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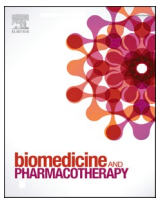

Review

Harnessing the multifunctionality of lipid-based drug delivery systems for the local treatment of osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a widespread joint condition affecting millions globally, presenting a growing socioeconomic burden thus making the development of more effective therapeutic strategies crucial. This review emphasizes recent advancements in lipid-based drug delivery systems (DDSs) for intra-articular administration of OA therapeutics, encompassing non-steroidal anti-inflammatory drugs, corticosteroids, small molecule disease-modifying OA drugs, and RNA therapeutics. Liposomes, lipid nanoparticles, lipidic mesophases, extracellular vesicles and composite systems exhibit enhanced stability, targeted delivery, and extended joint retention, which contribute to improved therapeutic outcomes and minimized systemic drug exposure. Although active targeting strategies hold promise, further research is needed to assess their targeting efficiency in physiologically relevant conditions. Simultaneously, multifunctional DDSs capable of delivering combinations of distinct therapeutic classes offer synergistic effects and superior OA treatment outcomes. The development of such long-acting systems that resist rapid clearance from the joint space is crucial, where particle size and targeting capabilities emerge as vital factors. Additionally, combining cartilage lubrication properties with sustained drug delivery has demonstrated potential in animal models, meriting further investigation in human clinical trials. This review highlights the crucial need for direct, head-to-head comparisons of novel DDSs with standard treatments, particularly within the same drug class. These comparisons are essential in accurately evaluating their effectiveness, safety, and clinical applicability, and are set to significantly shape the future of OA therapy.

1. Introduction

Osteoarthritis (OA) is a widespread, long-lasting joint condition affecting over 590 million people globally [1]. The rapid growth in its prevalence in recent years can be largely attributed to factors such as increased life expectancy and escalating body weight [2–4]. According to the Global Burden of Disease study 2021, there was a 134 % surge in OA total cases between 1990 and 2020 [1,4–6]. By 2020, the highest age-standardized prevalence of OA was reported in high-income Asia Pacific, high-income North America and Eastern Europe, with the highest age-standardized prevalence in the USA, with a prevalence greater among women (2020 global age-standardised prevalence of 8059 per 100 000) [1]. The economic burden of OA is substantial and growing, with OA-related medical costs reaching $460 billion globally in 2019 [7]. Patients with OA face medical costs that are four times greater than those without the condition [8]. Additional indirect expenses, such as job loss and premature retirement, further contribute to the economic burden [4]. OA has emerged as a leading cause of global disability, listed among the top 10 leading causes of years lived with disability (YLD) for adults aged 70 years and older, presenting significant healthcare and socioeconomic challenges [9]. If no policy decisions are taken and implemented globally, it is estimated that almost 1 billion individuals will experience some form of OA by 2050 [1].

Risk factors for OA include obesity and metabolic diseases, gender, age, knee injuries, and participation in high-impact sports, bone deformities, genetics [10–12]. Ageing is considered the most significant risk factor, as age-related biological and molecular changes can disrupt joint structures and contribute to OA development [4,12]. Obesity is another major risk factor, as excess weight increases mechanical stress on joints, leading to cartilage and ligament damage [13,14]. In addition, low-grade systemic inflammation caused by obesity and metabolic diseases is also implicated, involving the role of cytokines called adipokines

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released by metabolically abnormal adipose tissue [15].

1.1. OA pathology

Complying with the call for a standardized definition of OA by the OA Research Society International (OARSI), OA can be defined as a "disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness" [16]. Its pathogenesis includes mechanical, inflammatory, fibrotic and metabolic factors, ultimately culminating in joint failure [17,18]. Rather than being a mere passive degenerative disease, OA is an active process that arises from an imbalance between joint tissue repair and destruction[17].

As the disease progresses, alterations in the composition of cartilage can cause erosion and heighten its susceptibility to mechanical disruption [12]. This leads to chondrocytes to generate matrix degradation products and proinflammatory mediators, which are the body's attempt to repair the eroded cartilage, as is illustrated in Fig. 1. Despite being the only cell type within the articular cartilage, chondrocytes possess an endogenous heterogeneity and are present in several subtypes exerting different functions – as proven by single-cell RNA-seq analysis [19] – among which generating matrix degradation products stimulate proliferative and proinflammatory responses in the adjacent synovial macrophages, which reside inside the synovial membrane. Activated macrophages start secreting proinflammatory cytokines, such as IL1β, IL6, and TNFα, as well as profibrotic TGFβ [17,20,21]. This leads to the activation of another cell type that resides within the synovial membrane – the synovial fibroblasts (SFs). SFs are key drivers of synovial fibrosis, which is manifested by excessive extracellular matrix (ECM) deposition and is associated with joint stiffness and chronic pain in OA patients [18]. In addition to proinflammatory and profibrotic mediators, the activation of SFs is also strongly correlated with the presence of cartilage wear particles that are formed during cartilage erosion [22,23]. The formation of these particles is closely linked to the increased roughness of the cartilage surface in OA, which results in increased friction elevating the mechanical wear. Healthy joints are lubricated by natural biolubricants, including proteoglycan 4, phospholipids, chondroitin sulphate, and hyaluronan, preventing cartilage wear. However, in OA, diminished levels of these biolubricants impair synovial fluid lubrication, leading to increased friction and cartilage degradation [24–26]. Moreover, the remodelling of the subchondral bone, involving heightened bone turnover and vascular invasion into the cartilage, is associated with the development of bone marrow lesions. These lesions are associated with increased severity of the disease and joint pain. Similarly, the formation of osteophytes, or bone spurs at the joint margins, is strongly influenced by inflammatory factors and abnormal joint movement and contributes to the disease's impact [17,27].

To summarize, OA is a multifaceted disease with varying underlying mechanisms that ultimately result in joint damage. It can be seen as a syndrome rather than a single disease, where different risk factors associated with OA can initiate different pathways leading to the pathology. This means that the factors that cause OA in older adults may be different from those that cause it in younger adults who have suffered a joint injury or in individuals who are obese [17]. While a standardized classification of the multiple OA subtypes has not been achieved yet, OA clinical research and practice has acknowledged as compelling the need

