also show promise for OA diagnosis. Recent advancements include the development by Zhang et al.[174] of multi-arm avidin NPs conjugated with anionic ioxaglate, designed for computed tomography imaging (**Figure 4A**). When these NPs were modified with a cartilage-targeting cationic peptide, they demonstrated

rapid penetration through the entire thickness of cartilage within six hours. Impressively, these modified NPs produced a comparable computed tomography signal intensity to anionic ioxaglate alone but at approximately 40 times lower dose, facilitating the clear distinction between cartilage, subchondral bone, and other soft tissues in rat tibial joints at reduced contrast agent concentrations. Moreover, Chen et al.[175] developed cationic melanin NPs coated with poly-L-lysine, which exhibited strong affinity to GAGs in cartilage (**Figure 4B**). This property allows these NPs to be used in photoacoustic imaging for detecting the loss of ECM content in OA joints, offering a novel way to monitor disease progression and ECM degradation.[175] Additionally, iron-based magnetic NPs have gained attention for their biocompatibility and extensive functionalisation possibilities.[176-178] For instance, superparamagnetic iron oxide NPs have been explored as the contrast agents of magnetic resonance imaging (**Figure 4C**).[179] Their ability to enhance image contrast makes them valuable tools for non-invasively studying biological tissues and tracking disease progression, including in OA where early detection and monitoring are crucial for effective management and treatment.

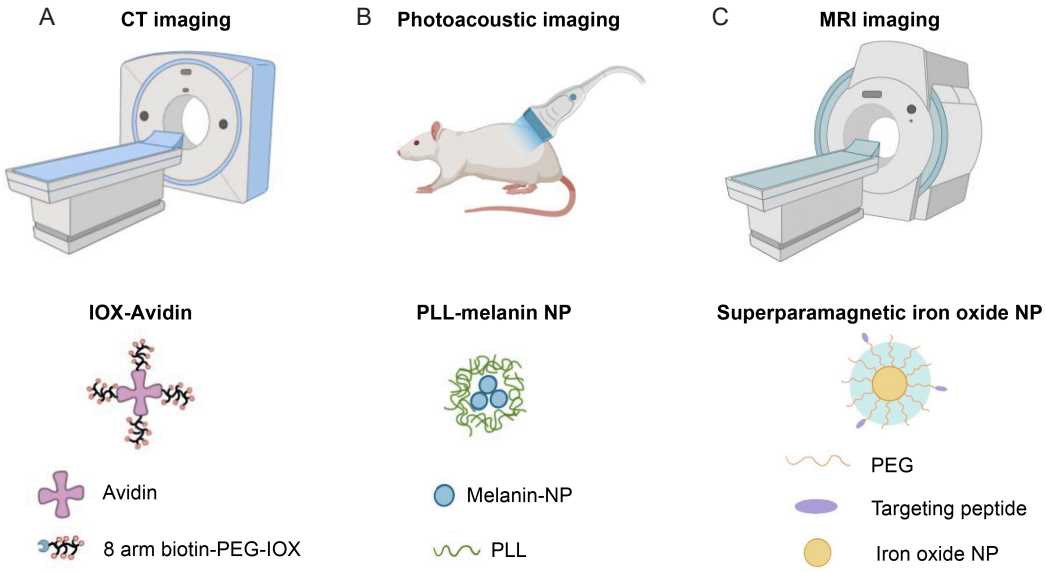

Figure 4. Imaging techniques for OA diagnosis utilizing NPs. (A) CT imaging employing multi-arm avidin NPs conjugated with anionic ioxaglate, developed by Zhang et al.[174] (B) Photoacoustic imaging facilitated by PLL-coated cationic melanin NPs, as devised by Chen et al.[175] (C) MRI employing superparamagnetic iron oxide NPs coated with PEG and cartilage-targeting peptide, engineered by Wu et al.[179] Created with BioRender.com, Procreate and Microsoft PowerPoint. CT: computed tomography; IOX: ioxaglate; MRI: magnetic resonance imaging; NP: nanoparticle; OA: osteoarthritis; PEG: polyethylene glycol; PLL: poly-L-lysine.

Challenges and Future Perspectives

Current OA treatments primarily offer symptomatic relief rather than halting or reversing the disease's progression. Moreover, the effectiveness of many small-molecule drugs is compromised by the altered structure and composition of OA-affected joints. The integration of nanotechnology into OA therapy has markedly enhanced drug performance, including stability, retention, release, and targeted delivery. NPs, made from a variety of materials such as lipids, polymers, metals, peptides, proteins, and extracellular vesicles, can deliver a range of cargos from small molecules to nucleic acids. By functionalising NPs with antibodies or specific targeting peptides, precise drug delivery can also be achieved.

The future direction of NPs in OA management is poised for diversification, particularly towards more complex functionalisation of nanomaterials. An increasing amount of research focuses on immunomodulatory treatments that target M1 and M2 macrophage polarisation.[180, 181] Thus, it is possible for NPs to shift the joint milieu from pro-inflammatory to pro-regenerative by acting on macrophages. Additionally, NPs designed with engineered peptides show promising prospects for clinical adoption, allowing precise therapeutic delivery and the capability to diagnose OA at its early stages simultaneously.[149, 172, 173] Beyond nonsteroidal anti-inflammatory drugs, researchers are delving into enzymes and siRNAs targeting various inflammatory pathways, oxidative stress, cellular apoptosis, and other metabolic activities.[87, 103, 149] Consequently, a trend towards combination therapies that concurrently target multiple pathological processes is emerging. For example, innovative NPs designed to carry multiple agents for both ROS neutralisation and chondroprotection could be developed, representing a holistic approach to managing OA.

Additionally, the next generation of NPs for OA treatment is also aimed for advancements in structural design. Future NP development will likely emphasize environmentally-responsive NPs and biomimetic nanosystems. ROS- and pH-

responsive materials, such as thioketal linkers, NH_4HCO_3, and chitosan, are being integrated into OA nanomedicines to create smart delivery systems that release their payload in response to the OA joint environment.[182]

Despite the progress in biomedical applications of NPs, concerns regarding their toxicity and safety remain paramount. Metal NPs, for example, have been associated with mitochondrial and DNA damage upon cellular uptake.[183-185] Similarly, polymer-based NPs face scrutiny over potential issues related to monomer aggregation, toxic degradation byproducts, and increased oxidative stress, which could impede their path to clinical application.[186] Although there are limited studies systematically evaluating the toxicity profiles of various NPs in OA-specific contexts, strategies like integrating biodegradable hydrogel scaffolds or combining NPs with natural biopolymers such as gelatin or chitosan could enhance biocompatibility. Such approaches may reduce immunogenicity and minimise the long-term toxicity risks associated with current NP formulations, thereby aligning more closely with clinical translation requirements and patient safety standards.

While preclinical studies have underscored the potential of NPs in various animal models, the transition to clinical trials and the availability of NP-based nanomedicines on the market that fulfill clinical needs remain limited. As a multifaceted whole-joint disease, current understanding of OA pathophysiology is still in its early stage. Additionally, prevalent animal models for OA research, primarily those that are surgery- or chemically-induced, cannot mimic the naturally occurring progression of the disease in human. These models, while time-saving, may not ideally represent early-stage OA, as they introduce extraneous variables from surgical or chemical interventions. In terms of NPs, their stability during preparation, storage, and transport can be affected by various environmental conditions, including light exposure and temperature fluctuations.[186, 187] The complexity of manufacturing techniques, coupled with challenges in scalability, positions NPs among the more expensive pharmaceutical developments.[188, 189] During post-administration, issues such as burst release and off-target effects still necessitate further investigation. Moreover, the detailed structure-function relationships of NPs and their interactions with joint tissues remain inadequately understood.[87] Consequently, gaps in our understanding of OA, differences between animal models and human pathology, the absence of standardised manufacturing and administration protocols, and the need for more refined structural designs of NPs could impede their clinical application. Nevertheless, the application of NPs will still extend beyond conventional drug delivery. Gene therapy represents a promising avenue, with NPs designed to deliver genetic material, such as siRNA or CRISPR/Cas9 components, to modulate gene expression in OA-affected cells.[190] Furthermore, regenerative medicine will benefit from NPs engineered to deliver growth factors, cytokines, or stem cells to damaged joints, promoting tissue regeneration and healing.[191] In diagnostics, NPs engineered as contrast agents enhanced with imaging capabilities may also improve the early detection and monitoring of OA, enabling interventions at a stage where the disease is most amenable to treatment.[192, 193]

Author contributions

Conceptualization, resources and supervision: ZC, LQ; literature research and analysis, writing - original draft and figures and tables preparation: QL; writing - review & editing: QL, ZC, LQ; project administration: LQ. All authors approved the final version of the manuscript.