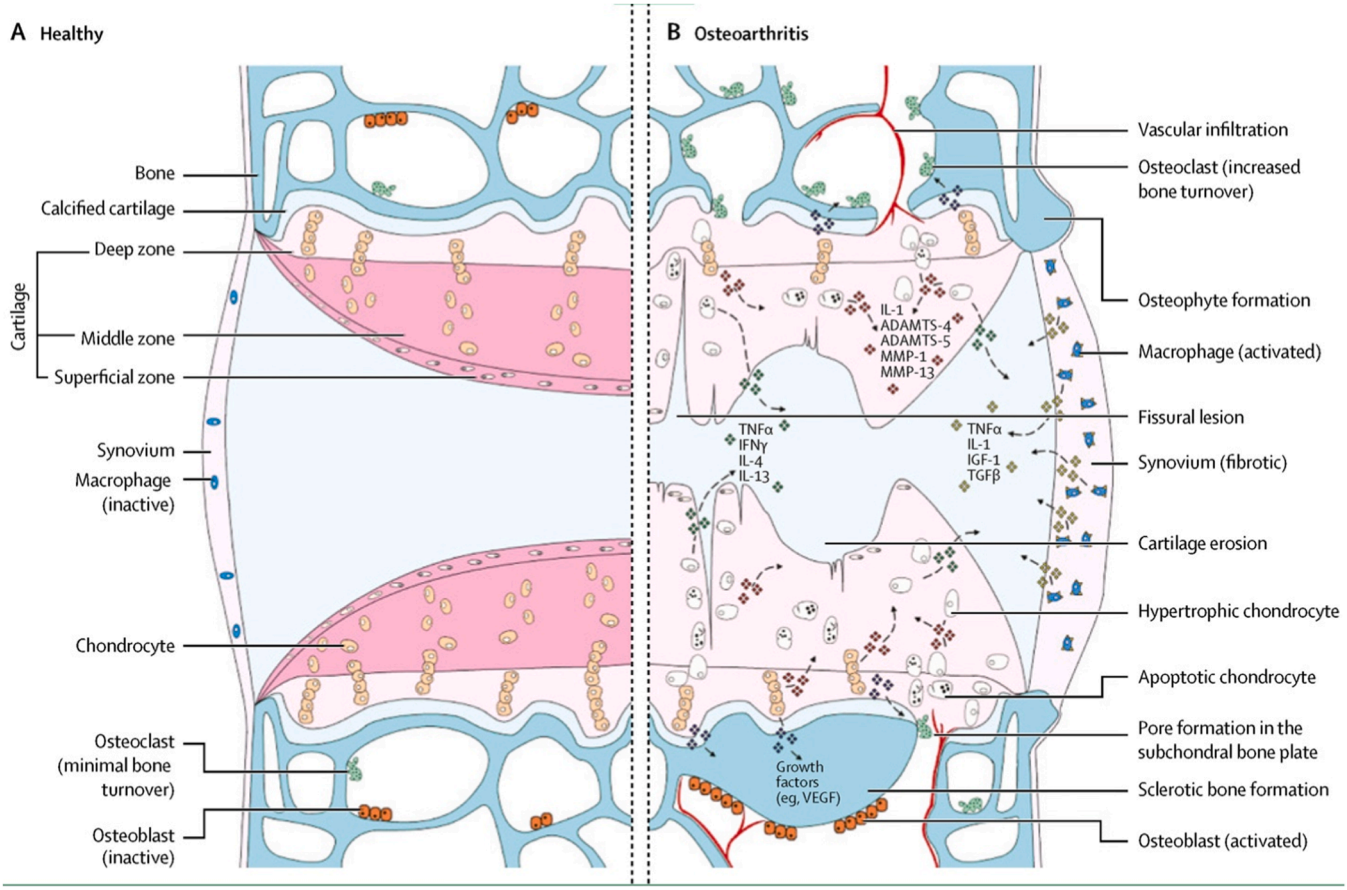

Fig. 1. Signalling pathways and structural changes in the development of osteoarthritis. Reproduced from D. J. Hunter and S. Bierma-Zeinstra [17] with permission.

to better understand the relationship between the complex molecular patho-mechanisms ("OA endotype") to better predict and treat the "OA phenotypes" with their possible diverse clinical manifestations [28].

1.2. Management of OA

Currently, there are no definitive cures for OA, but there are treatment options that help with the management of the disease that can be classified into five distinct categories: lifestyle changes, small-molecule pain medication, large-molecule viscosupplementation, cell therapy, and surgical procedures [29]. As a widely recommended initial approach, patients are directed toward nonpharmacological methods, such as exercise, weight loss, and walking aids, which are considered first-line treatments. Over the past decade, research has demonstrated that exercise therapy partnered with patient education effectively reduces pain and enhances joint mobility. Consequently, exercise has emerged as a crucial aspect of OA management [30–32]. The subsequent treatment strategy is pharmacological pain relief, where non-steroid anti-inflammatory drugs (NSAIDs) are commonly used as well as intra-articular (IA) corticosteroids and paracetamol [29]. Although still widely prescribed, opioids, including tramadol, are not recommended as a treatment for OA, due to the frequency and sometimes severity of side effects, including dependence problems in the event of prolonged use [33]. Additionally, large molecules such as HA have been used for improving lubrication of the cartilage and consecutive pain relief, however, the clinical results of HA's benefits are inconclusive [34]. The third emerging pillar of OA management is cell therapy, which includes IA injections of cell concentrates (mainly platelet-rich plasma [35] and bone marrow aspirate concentrate), adipose tissue, and mesenchymal stem cells. While there are some reports supporting the use of platelet-rich plasma, the use of cell concentrates is not well supported by clinical data, and their use is mostly limited and off-label. Initial clinical data with stem cell therapy showed promise, but better quality large-scale clinical trials are needed [34,36]. When OA progresses to the end stage, joint replacement surgery is the most relevant procedure. It is also considered the most cost-effective procedure for severely-affected patients with better functional improvements than non-surgical treatments. However, the procedure is also associated with more serious adverse events (e.g. more than 20 % of the patients report chronic pain after total knee replacement) which limits its use for some segments of the patient population [37]. In summary, given the absence of approved disease-modifying therapies and considerable side effects associated with long-term pharmacological treatments, the development of superior therapeutic options is crucial for enhancing patients' quality of life. Due to the rising prevalence and economic burden of OA, there is an urgent need for more effective treatments and preventive measures.

1.3. Newer drug treatments

Lately, drug testing of molecules already approved for other conditions, known as drug repurposing, has shown promise in slowing the progression of OA and protecting cartilage from further degradation, which is hinting at the potential development of disease-modifying OA drugs (DMOADs). A recent, promising strategy is based on the use of IA liraglutide, a modified human glucagon-like peptide-1 (GLP-1), as DMOAD [38]. The anti-inflammatory and anti-catabolic effects of liraglutide, currently marketed under the name of Victoza® as a subcutaneous treatment for type II diabetes, have been investigated upon IA administration, hypothesizing that also its potential analgesic properties could justify its repurposing for OA. Testing liraglutide in an experimental model of OA in mice successfully proved that IA stimulation of the liraglutide/ GLP-1R axis has analgesic, anabolic and anti-degradative effects in vivo, opening the doors to an ongoing phase I clinical trial (ClinicalTrials.gov identifier: NCT05419856). A different approach hinges on interfering with the mammalian target of rapamycin (mTOR) pathway, whose upregulation is known to dampen autophagy. mTOR inhibition with rapamycin (RAPA) has been found to lower chondrocyte apoptosis and inflammation, thereby safeguarding the cartilage from further deterioration [39,40]. Multiple studies conducted in live animals have validated these outcomes, indicating that RAPA can meaningfully alleviate the severity of OA and mitigate damage to the articular cartilage [41–43]. In addition to RAPA, another promising strategy for OA treatment involves boosting the production of all-trans retinoic acid (atRA), which is an endogenous anti-inflammatory molecule in chondrocytes. Researchers found that increasing atRA with talarozole, a retinoic acid metabolism-blocking agent (RAMBA), significantly dampened the inflammation in articular cartilage in vitro and in vivo as well as reduced cartilage degradation and osteophyte formation [44]. Two recent reviews highlight various additional pathways that have been recently identified in scientific literature as having the potential to be targeted for modifying the progression of the disease [45,46]. While these results offer a hopeful prospect for the future of OA therapy, the potential side effects associated with long-term systemic administration may undermine the therapy's benefits.

In recent years, there has been significant interest in pharmacological therapy through IA administration because of the reduction of systemic exposure, fewer side effects, and increased local bioavailability of the drugs. However, the drugs' residence time in the joint upon administration is still a major challenge that limits the efficacy of IA injections [47,48]. The fast clearance of the molecules from the joint leads to a higher frequency of administration, which increases the risk of infections, usually not opportunistic, during injections, [49]. Larger molecules, such as proteins (>40 kDa), predominantly exit the joint via lymphatic drainage rather than through vasculature, with the clearance rates reducing as the size of these molecules increases [50]. Interestingly, inflammatory conditions, like those seen in arthritis, have been found to amplify these clearance rates [51]. Considering these clearance dynamics, investigators have turned to three main strategies to decrease the drug clearance rate. The first one is to chemically modify the drugs: in the case of triamcinolone, increasing the hydrophobicity by forming hexacetonide, resulted in a significantly slower rate of systemic absorption compared with triamcinolone acetonide [52]. The second strategy involves formulating the drug with amphiphilic excipients such as polysorbate 80, which significantly increased the efficacy of a single injection of triamcinolone acetonide (TA) over a longer time period [53]. However, these two strategies still cannot provide long-term efficacy at the level of encapsulating the drugs into a drug delivery system (DDS). DDSs can provide several benefits beyond increasing the drug's residence time by avoiding lymphatic and vascular drainage. These advantages include targeting cartilage to improve drug retention inside the joint [48,54], allowing on-demand drug release triggered by disease-associated cues to limit drug exposure when less urgently needed [55,56], and providing lubrication to articulate cartilage, which reduces its wear and tear [25]. DDSs commonly take the form of nanoparticles, microparticles and gels. In the case of particulate systems, another pharmacokinetic consideration is important – phagocytosis by immune cells, namely macrophages and dendritic cells [53]. This process can result in the elimination of these particles by resident and recruited cells, causing an inflammatory response and T cell activation. Additionally, particles may undergo surface adsorption of complement proteins found in synovial fluid, leading to their elimination by mast cells through opsonin-dependent phagocytosis. However, by applying neutralizing cationic coatings on nanoparticles and minimizing non-specific interactions between particles and proteins in the synovial fluid, both hydrophobic and hydrophilic, there has been a demonstrated decrease in particle uptake by immune cells [53]. Other research also showed that increasing the particle size beyond 10 μm significantly decreased the uptake by the macrophages, providing avenues to improve the retention inside joints [57,58]. The growing body of work in the field of DDSs for IA administration has explored various therapeutic strategies, including the use of NSAIDs, corticosteroids, DMOADs, and RNA therapeutics. While polymer-based systems (natural and

artificial) and biomaterials have been well described elsewhere [59–61], this review will primarily focus on the lipid-based systems developed in the last 3 years for each of these therapeutic categories, as presented in Fig. 2.

2. Therapeutic strategies with lipid-based DDSs

In this section, we will discuss the applications of lipid-based DDSs in the context of different drug classes for osteoarthritis treatment via IA route. Table 1 provides an overview of the systems and functions associated with each drug class, serving as a reference for the following sections. We will explore each category in detail, highlighting the unique features, challenges, and potential future directions for lipid-based DDSs in OA treatment.

2.1. NSAIDs delivery

Oral NSAIDs are commonly prescribed for OA management due to their proven anti-inflammatory and pain-relieving properties. These effects are achieved by reversibly inhibiting cyclooxygenase isoenzymes COX-1 and COX-2, leading to a reduction in prostanoid synthesis, including prostaglandins [85]. Although their therapeutic advantages and guideline recommendations [86–89] are well-established, NSAIDs carry potential risks for gastrointestinal, cardiovascular, and renal toxicity [85,90,91]. Gastrointestinal complications may involve gastric mucosal damage, nausea, gastric or duodenal ulcers, and in more severe cases, gastrointestinal bleeding [85,90]. Nephrotoxicity is also a concern, potentially causing renal failure or additional complications in patients with pre-existing conditions [85,92]. Furthermore, NSAIDs are linked to an elevated risk of acute cardiovascular events and heart failure [90,91]. Owing to the toxicity issues associated with oral NSAIDs, alternative administration routes that can alleviate these side effects are warranted. Topical NSAIDs are sometimes prescribed in knee and hand OA, as they limit systemic exposure and side effects [85], but their poor solubility can limit their penetration through the skin and therefore their effectiveness [93]. IA administration emerges as a promising option, offering targeted delivery to the diseased site and reduced systemic adverse events. In this regard, lipid-based DDSs for IA administration have attracted considerable attention, presenting novel therapeutic approaches for OA management while addressing the toxicity concerns related to oral NSAIDs.

Naproxen, a commonly prescribed drug for arthritic disorders, acts as a non-selective COX 1 and 2 inhibitor, which makes it a greater risk for gastrointestinal adverse effects than the COX 2 selective NSAIDs [94]. Due to this, the local IA administration is of great value. The researchers investigated the potential use of a nanostructured lipid carrier (NLC) formulation, a lipid-based nanoparticle (LNP), to deliver naproxen IA for the treatment of inflammation in temporomandibular joints [64]. NLCs, blending solid and liquid lipids, provide enhanced drug loading and stability compared to other LNPs, notably Solid Lipid Nanoparticles (SLNs). The contrasting structures are illustrated in Fig. 3 [95,96]. Indeed, the NLC-naproxen formulation showed stable structural properties for 12 months of storage at 25 °C. The drug encapsulation also resulted in a sustained release profile, prolonging its anti-inflammatory effect in rats for over a week [64].