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Conflicts of interest statement

The authors declare no competing interests.

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1. Hunter, D. J.; March, L.; Chew, M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet.* **2020**, *396*, 1711-1712.
2. Quicke, J. G.; Conaghan, P. G.; Corp, N.; Peat, G. Osteoarthritis year in review 2021: epidemiology & therapy. *Osteoarthritis Cartilage.* **2022**, *30*, 196-206.
3. Leifer, V. P.; Katz, J. N.; Losina, E. The burden of OA-health services and economics. *Osteoarthritis Cartilage.* **2022**, *30*, 10-16.
4. Thomas, A. C.; Hubbard-Turner, T.; Wikstrom, E. A.; Palmieri-Smith, R. M. Epidemiology of posttraumatic osteoarthritis. *J Athl Train.* **2017**, *52*, 491-496.
5. Øiestad, B. E.; Engebretsen, L.; Storheim, K.; Risberg, M. A. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med.* **2009**, *37*, 1434-1443.
6. Yao, Q.; Wu, X.; Tao, C.; Gong, W.; Chen, M.; Qu, M.; Zhong, Y.; He, T.; Chen, S.; Xiao, G. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. *Signal Transduct Target Ther.* **2023**, *8*, 56.
7. Hunter, D. J.; McDougall, J. J.; Keefe, F. J. The symptoms of osteoarthritis and the genesis of pain. *Rheum Dis Clin North Am.* **2008**, *34*, 623-643.
8. Deng, S.; Gu, J.; Jiang, Z.; Cao, Y.; Mao, F.; Xue, Y.; Wang, J.; Dai, K.; Qin, L.; Liu, K.; Wu, K.; He, Q.; Cai, K. Application of nanotechnology in the early diagnosis and comprehensive treatment of gastrointestinal cancer. *J Nanobiotechnology.* **2022**, *20*, 415.
9. Landowski, L. M.; Niego, B.; Sutherland, B. A.; Hagemeyer, C. E.; Howells, D. W. Applications of nanotechnology in the diagnosis and therapy of stroke. *Semin Thromb Hemost.* **2020**, *46*, 592-605.
10. Barani, M.; Mukhtar, M.; Rahdar, A.; Sargazi, S.; Pandey, S.; Kang, M. Recent advances in nanotechnology-based diagnosis and treatments of human osteosarcoma. *Biosensors (Basel).* **2021**, *11*, 55.
11. Loeser, R. F.; Goldring, S. R.; Scanzello, C. R.; Goldring, M. B. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum.* **2012**, *64*, 1697-1707.
12. Silva, J. C.; Carvalho, M. S.; Han, X.; Xia, K.; Mikael, P. E.; Cabral, J. M. S.; Ferreira, F. C.; Linhardt, R. J. Compositional and structural analysis of glycosaminoglycans in cell-derived extracellular matrices. *Glycoconj J.*

2019, *36*, 141-154.