In addition to naproxen, several selective COX 2 inhibitors have also

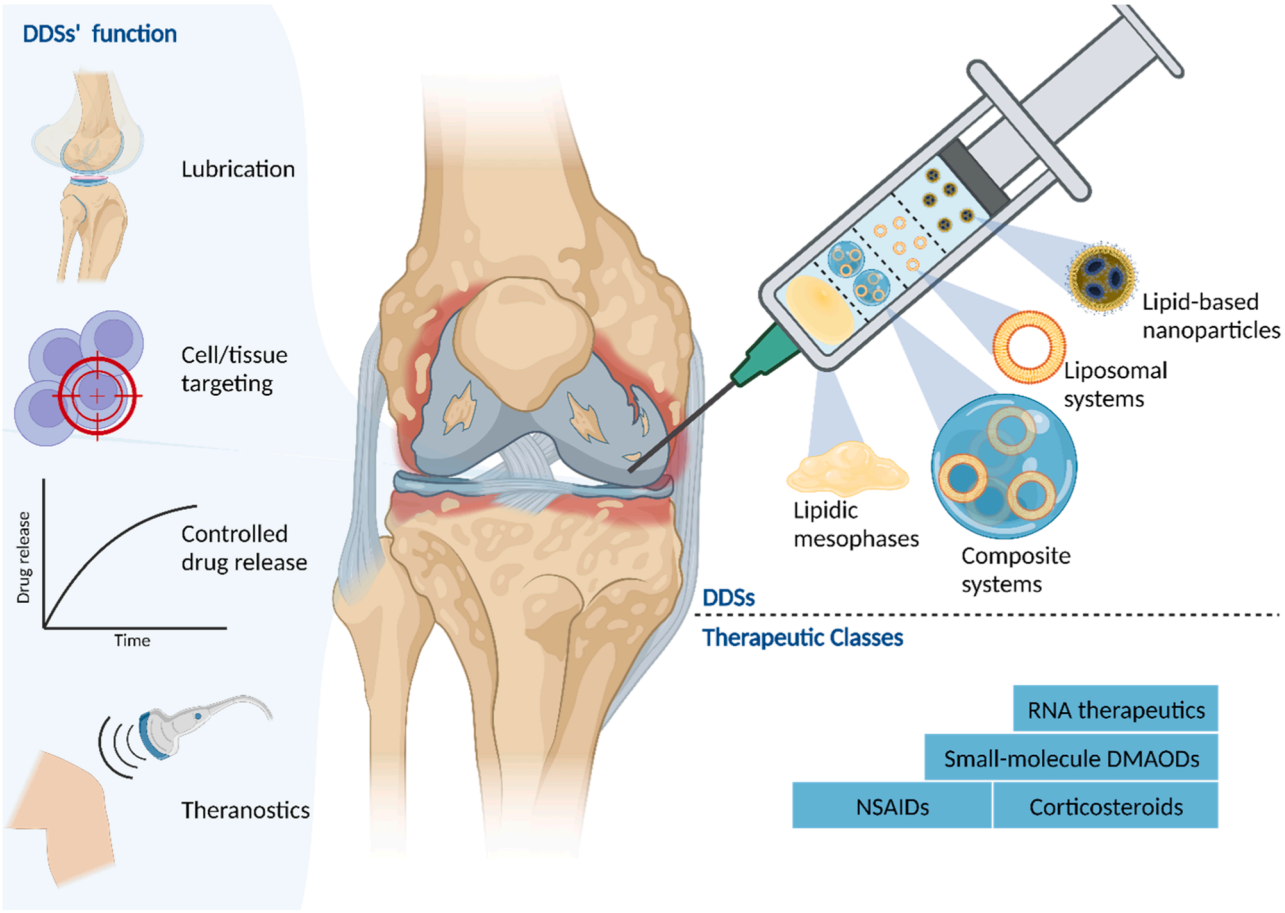

Fig. 2. Overview of lipid-based drug delivery systems (DDSs) for IA administration, their functions, and classes of encapsulated therapeutics including RNA therapeutics, small-molecule disease modifying anti-osteoarthritis drugs (DMOADs), non-steroid anti-inflammatory drugs (NSAIDs), and corticosteroids. Image created with BioRender®.

Table 1
Recent examples of lipid-based DDSs for IA administration of different drug classes for OA treatment. NSAIDs – non-steroid ant-inflammatory drugs, DMOADs – disease-modifying anti-OA drugs, miRNA – micro-RNA; siRNA – small interfering RNA; mRNA – messenger RNA; LNPs – lipid-based nanoparticles; SLNs – solid lipid nanoparticles; NLCs – nanostructured lipid nanoparticles.

Drug Class	Drug	DDS type and function
NSAIDs	Lornoxicam [62] meloxicam [63] naproxen [64] celecoxib [65,66]	Liposomes for sustained release and lubrication [62,63] NLCs for sustained release [64] Hydrogel-lipid composites for sustained release[65,66]
Corticosteroids	Dexamethasone [67,68]	Liposomes for prolonged joint retention [67] Nanobubbles for on-demand release and theranostics [68]
Small molecule DMOADs	Kartogenin [69] dasatinib [70] quercetin [70] rhein [71,72] sinomenine hydrochloride [73] MK-8722 [74] liquiritin [75] rapamycin [76–78]	Liposomes for sustained release [70,76,78], cartilage targeting [70], and cartilage lubrication [78] SLNs for sustained release and cartilage targeting [71,72] Lipidic mesophase for sustained release [73] Lipid composite micro-/nanoparticles for sustained release [74,75,77,79] and cartilage lubrication [77]
RNA therapeutics	miRNA [62,80–83] mRNA [84]	Liposomes for co-delivery of lornoxicam [62] Exosomes for chondrocyte targeting [80] Exosomes derived from bone marrow mesenchymal stem cells pretreated with decellularized ECM [81] Exosomes from umbilical-cord derived mesenchymal stem cells to rejuvenate ageing chondrocytes [82] Exosomes from hypoxia-cultured human adipose stem cells alleviating inflammaging of articular chondrocytes [83] LNPs for chondrocyte targeting [84]

been studied for IA delivery. Lornoxicam, for example, is a potent NSAID used to treat postoperative pain, OA, and RA [62,97]. Recently it was encapsulated in cationic liposomes together with microRNA-140 (miRNA) and used to achieve simultaneous anti-inflammatory and analgesic effects while promoting the cartilage repair in experimental models [62]. In the context of lornoxicam delivery, liposomes controlled the drug release over 48 h, although a burst release was apparent with 65 % of the drug released after 4 h. Another liposomal formulation was developed for COX 2 selective meloxicam, which is associated with fewer gastrointestinal adverse events, but inferior to equal efficacy to COX 1/2 non-selective inhibitors [45,63]. It is also known for its poor water solubility at 7.15 μg/mL and low bioavailability after oral administration [63]. In the study, meloxicam was actively loaded into PEGylated liposomes made from hydrogenated soybean phosphatidylcholine (HSPC) and cholesterol. To do this, a calcium acetate solution was used as a trapping agent to precipitate the drug inside the vesicle. The precipitated drug was added to the suspension as a meglumine complex, which is highly water-soluble. This process resulted in an encapsulation efficiency of over 98 % and achieved a meloxicam concentration of around 1 mg/mL. Actively encapsulated liposomes exhibited a significant decrease in the release rate compared to the passively loaded liposomes, reduced chondrocyte apoptosis, and decreased OA score according to the OARSI grading system in the in vivo rat model. Additionally, the authors showed that the liposomes were efficient in reducing friction compared to PBS on a nano-tribological level, where atomic force microscopy (AFM) was employed [63]. Another group developed a hydrogel-lipid composite system with cationic liposomes embedded into HA-based hydrogel and also tested it for its lubricating ability on a macro-tribological scale [66]. The drug that was encapsulated was celecoxib, a COX 2 selective inhibitor, which has been thoroughly studied in clinics for OA-related pain [98]. The composite system retarded the drug release compared to plain liposomes and reduced friction as well as wear compared with a plain hydrogel, as measured on a stainless-steel surface. These encouraging results were also noticeable in an in vivo rat model, where the composite system improved the cartilage integrity and reduced the catabolic marker MMP13. Interestingly, a significant improvement was observed even for the system without the drug, which authors ascribe to improved lubrication and reduction in wear that was observed in the tribological study [66]. A different approach to delivering celecoxib was taken by scientists who loaded the drug into nanocapsules with a liquid core composed of cationic surfactant and olive oil that is rich in lipids and designed to accommodate hydrophobic drugs [65]. The shell was polymer-based, where HA formed a coating around the oily phase and crosslinked with the cationic surfactant, cetyltrimethylammonium bromide. The system performed better in the in vivo rat model than the IA injection of celecoxib suspension with a lower joint swelling for 3 weeks after administration. Additionally, both the inflammation and the histopathological evaluation showed better scores after treatment with nanocapsules than with suspension, which was ascribed to the improved joint retention [65]. Although many of the discussed technologies aim to reduce off-target effects, this review has identified a general lack of pharmacokinetic data evaluating the claimed decrease in systemic circulation and off-target effects of NSAIDs. Moreover, not all articles compared the systems with a free drug. Nevertheless, it is apparent that formulating NSAIDs in lipid-based DDSs can improve therapeutic outcomes. These benefits arise not only from the prolonged drug retention in the joint but also from the lubricating ability of the lipids incorporated in DDSs. However, more translational research is needed to evaluate the merit of these systems and to compare them head-to-head with the standard of care in clinical settings.

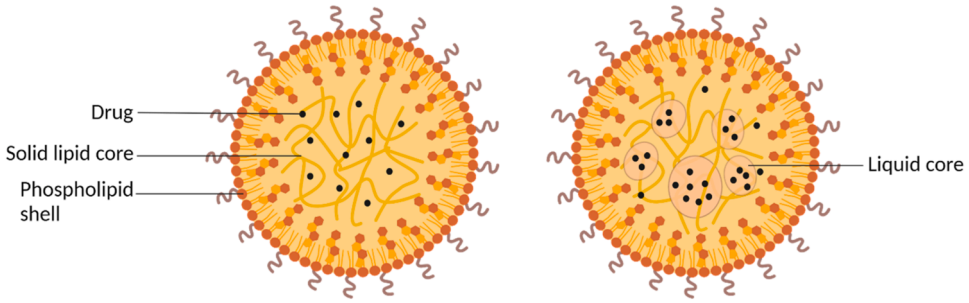

Fig. 3. Difference between conventional SLN (left) and NLC (right). Image adapted from R: Tenchov et al [96] with BioRender®.

2.2. Corticosteroid delivery

IA corticosteroids are used for short-term pain alleviation in osteoarthritis patients, with multiple guidelines supporting their use for knee, hip, and occasionally, hand OA [85–87]. Their mechanism of action involves interaction with nuclear steroid receptors, which influences mRNA and protein synthesis, modulates immune cell activities, and reduces pro-inflammatory cytokine levels [99]. Contemporary corticosteroid formulations increasingly employ nanomaterials or crystalline suspensions to enhance drug retention in the synovium and promote localization within joint tissues [85]. However, the long-term effects of corticosteroid injections on articular cartilage and potential adverse joint outcomes remain unclear [100]. Some in vivo studies have demonstrated the cytotoxic nature of corticosteroids on articular cartilage. Furthermore, corticosteroid injections have been linked to systemic side effects, including hormonal imbalances, such as diminished levels of sex hormones like estrogen and androgens [101]. Additionally, infrequent flares or localized reactions may occur as a result of post-corticosteroid injections, likely due to the crystalline formulation, but typically resolve spontaneously within three days [85]. The incorporation of DDSs could help mitigate such adverse events by providing localized sustained release and utilizing biocompatible lipid systems. Moreover, the hydrophobic nature of corticosteroids makes this drug class particularly well-suited for lipid-based DDSs, as encapsulation efficiencies of 90 % are commonly achieved [51].

A recent double-blind, placebo-controlled clinical trial involving 75 patients evaluated the effectiveness of a liposomal formulation of dexamethasone (TLC599) in providing sustained pain relief by increasing its residence time in the joint space [67]. In a single injection to the diseased knee, liposomes were able to reduce the Western Ontario and McMaster Universities Arthritis (WOMAC) pain index for up to 24 weeks. Patients who received the liposomal formulation also consumed less paracetamol over a 20-week period compared to those who received a sham injection, indicating less severe pain in the former group. The study showed that liposomes used for IA injection of dexamethasone can provide sustained pain relief for a longer period compared to the typically reported duration of injected solutions (less than 4 weeks) [67]. To validate these findings, a larger phase III trial was conducted (ClinicalTrials.gov identifier: NCT04123561), which included a head-to-head comparison with dexamethasone solution. Although the results of this trial have not been publicly released, they are expected to provide additional insights into the advantages of the liposomal system. Another group encapsulated the same corticosteroid in nanobubbles [68], which are tiny, gas-filled vesicles with a lipid bilayer shell that can encapsulate drugs or imaging contrast agents. These nanobubbles provide a versatile platform for targeted drug delivery and can be triggered to release their contents upon exposure to external stimuli like ultrasound, enabling precise, localized treatment [102]. This theranostic approach uses an echogenic contrasting agent to detect joint inflammation with ultrasound and trigger on-demand dexamethasone release. The study [68] achieved 70 % drug encapsulation and showed burst release triggered by a 30 s ultrasound pulse. They tested the system in a rat model of rheumatoid arthritis (RA), demonstrating improved joint swelling compared to controls. The anti-inflammatory effect was superior in vitro for ultrasound-triggered nanobubbles compared to untriggered ones and free drug. The echogenic effect was comparable to SonoVue® even after 6-month storage [59]. However, it is unclear if diagnostic ultrasound would trigger release, and if theranostic tools can be used for OA.

2.3. Delivery of small molecule DMOADs

In recent years, research has focused on the development of novel therapeutic agents for OA that target the underlying disease processes and have the potential to modify the disease course, as opposed to traditional treatments like corticosteroids and NSAIDs that primarily provide symptomatic relief. These emerging therapies include small molecule DMOADs and natural compounds, which have been shown to exhibit different mechanisms of action, such as targeting pro-inflammatory cytokines, proteolytic activities of catabolic enzymes, the Wnt pathway, autophagy, and stimulating the regenerative potential of cartilage. DMOADs can be small molecules or biotherapeutics, mirroring the heterogeneous nature of OA, a pathology involving multiple joint tissues differently affected by progressive deterioration in their biological, structural and/or mechanical properties. According to one of the possible classifications, based on their target, DMOADs could target synovitis, the subchondral bone, or the cartilage. Several recent reviews report extensive information on the pharmacological action of the most promising agents [103–106].

While some of these compounds are still in preclinical or clinical stages of development, they offer promising alternatives for OA treatment, with the potential to address the limitations of current therapeutic options [45,46]. Despite the diverse nature of these chemical compounds, several of them face challenges such as a narrow therapeutic index [107–110] and poor bioavailability [71,111] due to their poor water solubility. Consequently, considerable research efforts have been dedicated to formulating these compounds into DDSs that can mitigate these drawbacks and enhance therapeutic outcomes.

[103]In recent years, targeting cellular senescence has emerged as a promising treatment strategy for OA. Cellular senescence is a process in which synovial cells lose their ability to divide and become resistant to apoptosis. These senescent cells contribute to the creation of an inflammatory microenvironment that exacerbates the progression of the disease [112]. By focusing on the clearance of senescent cells, dasatinib and quercetin were recently co-delivered using a liposomal formulation in mice [70]. This drug combination is currently under investigation in clinical trials to treat idiopathic pulmonary fibrosis, a life-threatening disease that is related to cellular senescence [113,114]. The liposomes containing the drug combination were engineered with a targeting component specific to synovial fibroblasts, using an aptamer in this instance [70]. Aptamers are single-stranded DNA molecules that possess unique tertiary structures, allowing them to selectively bind to corresponding molecular targets. They are designed and identified through a technique known as systematic evolution of ligands by exponential enrichment (SELEX), which is commonly used to select ligands capable of specifically binding to molecular targets, thereby improving the therapeutic efficacy of the DDS [115]. The system exhibited remarkable selectivity towards synovial fibroblasts, diminished dasatinib-induced toxicity on healthy fibroblasts and chondrocytes and facilitated sustained drug release. *In vivo* studies demonstrated that, following a single IA injection in mice, the targeted liposomes were retained more effectively within the joint space compared to their untargeted counterparts over a 7-day period. This ultimately resulted in a significant attenuation of cartilage degradation [70]. Another DMOAD that is currently being studied in a couple of advanced clinical trials (ANZCTR ID: ACTRN12618001656224; Clinicaltrials.gov identifier; NCT04318041) is diacerein, which is a prodrug of the active metabolite rhein, also known as cassic acid [72,116]. Diacerein, which previously showed promise in slowing the progression of OA in animal models [117], is a semisynthetic anthraquinone derivative that blocks IL1β, an important mediator of synovitis in OA that is associated with higher disease severity [116]. However, in 2014 the European Medicines Agency (EMA) applied several restrictions on the use of this drug to manage the systemic risks of severe diarrhea and adverse effects on the liver [46,118]. This led to the development of DDSs for local IA delivery such as SLNs that are a type of LNP with a solid lipid core. Their architecture enables improved drug encapsulation, shields against degradation, and regulates release kinetics, particularly for lipophilic drugs, but also for hydrophilic ones [119]. In order to improve the solubility of rhein, the active compound of diacerein, and achieve high drug encapsulation, researchers utilized hydrophobic ion pairing with stearylamine. This approach enhanced the lipophilicity of rhein without altering its chemical composition, enabling its dissolution in the lipid phase. As a