13. Danalache, M.; Beutler, K. R.; Rolauffs, B.; Wolfgart, J. M.; Bonnaire, F. C.; Fischer, S.; Greving, I.; Hofmann, U. K. Exploration of changes in spatial chondrocyte organisation in human osteoarthritic cartilage by means of 3D imaging. *Sci Rep.* **2021**, *11*, 9783.
14. Akkiraju, H.; Nohe, A. Role of chondrocytes in cartilage formation, progression of osteoarthritis and cartilage regeneration. *J Dev Biol.* **2015**, *3*, 177-192.
15. Lin, W.; Klein, J. Recent progress in cartilage lubrication. *Adv Mater.* **2021**, *33*, e2005513.
16. Jiang, Y.; Tuan, R. S. Origin and function of cartilage stem/progenitor cells in osteoarthritis. *Nat Rev Rheumatol.* **2015**, *11*, 206-212.
17. Sophia Fox, A. J.; Bedi, A.; Rodeo, S. A. The basic science of articular cartilage: structure, composition, and function. *Sports Health.* **2009**, *1*, 461-468.
18. Gilbert, S. J.; Bonnet, C. S.; Blain, E. J. Mechanical cues: bidirectional reciprocity in the extracellular matrix drives mechano-signalling in articular cartilage. *Int J Mol Sci.* **2021**, *22*, 13595.
19. Primorac, D.; Molnar, V.; Rod, E.; Jeleč, Ž.; Čukelj, F.; Matišić, V.; Vrdoljak, T.; Hudetz, D.; Hajsok, H.; Borić, I. Knee osteoarthritis: a review of pathogenesis and state-of-the-art non-operative therapeutic considerations. *Genes (Basel).* **2020**, *11*, 854.
20. Hossain, M. A.; Adithan, A.; Alam, M. J.; Kopalli, S. R.; Kim, B.; Kang, C. W.; Hwang, K. C.; Kim, J. H. IGF-1 facilitates cartilage reconstruction by regulating PI3K/AKT, MAPK, and NF-kB signaling in rabbit osteoarthritis. *J Inflamm Res.* **2021**, *14*, 3555-3568.
21. Tang, Y.; Hong, F.; Ding, S.; Yang, J.; Zhang, M.; Ma, Y.; Zheng, Q.; Yang, D.; Jin, Y.; Ma, C. METTL3-mediated m(6)A modification of IGFBP7-OT promotes osteoarthritis progression by regulating the DNMT1/DNMT3a-IGFBP7 axis. *Cell Rep.* **2023**, *42*, 112589.
22. Wen, C.; Xu, L.; Xu, X.; Wang, D.; Liang, Y.; Duan, L. Insulin-like growth factor-1 in articular cartilage repair for osteoarthritis treatment. *Arthritis Res Ther.* **2021**, *23*, 277.
23. Yao, X.; Zhang, J.; Jing, X.; Ye, Y.; Guo, J.; Sun, K.; Guo, F. Fibroblast growth factor 18 exerts anti-osteoarthritic effects through PI3K-AKT signaling and mitochondrial fusion and fission. *Pharmacol Res.* **2019**, *139*, 314-324.
24. Lu, H.; Jia, C.; Wu, D.; Jin, H.; Lin, Z.; Pan, J.; Li, X.; Wang, W. Fibroblast growth factor 21 (FGF21) alleviates senescence, apoptosis, and extracellular matrix degradation in osteoarthritis via the SIRT1-mTOR signaling pathway. *Cell Death Dis.* **2021**, *12*, 865.
25. Hurley, M. M.; Coffin, J. D.; Doetschman, T.; Valera, C.; Clarke, K.; Xiao, L. FGF receptor inhibitor BGJ398 partially rescues osteoarthritis-like phenotype in older high molecular weight FGF2 transgenic mice via multiple mechanisms. *Sci Rep.* **2022**, *12*, 15968.
26. Su, W.; Zheng, X.; Zhou, H.; Yang, S.; Zhu, X. Fibroblast growth factor 10 delays the progression of osteoarthritis by attenuating synovial fibrosis via inhibition of IL-6/JAK2/STAT3 signaling in vivo and in vitro. *Mol Immunol.* **2023**, *159*, 46-57.
27. Du, X.; Cai, L.; Xie, J.; Zhou, X. The role of TGF-beta3 in cartilage development and osteoarthritis. *Bone Res.* **2023**, *11*, 2.
28. Zhen, G.; Guo, Q.; Li, Y.; Wu, C.; Zhu, S.; Wang, R.; Guo, X. E.; Kim, B. C.; Huang, J.; Hu, Y.; Dan, Y.; Wan, M.; Ha, T.; An, S.; Cao, X. Mechanical stress determines the configuration of TGFβ activation in articular cartilage. *Nat Commun.* **2021**, *12*, 1706.
29. Jaswal, A. P.; Kumar, B.; Roelofs, A. J.; Iqbal, S. F.; Singh, A. K.; Riemen, A. H. K.; Wang, H.; Ashraf, S.; Nanasaheb, S. V.; Agnihotri, N.; De Bari, C.; Bandyopadhyay, A. BMP signaling: A significant player and therapeutic target for osteoarthritis. *Osteoarthritis Cartilage.* **2023**, *31*, 1454-1468.
30. Luyten, F. P.; Chen, P.; Paralkar, V.; Reddi, A. H. Recombinant bone morphogenetic protein-4, transforming growth factor-beta 1, and activin A enhance the cartilage phenotype of articular chondrocytes in vitro. *Exp Cell Res.* **1994**, *210*, 224-229.
31. Zhou, N.; Li, Q.; Lin, X.; Hu, N.; Liao, J. Y.; Lin, L. B.; Zhao, C.; Hu, Z. M.; Liang, X.; Xu, W.; Chen, H.; Huang, W. BMP2 induces chondrogenic differentiation, osteogenic differentiation and endochondral ossification in stem cells. *Cell Tissue Res.* **2016**, *366*, 101-111.
32. Montaseri, A.; Busch, F.; Mobasheri, A.; Buhrmann, C.; Aldinger, C.; Rad, J. S.; Shakibaei, M. IGF-1 and PDGF-bb suppress IL-1β-induced cartilage degradation through down-regulation of NF-κB signaling: involvement of Src/PI-3K/AKT pathway. *PLoS One.* **2011**, *6*, e28663.
33. Cai, Y.; Wang, Z.; Liao, B.; Sun, Z.; Zhu, P. Anti-inflammatory and chondroprotective effects of platelet-derived growth factor-BB on osteoarthritis rat models. *J Gerontol A Biol Sci Med Sci.* **2023**, *78*, 51-59.
34. Cui, Z.; Wu, H.; Xiao, Y.; Xu, T.; Jia, J.; Lin, H.; Lin, R.; Chen, K.; Lin, Y.; Li, K.; Wu, X.; Li, C.; Yu, B. Endothelial PDGF-BB/PDGFR-β signaling promotes osteoarthritis by enhancing angiogenesis-dependent abnormal subchondral bone formation. *Bone Res.* **2022**, *10*, 58.
35. Appleton, C. T.; Usmani, S. E.; Bernier, S. M.; Aigner, T.; Beier, F. Transforming growth factor alpha suppression of articular chondrocyte phenotype and Sox9 expression in a rat model of osteoarthritis. *Arthritis Rheum.* **2007**, *56*, 3693-3705.
36. Usmani, S. E.; Ulici, V.; Pest, M. A.; Hill, T. L.; Welch, I. D.; Beier, F. Context-specific protection of TGFα null mice from osteoarthritis. *Sci Rep.* **2016**, *6*, 30434.
37. Gui, T.; Wei, Y.; Luo, L.; Li, J.; Zhong, L.; Yao, L.; Beier, F.; Nelson, C. L.; Tsourkas, A.; Liu, X. S.; Enomoto-Iwamoto, M.; Yu, F.; Cheng, Z.; Qin, L. Activating EGFR signaling attenuates osteoarthritis development following loading injury in mice. *J Bone Miner Res.* **2022**, *37*, 2498-2511.
38. Wei, Y.; Ma, X.; Sun, H.; Gui, T.; Li, J.; Yao, L.; Zhong, L.; Yu, W.; Han, B.; Nelson, C. L.; Han, L.; Beier, F.; Enomoto-Iwamoto, M.; Ahn, J.; Qin, L. EGFR signaling is required for maintaining adult cartilage homeostasis and attenuating osteoarthritis progression. *J Bone Miner Res.* **2022**, *37*, 1012-1023.
39. Geiger, B. C.; Wang, S.; Padera, R. F., Jr.; Grodzinsky, A. J.; Hammond, P. T. Cartilage-penetrating nanocarriers improve delivery and efficacy of growth factor treatment of osteoarthritis. *Sci Transl Med.* **2018**, *10*, eaat8800.
40. Loffredo, F. S.; Pancoast, J. R.; Cai, L.; Vannelli, T.; Dong, J. Z.; Lee, R. T.; Patwari, P. Targeted delivery to cartilage is critical for in vivo efficacy of insulin-like growth factor 1 in a rat model of osteoarthritis. *Arthritis Rheumatol.* **2014**, *66*, 1247-1255.
41. Wei, Y.; Luo, L.; Gui, T.; Yu, F.; Yan, L.; Yao, L.; Zhong, L.; Yu, W.; Han, B.; Patel, J. M.; Liu, J. F.; Beier, F.; Levin, L. S.; Nelson, C.; Shao, Z.; Han, L.; Mauck, R. L.; Tsourkas, A.; Ahn, J.; Cheng, Z.; Qin, L. Targeting cartilage EGFR pathway for osteoarthritis treatment. *Sci Transl Med.* **2021**, *13*, eabb3946.
42. Kurowska-Stolarska, M.; Alivernini, S. Synovial tissue macrophages in joint homeostasis, rheumatoid arthritis and disease remission. *Nat Rev Rheumatol.* **2022**, *18*, 384-397.
43. Abu-Hakmeh, A. E.; Fleck, A. K. M.; Wan, L. Q. Temporal effects of cytokine treatment on lubricant synthesis and matrix metalloproteinase activity of fibroblast-like synoviocytes. *J Tissue Eng Regen Med.* **2019**, *13*,

87-98.