result, the encapsulation efficiency reached nearly 100 % and the drug release was sustained for over 2 weeks. When administered to rats, SLNs were found in the joints for 3 weeks after injection and accumulated in the cartilage due to the targeting ability of the positively charged particles. Rhein encapsulation showed improved OARSI scores compared to the drug's suspension. Furthermore, the rhein SLNs significantly reduced IL1β levels over 8 weeks upon administration compared to the rhein suspension control. In a different study, the same research group further optimized the drug delivery system by incorporating chondroitin sulphate, an endogenous glycosaminoglycan known to exhibit targeting potential towards cartilage through its interaction with collagen type II [72]. The investigators demonstrated that adopting this active targeting strategy resulted in a decline in the levels of nitric oxide, IL1β, and catabolic MMP3 while augmenting aggrecan levels in rats 5–8 weeks post-injection, relative to passive targeting with cationic SLNs. Although the OARSI score showed a reduction in comparison to the drug's suspension, the improvement was not statistically significant compared to the SLNs with passive targeting [72]. Therefore, additional studies are necessary to confirm the improvement in therapeutic outcomes and clinical significance of the active targeting approach using SLNs. Chondroitin sulphate was also recently used to form hydrogel microparticle-microgels, which were embedded with liquiritin-loaded liposomes [75]. Liquiritin is a flavone compound derived from licorice, which was found to have anti-inflammatory and chondroprotective activity with a high potential for modifying the progression of OA [75,120]. Authors employed chondroitin sulphate as a hydrogel matrix, because of reports of its anti-inflammatory activity and antioxidant potential [121]. The microgels were produced by combining liposomes, alginate, and chondroitin sulphate and utilizing a customized electro-assisted bioprinter to generate droplets that were then deposited into a $CaCl_2$ crosslinking solution and irradiated with UV light. The composite system exhibited a prolonged drug release profile as compared to plain liposomes over 3 weeks, and its retention in the joint space was extended to 4 weeks. The antioxidant activity was demonstrated in vitro, while the therapeutic efficacy was observed in rats, as evidenced by the inhibition of cartilage matrix loss, reduction in osteophyte formation, and alleviation of subchondral bone changes [75]. Another composite system utilizing a combination of poly (lactic-co-glycolic acid) (PLGA) polymer core and PEGylated lipid shell was used for encapsulation of MK-8722 [74]. The latter is a potent activator of 5′-adenosine monophosphate-activated protein kinase (AMPK) known to joint homeostasis, limit oxidative stress and the cartilage and alleviate OA severity [122,123]. The integration of lipids into the composite system enabled the functionalization of the nanoparticle surface with targeting moieties, such as a short collagen-binding peptide, allowing the researchers to target cartilage for deeper penetration and enhanced retention in the joint 48 h post-IA injection in mice. The system exhibited significantly superior cartilage protection compared to nanoparticles lacking the targeting peptide and demonstrated greater efficiency in reducing proinflammatory markers at the endpoint of the 13 day-long animal study, with IA injections administered every other day. Although the results seem promising, the lipid-polymer nanoparticles achieved only modest drug retention, with a complete release at 48 h [74]. This phenomenon may be connected to the small particle size, below 40 nm, which results in an increased surface area and facilitates the swift clearance of the nanoparticles from the joint [58,124]. Consequently, the requirement for frequent administration of the system might present obstacles regarding patient adherence to the therapy. Slightly slower-release kinetics were achieved with a liposomal formulation of rapamycin [76], whose mechanism of action was discussed in section 1.2.1. The treatment was combined with low-intensity pulsed ultrasound (LIPUS), which has been reported to attenuate the destruction of the cartilage [125]. The findings revealed that the synergistic effect of LIPUS and liposomal formulation played a crucial role in reducing catabolic and inflammatory markers in an in vitro human OA chondrocyte model. In an animal study involving guinea pigs, subjects received IA injections of the formulations every three days and underwent LIPUS treatment on alternate days. This regimen led to a decrease in catabolic markers and an increase in collagen type II [76]. However, concerns regarding patient compliance should be addressed due to the demanding nature of the treatment schedule. Recently, our group developed another liposomal DDS for rapamycin, where liposomes were loaded into anionic unilamellar vesicles with encapsulation efficiency above 90 % and aggregated with Zn^{2+} [78]. The aggregation produced irreversible aggregates with nearly 100 μm in diameter, which was previously reported to increase joint retention time [58,78,124]. The irreversible nature of aggregates allowed further purification of excess Zn^{2+} with dialysis and the system produced a sustained release beyond that of plain liposomes. The tribological experiments showed excellent lubrication on a nano-tribological scale and the particles' ability to protect *ex vivo* cartilage from friction on a macro-tribological scale [78]. A 3-week release of rapamycin was achieved in a hydrogel-lipid composite formulation involving liposome-embedded microgels [77]. The positively charged liposomes were combined with methacrylated HA and extruded through a microfluidic nozzle into paraffin oil, after which the hydrogel was crosslinked using UV irradiation, as depicted in Fig. 4. The paraffin was subsequently removed through dialysis. Macro-tribological analysis demonstrated that the microgels reduced friction in comparison to phosphate-buffered saline (PBS), while the composite liposomal microgels provided even superior lubrication, attributed to the highly hydrated phospholipid headgroups. In OA rats, the lubricating properties of the composite formulation, through minimizing cartilage wear, contributed to the preservation of cartilage structure. This effect was further enhanced by the encapsulated rapamycin. Moreover, significant increases in aggrecan and collagen type II expressions were observed with the liposomal microgels, and the articular space improved after 8 weeks of treatment during which animals received two injections. Notably, in vivo imaging revealed that the liposomes were retained in the joint for nearly two months, highlighting the potential of this approach [77]. For delivery of kartogenin, a similar system was employed, utilizing methacrylated gelatin and liposomes [69]. Kartogenin promotes cartilage regeneration by stimulating chondrogenic differentiation of mesenchymal stem cells and upregulating the expression of type II collagen and aggrecan [45]. However, its poor water solubility limits its efficacy in clinical use due to low drug dose in aqueous solution, leading to reduced IA delivery efficiency. To overcome this limitation, a system was developed using methacrylated gelatin and liposomes, resulting in a composite that exhibited attenuated drug release for over 3 weeks when produced through microfluidics and UV crosslinking, similar to the process in Fig. 4. In mouse joints, the composite system prolonged the drug retention period from 2 weeks for plain liposomes to 35 days. The therapeutic efficacy of this delivery system was demonstrated in rats, showing a considerable decrease in OARSI score, osteophyte volume, and cartilage lesions, while the expression of collagen type II and aggrecan was increased [69].