44. Huang, Z. Y.; Luo, Z. Y.; Cai, Y. R.; Chou, C. H.; Yao, M. L.; Pei, F. X.; Kraus, V. B.; Zhou, Z. K. Single cell transcriptomics in human osteoarthritis synovium and in silico deconvoluted bulk RNA sequencing. *Osteoarthritis Cartilage.* **2022**, *30*, 475-480.
45. Li, J.; Gui, T.; Yao, L.; Guo, H.; Lin, Y. L.; Lu, J.; Duffy, M.; Zgonis, M.; Mauck, R.; Dyment, N.; Zhang, Y.; Scanzello, C.; Seale, P.; Qin, L. Synovium and infrapatellar fat pad share common mesenchymal progenitors and undergo coordinated changes in osteoarthritis. *J Bone Miner Res.* **2024**. doi: 10.1093/jbmr/zjad009.
46. Tang, S.; Yao, L.; Ruan, J.; Kang, J.; Cao, Y.; Nie, X.; Lan, W.; Zhu, Z.; Han, W.; Liu, Y.; Tian, J.; Seale, P.; Qin, L.; Ding, C. Single-cell atlas of human infrapatellar fat pad and synovium implicates APOE signaling in osteoarthritis pathology. *Sci Transl Med.* **2024**, *16*, eadf4590.
47. Knights, A. J.; Farrell, E. C.; Ellis, O. M.; Song, M. J.; Appleton, C. T.; Maerz, T. Synovial macrophage diversity and activation of M-CSF signaling in post-traumatic osteoarthritis. *bioRxiv.* **2023**, 2023.2010.2003.559514.
48. Cao, M.; Ong, M. T. Y.; Yung, P. S. H.; Tuan, R. S.; Jiang, Y. Role of synovial lymphatic function in osteoarthritis. *Osteoarthritis Cartilage.* **2022**, *30*, 1186-1197.
49. Mathiessen, A.; Conaghan, P. G. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther.* **2017**, *19*, 18.
50. Sanchez-Lopez, E.; Coras, R.; Torres, A.; Lane, N. E.; Guma, M. Synovial inflammation in osteoarthritis progression. *Nat Rev Rheumatol.* **2022**, *18*, 258-275.
51. Lieberthal, J.; Sambamurthy, N.; Scanzello, C. R. Inflammation in joint injury and post-traumatic osteoarthritis. *Osteoarthritis Cartilage.* **2015**, *23*, 1825-1834.
52. Luo, P.; Yuan, Q.; Wan, X.; Yang, M.; Xu, P. Effects of immune cells and cytokines on different cells in OA. *J Inflamm Res.* **2023**, *16*, 2329-2343.
53. Brito, R.; Costa, D.; Dias, C.; Cruz, P.; Barros, P. Chondroitin sulfate supplements for osteoarthritis: a critical review. *Cureus.* **2023**, *15*, e40192.
54. Gui, T.; Luo, L.; Chhay, B.; Zhong, L.; Wei, Y.; Yao, L.; Yu, W.; Li, J.; Nelson, C. L.; Tsourkas, A.; Qin, L.; Cheng, Z. Superoxide dismutase-loaded porous polymersomes as highly efficient antioxidant nanoparticles targeting synovium for osteoarthritis therapy. *Biomaterials.* **2022**, *283*, 121437.
55. Liu, Y.; Hao, R.; Lv, J.; Yuan, J.; Wang, X.; Xu, C.; Ma, D.; Duan, Z.; Zhang, B.; Dai, L.; Cheng, Y.; Lu, W.; Zhang, X. Targeted knockdown of PGAM5 in synovial macrophages efficiently alleviates osteoarthritis. *Bone Res.* **2024**, *12*, 15.
56. Lv, Z.; Xu, X.; Sun, Z.; Yang, Y. X.; Guo, H.; Li, J.; Sun, K.; Wu, R.; Xu, J.; Jiang, Q.; Ikegawa, S.; Shi, D. TRPV1 alleviates osteoarthritis by inhibiting M1 macrophage polarization via Ca(2+)/CaMKII/Nrf2 signaling pathway. *Cell Death Dis.* **2021**, *12*, 504.
57. Zhu, X.; Chan, Y. T.; Yung, P. S. H.; Tuan, R. S.; Jiang, Y. Subchondral bone remodeling: a therapeutic target for osteoarthritis. *Front Cell Dev Biol.* **2020**, *8*, 607764.
58. Hu, Y.; Chen, X.; Wang, S.; Jing, Y.; Su, J. Subchondral bone microenvironment in osteoarthritis and pain. *Bone Res.* **2021**, *9*, 20.
59. Burr, D. B.; Gallant, M. A. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol.* **2012**, *8*, 665-673.
60. Li, G.; Yin, J.; Gao, J.; Cheng, T. S.; Pavlos, N. J.; Zhang, C.; Zheng, M. H. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res Ther.* **2013**, *15*, 223.
61. Bailey, A. J.; Mansell, J. P.; Sims, T. J.; Banse, X. Biochemical and mechanical properties of subchondral bone in osteoarthritis. *Biorheology.* **2004**, *41*, 349-358.
62. Bettica, P.; Cline, G.; Hart, D. J.; Meyer, J.; Spector, T. D. Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. *Arthritis Rheum.* **2002**, *46*, 3178-3184.
63. Funck-Brentano, T.; Cohen-Solal, M. Crosstalk between cartilage and bone: when bone cytokines matter. *Cytokine Growth Factor Rev.* **2011**, *22*, 91-97.
64. Gobbi, A.; Dallo, I.; Frank, R. M.; Bradsell, H.; Saenz, I.; Murrel, W. A review of bone marrow lesions in the arthritic knee and description of a technique for treatment. *J Cartil Jt Preserv.* **2021**, *1*, 100021.
65. Funck-Brentano, T.; Cohen-Solal, M. Subchondral bone and osteoarthritis. *Curr Opin Rheumatol.* **2015**, *27*, 420-426.
66. McDevitt, C. A.; Mukherjee, S.; Kambic, H.; Parker, R. Emerging concepts of the cell biology of the meniscus. *Curr Opin Orthop.* **2002**, *13*, 345-350.
67. Day, B.; Mackenzie, W. G.; Shim, S. S.; Leung, G. The vascular and nerve supply of the human meniscus. *Arthroscopy.* **1985**, *1*, 58-62.
68. Gupta, T.; Zielinska, B.; McHenry, J.; Kadmiel, M.; Haut Donahue, T. L. IL-1 and iNOS gene expression and NO synthesis in the superior region of meniscal explants are dependent on the magnitude of compressive strains. *Osteoarthritis Cartilage.* **2008**, *16*, 1213-1219.
69. Crema, M. D.; Roemer, F. W.; Felson, D. T.; Englund, M.; Wang, K.; Jarraya, M.; Nevitt, M. C.; Marra, M. D.; Torner, J. C.; Lewis, C. E.; Guermazi, A. Factors associated with meniscal extrusion in knees with or at risk for osteoarthritis: the Multicenter Osteoarthritis study. *Radiology.* **2012**, *264*, 494-503.
70. Eymard, F.; Chevalier, X. Inflammation of the infrapatellar fat pad. *Joint Bone Spine.* **2016**, *83*, 389-393.
71. Belluzzi, E.; Stocco, E.; Pozzuoli, A.; Granzotto, M.; Porzionato, A.; Vettor, R.; De Caro, R.; Ruggieri, P.; Ramonda, R.; Rossato, M.; Favero, M.; Macchi, V. Contribution of infrapatellar fat pad and synovial membrane to knee osteoarthritis pain. *Biomed Res Int.* **2019**, *2019*, 6390182.
72. Edama, M.; Otsuki, T.; Yokota, H.; Hirabayashi, R.; Sekine, C.; Maruyama, S.; Kageyama, I. Morphological characteristics of the infrapatellar fat pad. *Sci Rep.* **2022**, *12*, 8923.
73. Schulze-Tanzil, G. Intraarticular ligament degeneration is interrelated with cartilage and bone destruction in osteoarthritis. *Cells.* **2019**, *8*, 990.
74. Binks, D. A.; Bergin, D.; Freemont, A. J.; Hodgson, R. J.; Yonenaga, T.; McGonagle, D.; Radjenovic, A. Potential role of the posterior cruciate ligament synovio-entheseal complex in joint effusion in early osteoarthritis: a magnetic resonance imaging and histological evaluation of cadaveric tissue and data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage.* **2014**, *22*, 1310-1317.
75. Abraham, A. C.; Pauly, H. M.; Donahue, T. L. Deleterious effects of osteoarthritis on the structure and function of the meniscal enthesis. *Osteoarthritis Cartilage.* **2014**, *22*, 275-283.
76. Nakahara, H.; Hasegawa, A.; Otabe, K.; Ayabe, F.; Matsukawa, T.; Onizuka, N.; Ito, Y.; Ozaki, T.; Lotz, M. K.; Asahara, H. Transcription factor Mohawk and the pathogenesis of human anterior cruciate ligament degradation. *Arthritis Rheum.* **2013**, *65*, 2081-2089.
77. Kumagai, K.; Sakai, K.; Kusayama, Y.; Akamatsu, Y.; Sakamaki, K.; Morita, S.; Sasaki, T.; Saito, T.; Sakai, T. The extent of degeneration of cruciate ligament is associated with chondrogenic differentiation in

patients with osteoarthritis of the knee. *Osteoarthritis Cartilage.* **2012**, *20*, 1258-1267.

78. Lorda-Diez, C. I.; Canga-Villegas, A.; Cerezal, L.; Plaza, S.; Hurlé, J. M.; García-Porrero, J. A.; Montero, J. A. Comparative transcriptional analysis of three human ligaments with distinct biomechanical properties. *J Anat.* **2013**, *223*, 593-602.
79. Nagelli, C. V.; Cook, J. L.; Kuroki, K.; Bozynski, C.; Ma, R.; Hewett, T. E. Does anterior cruciate ligament innervation matter for joint function and development of osteoarthritis? *J Knee Surg.* **2017**, *30*, 364-371.
80. Salaffi, F.; Ciapetti, A.; Carotti, M. The sources of pain in osteoarthritis: a pathophysiological review. *Reumatismo.* **2014**, *66*, 57-71.
81. Altman, R. D.; Gold, G. E. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage.* **2007**, *15 Suppl A*, A1-56.
82. Hayashi, D.; Roemer, F. W.; Guermazi, A. Imaging for osteoarthritis. *Ann Phys Rehabil Med.* **2016**, *59*, 161-169.
83. Wang, X.; Oo, W. M.; Linklater, J. M. What is the role of imaging in the clinical diagnosis of osteoarthritis and disease management? *Rheumatology (Oxford).* **2018**, *57*, iv51-iv60.
84. Domb, B. G.; Gui, C.; Lodhia, P. How much arthritis is too much for hip arthroscopy: a systematic review. *Arthroscopy.* **2015**, *31*, 520-529.
85. Gay, C.; Chabaud, A.; Guilley, E.; Coudeyre, E. Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. Systematic literature review. *Ann Phys Rehabil Med.* **2016**, *59*, 174-183.
86. Corbett, M. S.; Rice, S. J.; Madurasinghe, V.; Slack, R.; Fayter, D. A.; Harden, M.; Sutton, A. J.; Macpherson, H.; Woolacott, N. F. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. *Osteoarthritis Cartilage.* **2013**, *21*, 1290-1298.
87. Maudens, P.; Jordan, O.; Allémann, E. Recent advances in intra-articular drug delivery systems for osteoarthritis therapy. *Drug Discov Today.* **2018**, *23*, 1761-1775.
88. Savvidou, O.; Milonaki, M.; Goumenos, S.; Flevas, D.; Papagelopoulos, P.; Moutsatsou, P. Glucocorticoid signaling and osteoarthritis. *Mol Cell Endocrinol.* **2019**, *480*, 153-166.
89. Zhou, J.; Liu, B.; Li, C.; Luo, Y.; Liu, T.; Wang, W. Treatment of hip osteoarthritis with glucocorticoids. *Ann Rheum Dis.* **2019**, *78*, e100.
90. Deyle, G. D.; Allen, C. S.; Allison, S. C.; Gill, N. W.; Hando, B. R.; Petersen, E. J.; Dusenberry, D. I.; Rhon, D. I. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. *N Engl J Med.* **2020**, *382*, 1420-1429.
91. Shep, D.; Khanwelkar, C.; Gade, P.; Karad, S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. *Trials.* **2019**, *20*, 214.
92. Liang, Q.; Ma, Y.; Yao, X.; Wei, W. Advanced 3D-printing bioinks for articular cartilage repair. *Int J Bioprint.* **2022**, *8*, 511.
93. Paget, L. D. A.; Reurink, G.; de Vos, R. J.; Weir, A.; Moen, M. H.; Bierma-Zeinstra, S. M. A.; Stufkens, S. A. S.; Kerkhoffs, G.; Tol, J. L.; PRIMA Study Group. Effect of platelet-rich plasma injections vs placebo on ankle symptoms and function in patients with ankle osteoarthritis: a randomized clinical trial. *JAMA.* **2021**, *326*, 1595-1605.
94. Harrell, C. R.; Markovic, B. S.; Fellabaum, C.; Arsenijevic, A.; Volarevic, V. Mesenchymal stem cell-based therapy of osteoarthritis: current knowledge and future perspectives. *Biomed Pharmacother.* **2019**, *109*, 2318-2326.
95. Frehner, F.; Benthien, J. P. Microfracture: state of the art in cartilage surgery? *Cartilage.* **2018**, *9*, 339-345.
96. Li, M. H.; Xiao, R.; Li, J. B.; Zhu, Q. Regenerative approaches for cartilage repair in the treatment of osteoarthritis. *Osteoarthritis Cartilage.* **2017**, *25*, 1577-1587.
97. Beard, D. J.; Davies, L. J.; Cook, J. A.; MacLennan, G.; Price, A.; Kent, S.; Hudson, J.; Carr, A.; Leal, J.; Campbell, H.; Fitzpatrick, R.; Arden, N.; Murray, D.; Campbell, M. K.; TOPKAT Study Group. The clinical and cost-effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial. *Lancet.* **2019**, *394*, 746-756.
98. Zeng, C.; Wei, J.; Persson, M. S. M.; Sarmanova, A.; Doherty, M.; Xie, D.; Wang, Y.; Li, X.; Li, J.; Long, H.; Lei, G.; Zhang, W. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. *Br J Sports Med.* **2018**, *52*, 642-650.
99. Wei, W.; Ma, Y.; Zhang, X.; Zhou, W.; Wu, H.; Zhang, J.; Lin, J.; Tang, C.; Liao, Y.; Li, C.; Wang, X.; Yao, X.; Koh, Y. W.; Huang, W.; Ouyang, H. Biomimetic joint paint for efficient cartilage repair by simultaneously regulating cartilage degeneration and regeneration in pigs. *ACS Appl Mater Interfaces.* **2021**, *13*, 54801-54816.
100. Xiong, F.; Qin, Z.; Chen, H.; Lan, Q.; Wang, Z.; Lan, N.; Yang, Y.; Zheng, L.; Zhao, J.; Kai, D. pH-responsive and hyaluronic acid-functionalized metal-organic frameworks for therapy of osteoarthritis. *J Nanobiotechnology.* **2020**, *18*, 139.
101. Loo, S. J. Q.; Wong, N. K. Advantages and challenges of stem cell therapy for osteoarthritis (Review). *Biomed Rep.* **2021**, *15*, 67.
102. Ruano-Ravina, A.; Jato Díaz, M. Autologous chondrocyte implantation: a systematic review. *Osteoarthritis Cartilage.* **2006**, *14*, 47-51.
103. Brown, S.; Kumar, S.; Sharma, B. Intra-articular targeting of nanomaterials for the treatment of osteoarthritis. *Acta Biomater.* **2019**, *93*, 239-257.
104. 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.
105. Gerwin, N.; Hops, C.; Lucke, A. Intraarticular drug delivery in osteoarthritis. *Adv Drug Deliv Rev.* **2006**, *58*, 226-242.
106. Buckwalter, J. A.; Mankin, H. J.; Grodzinsky, A. J. Articular cartilage and osteoarthritis. *Instr Course Lect.* **2005**, *54*, 465-480.
107. Nasir, A.; Khan, A.; Li, J.; Naeem, M.; Khalil, A. A. K.; Khan, K.; Qasim, M. Nanotechnology, a tool for diagnostics and treatment of cancer. *Curr Top Med Chem.* **2021**, *21*, 1360-1376.
108. Kamiya, M.; Matsumoto, M.; Yamashita, K.; Izumi, T.; Kawaguchi, M.; Mizukami, S.; Tsurumaru, M.; Mukai, H.; Kawakami, S. Stability study of mRNA-lipid nanoparticles exposed to various conditions based on the evaluation between physicochemical properties and their relation with protein expression ability. *Pharmaceutics.* **2022**, *14*, 2357.
109. Immordino, M. L.; Dosio, F.; Cattel, L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. *Int J Nanomedicine.* **2006**, *1*, 297-315.
110. Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S.; Joo, S. W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: classification, preparation, and applications. *Nanoscale Res Lett.* **2013**, *8*, 102.
111. Torchilin, V. P. Micellar nanocarriers: pharmaceutical perspectives. *Pharm Res.* **2007**, *24*, 1-16.
112. Kedar, U.; Phutane, P.; Shidhaye, S.; Kadam, V. Advances in polymeric micelles for drug delivery and tumor targeting. *Nanomedicine.* **2010**, *6*, 714-729.