Another system for sustained drug release was developed for sinomenine hydrochloride, a compound that is a soluble salt of sinomenium, derived from traditional Chinese medicinal herb *Sinomenium acutum*. The compound is known to have protective effects against cartilage degradation, as demonstrated by a reduction in MMP-13 and an increase in collagen type II expression in OA rats [126]. Furthermore, in animal models of sepsis, sinomenium was shown to regulate autophagy, improving survival rates, reducing organ damage, and attenuating the release of inflammatory cytokines [127]. A China-based phase 3 clinical trial (Clinicaltrials.gov identifier: NCT05764304) is expected to start recruiting patients soon to evaluate the efficacy of sinomenine compared to corticosteroids for knee OA. On the other hand, the drug's potentially limited potential can be attributed to its short plasma half-life and associated systemic side effects. To address this issue, researchers have formulated the drug within a lipidic mesophase system, consisting of amphiphilic lipids and additives that self-assemble into liquid crystal

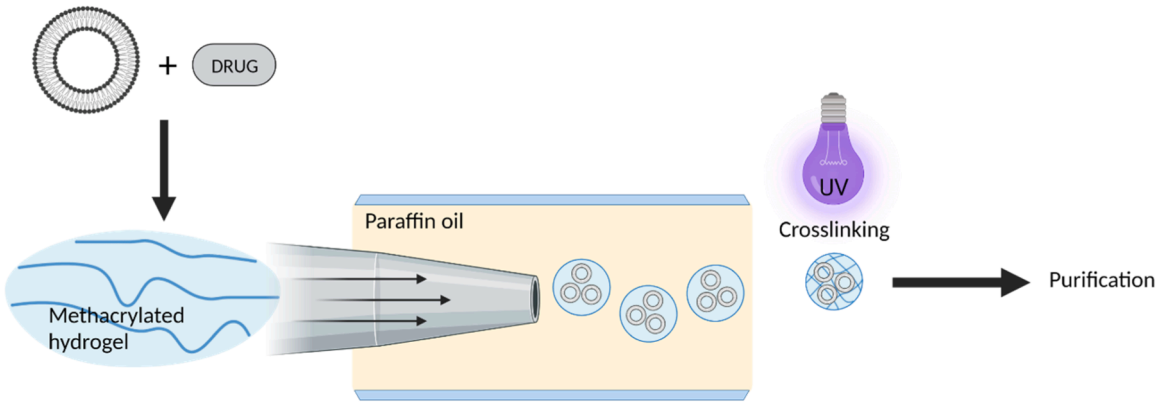

Fig. 4. Production of lipid-hydrogel composite microparticles. Image was created with BioRender®.

structures upon contact with water [73]. Depending on the composition, the system can form lamellar, hexagonal, and cubic phases, wherein the lipids create distinct architectures with varying water channel sizes that yield unique rheological and release properties. Phase diagrams delineate the presence of specific phases under certain conditions, with temperature and water content serving as critical determinants.[128]. The hydrophilic sinomenine hydrochloride was encapsulated in a system composed mainly of amphiphilic phytantriol and vitamin E acetate, which formed a hexagonal phase inside rats' synovial joints. The in vitro study showed a prolonged release of over 9 days, which resulted in increased drug concentration in animals' synovial fluid throughout 7 days of the in vivo study. The lipidic mesophases successfully decreased the systemic exposure of the drug compared to the drug's solution and reduced IL1β expression in synovium [73].

2.4. RNA delivery

Non-coding RNAs (ncRNAs) have recently emerged as a promising alternative to small-molecule and antibody-based therapeutics in the treatment of OA. These RNA-based molecules, including small interfering RNAs (siRNAs), miRNAs, and antisense oligonucleotides (ASOs), offer enhanced versatility in design, allowing for targeted modulation of gene expression while mitigating off-target effects [45]. Each type of RNA molecule differs in its mode of action and target range: siRNAs are designed to exclusively knock down a single target gene, while miRNAs can regulate multiple genes simultaneously, and ASOs can degrade target RNAs that promote OA [129–131]. Prime targets for RNA-based therapies in OA include key catabolic enzymes such as MMP-13 and ADAMTS-5, which are responsible for the degradation of type II collagen and aggrecan, respectively, as well as the NF-κB pathway, a significant regulatory pathway governing inflammatory responses in OA, and the hypoxia-inducible factor-2α (HIF-2α), a key transcription factor controlling matrix-degrading enzymes during OA development. These targets have been chosen due to their crucial roles in OA pathogenesis and the potential for RNA therapeutics to modulate their expression [45]. Despite their potential, RNA therapeutics face challenges in stability and in vivo delivery, which have limited their clinical application. Issues such as rapid degradation, immunogenicity, and inefficient cellular uptake pose significant barriers to their therapeutic efficacy [132]. However, LNP formulations have shown promise in addressing these issues, improving both stability and delivery of RNA molecules [45].

Section 2.1 touched on the delivery of miRNA-140, which downregulates the expression of ADAMTS-5 with cationic liposomes that were co-loaded with NSAID lornoxicam. The DDS protected miRNA cargo from nuclease degradation and efficient uptake by chondrocytes, which resulted in the upregulated expression of Col2A1 gene. In rats, the liposomal system decreased the histologic Mankin score, which assesses cartilage structure, cellularity, Safranin O staining, and tidemark integrity [62,133]. As miRNA is specifically expressed in chondrocytes, where it exerts its chondroprotective properties, the delivery in this cell type is particularly important. However, the specific delivery to chondrocytes is no easy feat, as they reside in densely-structured cartilage. One research group has recently employed dendritic cell-derived exosomes that were engineered to actively target chondrocytes [80]. Exosomes, nanoscale vesicles produced by cells, serve as natural communicators between cells, transporting biologically active components like nucleic acids and proteins within their lipid bilayer membrane. These vesicles present advantages over synthetic drug carriers, including reduced cytotoxicity, enhanced tissue and cell permeability, and the capacity for targeted delivery through genetic or chemical modification [134]. In this study, active targeting was achieved by genetically engineering dendritic cells to express a chondrocyte-specific targeting peptide, as in Fig. 5. After cell culture, supernatants were collected, exosomes isolated and miRNA-140 was loaded with electroporation. The resulting DDS demonstrated preferential uptake into chondrocytes in vitro, as opposed to synovial mesenchymal stem cells, leading to decreased IL1β and MMP13 expression levels. The targeted exosomes exhibited increased retention in the joint 24 h post IA injection compared to untargeted vesicles, which were found in other body parts, including the kidneys. MMP13 expression in cartilage was significantly reduced, while detected miRNA levels increased with targeted exosomes. Furthermore, the OARSI score improved four weeks post-injection of the miRNA system, indicating the potential of targeted RNA interference (RNAi) therapy for OA treatment [80].

The possible therapeutic role of lncRNA KLF3-AS1 in exosomes derived from human MSC (MSC-exo) was investigated in an experimental model of OA in rats [135]. A single IA administration of MSC-exo, harvested and purified from MSCs transfected either with siRNA targeting KLF3-AS1 or with a scrambled siRNA, revealed that MSC-exo enriched with lncRNA KLF3-AS1 promoted cartilage repair and chondrocyte proliferation.