113. Kahraman, E.; Güngör, S.; Özsoy, Y. Potential enhancement and targeting strategies of polymeric and lipid-based nanocarriers in dermal drug delivery. *Ther Deliv.* **2017**, *8*, 967-985.
114. Fonseca, M.; Jarak, I.; Victor, F.; Domingues, C.; Veiga, F.; Figueiras, A. Polymersomes as the next attractive generation of drug delivery systems: definition, synthesis and applications. *Materials (Basel).* **2024**, *17*, 319.
115. Discher, D. E.; Eisenberg, A. Polymer vesicles. *Science.* **2002**, *297*, 967-973.
116. Rafael, D.; Andrade, F.; Arranja, A.; Luís, S.; Videira, M. Lipoplexes and polyplexes: gene therapy. In *Encyclopedia of biomedical polymers and polymeric biomaterials, 11 volume set*, Mishra, M., ed. CRC Press: 2015.
117. Milligan, J. J.; Saha, S. A nanoparticle's journey to the tumor: strategies to overcome first-pass metabolism and their limitations. *Cancers (Basel).* **2022**, *14*, 1741.
118. Lamberti, M.; Zappavigna, S.; Sannolo, N.; Porto, S.; Caraglia, M. Advantages and risks of nanotechnologies in cancer patients and occupationally exposed workers. *Expert Opin Drug Deliv.* **2014**, *11*, 1087-1101.
119. Jain, A.; Cheng, K. The principles and applications of avidin-based nanoparticles in drug delivery and diagnosis. *J Control Release.* **2017**, *245*, 27-40.
120. Cheng, L.; Zhang, K.; Wu, S.; Cui, M.; Xu, T. Focus on mesenchymal stem cell-derived exosomes: opportunities and challenges in cell-free therapy. *Stem Cells Int.* **2017**, *2017*, 6305295.
121. de la Torre, P.; Pérez-Lorenzo, M. J.; Alcázar-Garrido, Á.; Flores, A. I. Cell-based nanoparticles delivery systems for targeted cancer therapy: lessons from anti-angiogenesis treatments. *Molecules.* **2020**, *25*, 715.
122. Almeida, B.; Nag, O. K.; Rogers, K. E.; Delehanty, J. B. Recent progress in bioconjugation strategies for liposome-mediated drug delivery. *Molecules.* **2020**, *25*, 5672.
123. Corciulo, C.; Castro, C. M.; Coughlin, T.; Jacob, S.; Li, Z.; Fenyö, D.; Rifkin, D. B.; Kennedy, O. D.; Cronstein, B. N. Intraarticular injection of liposomal adenosine reduces cartilage damage in established murine and rat models of osteoarthritis. *Sci Rep.* **2020**, *10*, 13477.
124. Dravid, A. A.; Dhanabalan, K. M.; Naskar, S.; Vashistha, A.; Agarwal, S.; Padhan, B.; Dewani, M.; Agarwal, R. Sustained release resolvin D1 liposomes are effective in the treatment of osteoarthritis in obese mice. *J Biomed Mater Res A.* **2023**, *111*, 765-777.
125. Zhong, Y.; Zhou, Y.; Ding, R.; Zou, L.; Zhang, H.; Wei, X.; He, D. Intra-articular treatment of temporomandibular joint osteoarthritis by injecting actively-loaded meloxicam liposomes with dual-functions of anti-inflammation and lubrication. *Mater Today Bio.* **2023**, *19*, 100573.
126. Esparza, K.; Jayawardena, D.; Onyuksel, H. Phospholipid micelles for peptide drug delivery. *Methods Mol Biol.* **2019**, *2000*, 43-57.
127. Gill, K. K.; Kaddoumi, A.; Nazzal, S. PEG-lipid micelles as drug carriers: physiochemical attributes, formulation principles and biological implication. *J Drug Target.* **2015**, *23*, 222-231.
128. Wei, Y.; Yan, L.; Luo, L.; Gui, T.; Jang, B.; Amirshaghaghi, A.; You, T.; Tsourkas, A.; Qin, L.; Cheng, Z. Phospholipase A(2) inhibitor-loaded micellar nanoparticles attenuate inflammation and mitigate osteoarthritis progression. *Sci Adv.* **2021**, *7*, eabe6374.
129. Perumal, S.; Atchudan, R.; Lee, W. A review of polymeric micelles and their applications. *Polymers (Basel).* **2022**, *14*, 2510.
130. Kotta, S.; Aldawsari, H. M.; Badr-Eldin, S. M.; Nair, A. B.; Yt, K. Progress in polymeric micelles for drug delivery applications. *Pharmaceutics.* **2022**, *14*, 1636.
131. Kang, C.; Jung, E.; Hyeon, H.; Seon, S.; Lee, D. Acid-activatable polymeric curcumin nanoparticles as therapeutic agents for osteoarthritis. *Nanomedicine.* **2020**, *23*, 102104.
132. Shen, C.; Gao, M.; Chen, H.; Zhan, Y.; Lan, Q.; Li, Z.; Xiong, W.; Qin, Z.; Zheng, L.; Zhao, J. Reactive oxygen species (ROS)-responsive nanoprobe for bioimaging and targeting therapy of osteoarthritis. *J Nanobiotechnology.* **2021**, *19*, 395.
133. Urich, J.; Cucchiarini, M.; Rey-Rico, A. Therapeutic delivery of rAAV sox9 via polymeric micelles counteracts the effects of osteoarthritis-associated inflammatory cytokines in human articular chondrocytes. *Nanomaterials (Basel).* **2020**, *10*, 1238.
134. Deng, J.; Fukushima, Y.; Nozaki, K.; Nakanishi, H.; Yada, E.; Terai, Y.; Fueki, K.; Itaka, K. Anti-inflammatory therapy for temporomandibular joint osteoarthritis using mrna medicine encoding interleukin-1 receptor antagonist. *Pharmaceutics.* **2022**, *14*, 1785.
135. Duan, X.; Cai, L.; Pham, C. T. N.; Abu-Amer, Y.; Pan, H.; Brophy, R. H.; Wickline, S. A.; Rai, M. F. Amelioration of posttraumatic osteoarthritis in mice using intraarticular silencing of periostin via nanoparticle-based small interfering RNA. *Arthritis Rheumatol.* **2021**, *73*, 2249-2260.
136. Hu, Q.; Ding, B.; Yan, X.; Peng, L.; Duan, J.; Yang, S.; Cheng, L.; Chen, D. Polyethylene glycol modified PAMAM dendrimer delivery of kartogenin to induce chondrogenic differentiation of mesenchymal stem cells. *Nanomedicine.* **2017**, *13*, 2189-2198.
137. Shin, H. J.; Park, H.; Shin, N.; Shin, J.; Gwon, D. H.; Kwon, H. H.; Yin, Y.; Hwang, J. A.; Hong, J.; Heo, J. Y.; Kim, C. S.; Joo, Y.; Kim, Y.; Kim, J.; Beom, J.; Kim, D. W. p66shc siRNA nanoparticles ameliorate chondrocytic mitochondrial dysfunction in osteoarthritis. *Int J Nanomedicine.* **2020**, *15*, 2379-2390.
138. Shin, H. J.; Park, H.; Shin, N.; Kwon, H. H.; Yin, Y.; Hwang, J. A.; Kim, S. I.; Kim, S. R.; Kim, S.; Joo, Y.; Kim, Y.; Kim, J.; Beom, J.; Kim, D. W. p47phox siRNA-loaded PLGA nanoparticles suppress ROS/oxidative stress-induced chondrocyte damage in osteoarthritis. *Polymers (Basel).* **2020**, *12*, 443.
139. Chen, X.; Liu, Y.; Wen, Y.; Yu, Q.; Liu, J.; Zhao, Y.; Liu, J.; Ye, G. A photothermal-triggered nitric oxide nanogenerator combined with siRNA for precise therapy of osteoarthritis by suppressing macrophage inflammation. *Nanoscale.* **2019**, *11*, 6693-6709.
140. He, T.; Zhang, C.; Vedadghavami, A.; Mehta, S.; Clark, H. A.; Porter, R. M.; Bajpayee, A. G. Multi-arm Avidin nano-construct for intra-cartilage delivery of small molecule drugs. *J Control Release.* **2020**, *318*, 109-123.
141. Liang, Y.; Xu, X.; Xu, L.; Iqbal, Z.; Ouyang, K.; Zhang, H.; Wen, C.; Duan, L.; Xia, J. Chondrocyte-specific genomic editing enabled by hybrid exosomes for osteoarthritis treatment. *Theranostics.* **2022**, *12*, 4866-4878.
142. Jin, Z.; Ren, J.; Qi, S. Exosomal miR-9-5p secreted by bone marrow-derived mesenchymal stem cells alleviates osteoarthritis by inhibiting syndecan-1. *Cell Tissue Res.* **2020**, *381*, 99-114.
143. Meng, F.; Zhong, Z. Polymersomes spanning from nano- to microscales: advanced vehicles for controlled drug delivery and robust vesicles for virus and cell mimicking. *J Phys Chem Lett.* **2011**, *2*, 1533-1539.
144. Sharma, A. K.; Prasher, P.; Aljabali, A. A.; Mishra, V.; Gandhi, H.; Kumar, S.; Mutalik, S.; Chellappan, D. K.; Tambuwala, M. M.; Dua, K.; Kapoor, D. N. Emerging era of "somes": polymersomes as versatile drug delivery carrier for cancer diagnostics and therapy. *Drug Deliv Transl Res.* **2020**, *10*, 1171-1190.
145. Singh, K.; Biharee, A.; Vyas, A.; Thareja, S.; Jain, A. K. Recent

advancement of polymersomes as drug delivery carrier. *Curr Pharm Des.* **2022**, *28*, 1621-1631.

146. Lee, J. S.; Feijen, J. Polymersomes for drug delivery: design, formation and characterization. *J Control Release.* **2012**, *161*, 473-483.
147. Jackson, D. A.; Juranek, S.; Lipps, H. J. Designing nonviral vectors for efficient gene transfer and long-term gene expression. *Mol Ther.* **2006**, *14*, 613-626.
148. Fernandez, C. A.; Rice, K. G. Engineered nanoscaled polyplex gene delivery systems. *Mol Pharm.* **2009**, *6*, 1277-1289.
149. Jin, G. Z. Current nanoparticle-based technologies for osteoarthritis therapy. *Nanomaterials (Basel).* **2020**, *10*, 2368.
150. Yousefi, M.; Narmani, A.; Jafari, S. M. Dendrimers as efficient nanocarriers for the protection and delivery of bioactive phytochemicals. *Adv Colloid Interface Sci.* **2020**, *278*, 102125.
151. Chis, A. A.; Dobrea, C.; Morgovan, C.; Arseniu, A. M.; Rus, L. L.; Butuca, A.; Juncan, A. M.; Totan, M.; Vonica-Tincu, A. L.; Cormos, G.; Muntean, A. C.; Muresan, M. L.; Gligor, F. G.; Frum, A. Applications and limitations of dendrimers in biomedicine. *Molecules.* **2020**, *25*, 3982.
152. Hu, X.; Zhang, Y.; Ding, T.; Liu, J.; Zhao, H. Multifunctional gold nanoparticles: a novel nanomaterial for various medical applications and biological activities. *Front Bioeng Biotechnol.* **2020**, *8*, 990.
153. Contini, C.; Hindley, J. W.; Macdonald, T. J.; Barritt, J. D.; Ces, O.; Quirke, N. Size dependency of gold nanoparticles interacting with model membranes. *Commun Chem.* **2020**, *3*, 130.
154. Singh, P.; Pandit, S.; Mokkapati, V.; Garg, A.; Ravikumar, V.; Mijakovic, I. Gold nanoparticles in diagnostics and therapeutics for human cancer. *Int J Mol Sci.* **2018**, *19*, 1979.
155. Fan, J.; Cheng, Y.; Sun, M. Functionalized gold nanoparticles: synthesis, properties and biomedical applications. *Chem Rec.* **2020**, *20*, 1474-1504.
156. Snider, C.; Grant, D.; Grant, S. A. Investigation of an injectable gold nanoparticle extracellular matrix. *J Biomater Appl.* **2022**, *36*, 1289-1300.
157. Filho, M. C. B.; Dos Santos Haupenthal, D. P.; Zaccaron, R. P.; de Bem Silveira, G.; de Roch Casagrande, L.; Lupselo, F. S.; Alves, N.; de Sousa Mariano, S.; do Bomfim, F. R. C.; de Andrade, T. A. M.; Machado-de-Ávila, R. A.; Silveira, P. C. L. Intra-articular treatment with hyaluronic acid associated with gold nanoparticles in a mechanical osteoarthritis model in Wistar rats. *J Orthop Res.* **2021**, *39*, 2546-2555.
158. Sarkar, A.; Carvalho, E.; D'Souza A, A.; Banerjee, R. Liposome-encapsulated fish oil protein-tagged gold nanoparticles for intra-articular therapy in osteoarthritis. *Nanomedicine (Lond).* **2019**, *14*, 871-887.
159. Pitou, M.; Papi, R. M.; Tzavellas, A. N.; Choli-Papadopoulou, T. ssDNA-modified gold nanoparticles as a tool to detect miRNA biomarkers in osteoarthritis. *ACS Omega.* **2023**, *8*, 7529-7535.
160. Livnah, O.; Bayer, E. A.; Wilchek, M.; Sussman, J. L. Three-dimensional structures of avidin and the avidin-biotin complex. *Proc Natl Acad Sci U S A.* **1993**, *90*, 5076-5080.
161. Bajpayee, A. G.; Wong, C. R.; Bawendi, M. G.; Frank, E. H.; Grodzinsky, A. J. Avidin as a model for charge driven transport into cartilage and drug delivery for treating early stage post-traumatic osteoarthritis. *Biomaterials.* **2014**, *35*, 538-549.
162. He, T.; Shaw, I.; Vedadghavami, A.; Bajpayee, A. G. Single-dose intra-cartilage delivery of kartogenin using a cationic multi-arm avidin nanocarrier suppresses cytokine-induced osteoarthritis-related catabolism. *Cartilage.* **2022**, *13*, 19476035221093072.
163. Doyle, L. M.; Wang, M. Z. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. *Cells.* **2019**, *8*, 727.
164. Zhou, L.; Ye, H.; Liu, L.; Chen, Y. Human bone mesenchymal stem cell-derived exosomes inhibit IL-1β-induced inflammation in osteoarthritis chondrocytes. *Cell J.* **2021**, *23*, 485-494.
165. Adepu, S.; Ramakrishna, S. Controlled drug delivery systems: current status and future directions. *Molecules.* **2021**, *26*, 5905.
166. Yu, H.; Huang, C.; Kong, X.; Ma, J.; Ren, P.; Chen, J.; Zhang, X.; Luo, H.; Chen, G. Nanoarchitectonics of cartilage-targeting hydrogel microspheres with reactive oxygen species responsiveness for the repair of osteoarthritis. *ACS Appl Mater Interfaces.* **2022**, *14*, 40711-40723.
167. Zhang, Y. S.; Khademhosseini, A. Advances in engineering hydrogels. *Science.* **2017**, *356*, eaaf3627.
168. Lei, Y.; Wang, Y.; Shen, J.; Cai, Z.; Zhao, C.; Chen, H.; Luo, X.; Hu, N.; Cui, W.; Huang, W. Injectable hydrogel microspheres with self-renewable hydration layers alleviate osteoarthritis. *Sci Adv.* **2022**, *8*, eabl6449.
169. Zhou, T.; Ran, J.; Xu, P.; Shen, L.; He, Y.; Ye, J.; Wu, L.; Gao, C. A hyaluronic acid/platelet-rich plasma hydrogel containing MnO(2) nanozymes efficiently alleviates osteoarthritis in vivo. *Carbohydr Polym.* **2022**, *292*, 119667.
170. Jin, J.; Liu, Y.; Jiang, C.; Shen, Y.; Chu, G.; Liu, C.; Jiang, L.; Huang, G.; Qin, Y.; Zhang, Y.; Zhang, C.; Wang, Y. Arbutin-modified microspheres prevent osteoarthritis progression by mobilizing local anti-inflammatory and antioxidant responses. *Mater Today Bio.* **2022**, *16*, 100370.
171. Wang, S.; Su, S.; Yu, C.; Gopinath, S. C. B.; Yang, Z. Immunodetection of urinary C-terminal telopeptide fragment of type II collagen: An osteoarthritis biomarker analysis. *Biotechnol Appl Biochem.* **2021**, *68*, 726-731.
172. Xu, S.; Li, W.; Zhao, X.; Wu, T.; Cui, Y.; Fan, X.; Wang, W.; Luo, X. Ultrahighly efficient and stable fluorescent gold nanoclusters coated with screened peptides of unique sequences for effective protein and serum discrimination. *Anal Chem.* **2019**, *91*, 13947-13952.
173. Liu, Z.; Hu, X.; Yang, P.; Zhang, J.; Zhou, C.; Ao, Y. Diagnostic utility of fluorogenic peptide-conjugated Au nanoparticle probe corroborated by rabbit model of mild cartilage injury and panel of osteoarthritic patients. *Am J Transl Res.* **2018**, *10*, 2277-2289.
174. Zhang, C.; Vedadghavami, A.; He, T.; Charles, J. F.; Bajpayee, A. G. Cationic carrier mediated delivery of anionic contrast agents in low doses enable enhanced computed tomography imaging of cartilage for early osteoarthritis diagnosis. *ACS Nano.* **2023**, *17*, 6649-6663.
175. Chen, L.; Ji, Y.; Hu, X.; Cui, C.; Liu, H.; Tang, Y.; Qi, B.; Niu, Y.; Hu, X.; Yu, A.; Fan, Q. Cationic poly-l-lysine-encapsulated melanin nanoparticles as efficient photoacoustic agents targeting to glycosaminoglycans for the early diagnosis of articular cartilage degeneration in osteoarthritis. *Nanoscale.* **2018**, *10*, 13471-13484.
176. Rahman, M. Magnetic resonance imaging and iron-oxide nanoparticles in the era of personalized medicine. *Nanotheranostics.* **2023**, *7*, 424-449.
177. Jin, R.; Lin, B.; Li, D.; Ai, H. Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: design considerations and clinical applications. *Curr Opin Pharmacol.* **2014**, *18*, 18-27.
178. Mohammadinejad, R.; Ashrafizadeh, M.; Pardakhty, A.; Uzieliene, I.; Denkovskij, J.; Bernotiene, E.; Janssen, L.; Lorite, G. S.; Saarakkala, S.; Mobasheri, A. Nanotechnological strategies for osteoarthritis diagnosis, monitoring, clinical management, and regenerative medicine: recent advances and future opportunities. *Curr Rheumatol Rep.* **2020**, *22*, 12.
179. Wu, J.; Wu, C.; Cai, Z.; Gu, H.; Liu, L.; Xia, C.; Lui, S.; Gong, Q.; Song, B.; Ai, H. Ultra-small superparamagnetic iron oxide nanoparticles for intra-articular targeting of cartilage in early osteoarthritis. *Regen*

Biomater. **2023**, *10*, rbad052.

180. Bolander, J.; Moviglia Brandolina, M. T.; Poehling, G.; Jochl, O.; Parsons, E.; Vaughan, W.; Moviglia, G.; Atala, A. The synovial environment steers cartilage deterioration and regeneration. *Sci Adv.* **2023**, *9*, eade4645.
181. Zeng, J.; Huang, L.; Xiong, H.; Li, Q.; Wu, C.; Huang, Y.; Xie, H.; Shen, B. Injectable decellularized cartilage matrix hydrogel encapsulating urine-derived stem cells for immunomodulatory and cartilage defect regeneration. *NPJ Regen Med.* **2022**, *7*, 75.
182. Jin, T.; Wu, D.; Liu, X. M.; Xu, J. T.; Ma, B. J.; Ji, Y.; Jin, Y. Y.; Wu, S. Y.; Wu, T.; Ma, K. Intra-articular delivery of celastrol by hollow mesoporous silica nanoparticles for pH-sensitive anti-inflammatory therapy against knee osteoarthritis. *J Nanobiotechnology.* **2020**, *18*, 94.
183. Xiong, P.; Huang, X.; Ye, N.; Lu, Q.; Zhang, G.; Peng, S.; Wang, H.; Liu, Y. Cytotoxicity of metal-based nanoparticles: from mechanisms and methods of evaluation to pathological manifestations. *Adv Sci (Weinh).* **2022**, *9*, e2106049.
184. Buchman, J. T.; Hudson-Smith, N. V.; Landy, K. M.; Haynes, C. L. Understanding nanoparticle toxicity mechanisms to inform redesign strategies to reduce environmental impact. *Acc Chem Res.* **2019**, *52*, 1632-1642.
185. Bhargava, A.; Dev, A.; Mohanbhai, S. J.; Pareek, V.; Jain, N.; Choudhury, S. R.; Panwar, J.; Karmakar, S. Pre-coating of protein modulate patterns of corona formation, physiological stability and cytotoxicity of silver nanoparticles. *Sci Total Environ.* **2021**, *772*, 144797.
186. Elmowafy, M.; Shalaby, K.; Elkomy, M. H.; Alsaidan, O. A.; Gomaa, H. A. M.; Abdelgawad, M. A.; Mostafa, E. M. Polymeric nanoparticles for delivery of natural bioactive agents: recent advances and challenges. *Polymers (Basel).* **2023**, *15*, 1123.
187. Chen, X.; Chen, Y.; Zou, L.; Zhang, X.; Dong, Y.; Tang, J.; McClements, D. J.; Liu, W. Plant-based nanoparticles prepared from proteins and phospholipids consisting of a core-multilayer-shell structure: fabrication, stability, and foamability. *J Agric Food Chem.* **2019**, *67*, 6574-6584.
188. Joseph, T. M.; Kar Mahapatra, D.; Esmaeili, A.; Piszczyk, Ł.; Hasanin, M. S.; Kattali, M.; Haponiuk, J.; Thomas, S. Nanoparticles: taking a unique position in medicine. *Nanomaterials (Basel).* **2023**, *13*, 574.
189. Huang, Y.; Guo, X.; Wu, Y.; Chen, X.; Feng, L.; Xie, N.; Shen, G. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. *Signal Transduct Target Ther.* **2024**, *9*, 34.
190. Li, X.; Shen, L.; Deng, Z.; Huang, Z. New treatment for osteoarthritis: Gene therapy. *Precis Clin Med.* **2023**, *6*, pbad014.
191. Umer, A.; Ghouri, M. D.; Muyizere, T.; Aqib, R. M.; Muhaymin, A.; Cai, R.; Chen, C. Engineered nano-bio interfaces for stem cell therapy. *Precis Chem.* **2023**, *1*, 341-356.
192. Han, X.; Xu, K.; Taratula, O.; Farsad, K. Applications of nanoparticles in biomedical imaging. *Nanoscale.* **2019**, *11*, 799-819.
193. Oei, E. H. G.; Runhaar, J. Imaging of early-stage osteoarthritis: the needs and challenges for diagnosis and classification. *Skeletal Radiol.* **2023**, *52*, 2031-2036.

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Corrigendum

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In the article titled "Enhanced angiogenesis in porous poly(ε-caprolactone) scaffolds fortified with methacrylated hyaluronic acid hydrogel after subcutaneous transplantation", published on pages 59-68, Issue 1, Volume 5 of *Biomaterials Translational*,[1] affiliation 2 was written incorrectly. The correct author affiliation is as follows: "Center for Pluripotent Stem Cell Research and Engineering, Research Institute of Tsinghua, Pearl River Delta, Guangzhou, Guangdong Province, China".

Reference

1. Yang, H.; Zheng, M.; Zhang, Y.; Li, C.; Lai, J. H. C.; Zhang, Q.; WY Chan, K.; Wang, H.; Zhao, X.; Yang, Z.; Xu, C. Enhanced angiogenesis in porous poly(ε-caprolactone) scaffolds fortified with methacrylated hyaluronic acid hydrogel after subcutaneous transplantation. *Biomater Transl*. **2024**, *5*, 59-68.