The regenerative ability of MSC-exo derived from umbilical cord (UCMSC-exo) has been harnessed to mitigate senescence by downregulating age-related genes in OA chondrocytes [75]. The in vivo targeting properties of UCMSC-exo were boosted via the conjugation of a chondrocyte-targeting peptide to the exosomal surface. To prolong the residence time in the joint, the engineered UCMSC-exo were loaded in an injectable thiolated hyaluronic acid microgel. The chondrocyte-specific targeting and the sustained release properties of the composite exo-gel were shown to be pivotal to the rejuvenation of the cartilage tissues observed after 8 weeks from the IA administration in a rat model of OA. The sequencing and analysis of miRNAs in UCMSC-exo identified 17 miRNAs involved in the cell ageing process through the inhibition of the p53 signal pathway. To unleash the full potential of this composite DDS, the role of other UCMSC-exo factors such as proteins, lipids, and other nucleic acids needs to be further

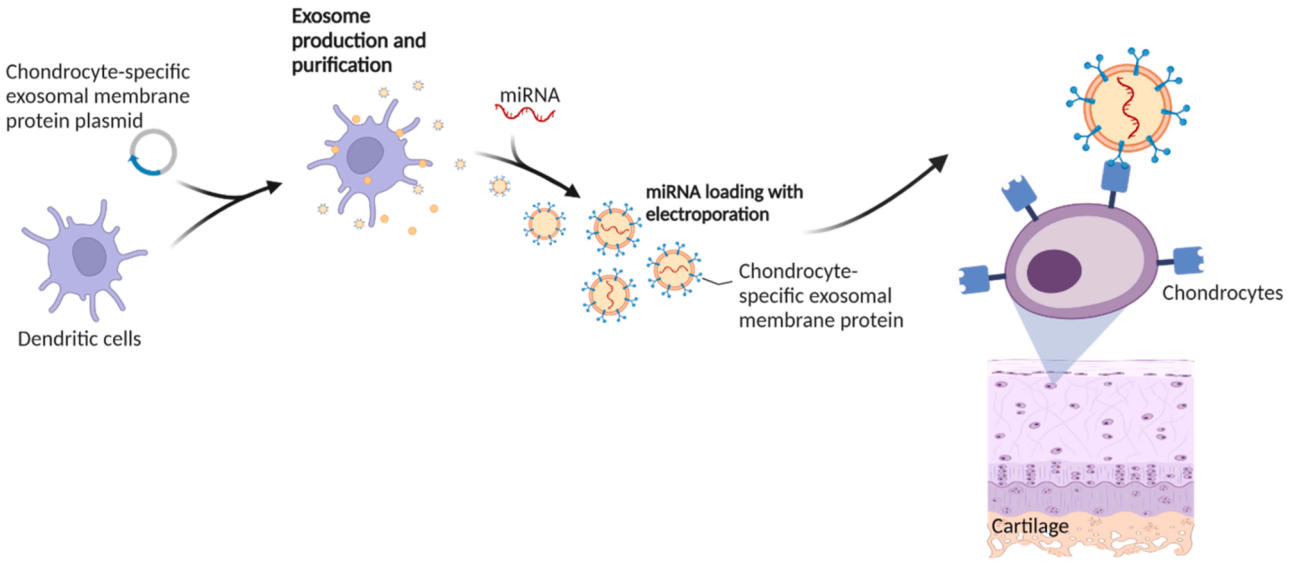

Fig. 5. Production of miRNA-loaded exosomes for chondrocyte targeting. Image created with BioRender®.

elucidated.

Overall, the cell-free tissue regeneration properties of extracellular vesicles have captured the attention of many but also highlighted the need for more complex biocompatible matrices, such as hydrogels or 3-D printed scaffold, in which extracellular vesicles can be embedded to improve their residence time in the joints, as extensively reviewed by de Looij and colleagues [136].

Apart from RNAi approaches, mRNA delivery, which gained traction during the COVID-19 pandemic, has also recently been employed for OA treatment by delivering relevant large-molecule DMOAD codes [137]. In recent research, mRNA was encapsulated in LNPs featuring aggrecan-targeting peptides on their surface to achieve prolonged joint space retention and enhanced cartilage penetration [84]. The insulin-like growth factor-1 (IGF-1) encoding mRNA was chemically modified, and when delivered with LNPs, stimulated the proliferation of IL1β-stimulated chondrocytes. LNPs were prepared using microfluidic mixing of an acidic aqueous phase with mRNA and an organic phase containing lipids—such as ionizable DLin-MC3-DMA, cholesterol zwitterionic DSPC, and DSPE-PEG2000 with or without the targeting peptide—dissolved in ethanol. Two weeks after IA injection, particles were still present in the mice's joint space, with luciferase-encoding mRNA expression observed up to four days after injection. Both outcomes were at least four times higher than those without the targeting moiety, highlighting the importance of active targeting following IA injection. This was also significantly greater than recombinant IGF-1 retention, which was no longer present in the joint after two days. The targeted LNPs exhibited deeper and more persistent cartilage penetration over two days in a human cartilage explant. *In vivo*, after a single injection, assessments at 4 and 8 weeks revealed that LNPs significantly decreased the number of apoptotic chondrocytes, enhanced interfacial cellularity, and augmented the presence of type II collagen in different groups. Targeted LNP mRNA delivery outperformed both untargeted delivery and recombinant IGF-1 administration [84].

Taken together, the wide range of RNA-based therapeutics examined present promising avenues for OA therapy, with advancements in lipid-based DDSs promoting enhanced stability, targeted delivery, and extended retention. Targeted approaches appear to hold a distinct advantage over their untargeted counterparts. Further research is needed to examine chondrocyte targeting in physiologically relevant settings with immune cells present, as this may significantly restrict uptake, mirroring challenges faced in systemic administration due to the reticuloendothelial system [138].

3. Clinical remarks on IA DDS

When considering treatments for OA patients, the clinical specialists circle around the fundamental concept of risk-benefit balance, with a primary focus on safety considerations. For pharmaceuticals designed to alleviate symptoms, it is imperative to demonstrate improved efficacy and/or an extended duration of clinical effect, coupled with a reduced incidence of adverse effects. The enhanced therapeutic properties should be attributable to the existence of a DDS and be confirmed for a local application of the active principle as opposed to systemic administration.

Ideally, thanks to a sustained release profile, an IA DDS should allow for a reduction in the drug concentration needed to obtain the expected therapeutic effect, even when employing the same route of administration, potentially resulting in a diminished occurrence of side effects. As an illustrative example, the randomized clinical trial by McAlindon and colleagues evaluating the effect of IA triamcinolone versus saline on knee cartilage volume and pain in OA patients, raised concerns on the IA use of corticosteroid regarding cartilage degradation [139]. If this deleterious effect is proven to be indeed dose-dependent, it follows that a lower dosage achievable through the continuous release of corticosteroids may present a viable strategy for mitigating this issue.

Among the plethora of lipid-based DDS proposed for OA treatment, the liposomal formulation MM-II from Moebius, drug-free, stands out as the most clinically advanced (Clinicaltrials.gov identifier: NCT04506463), suggesting the still largely unexplored clinical potential of phospholipid-based treatment for OA [140].

For more general advances in the clinical translation of IA DDS for OA, we refer the reader to a comprehensive review by Duvall and colleagues [141].

4. Conclusion and future perspectives

In this review, we have explored lipid-based DDSs for four major drug classes: NSAIDs, corticosteroids, small molecule DMAODs, and RNA therapeutics. Recent research efforts have demonstrated the multifunctionality of lipid-based DDSs to improve therapeutic outcomes and minimize side effects associated with these drugs when used for IA administration in the treatment of OA. Throughout our discussion, we have observed that the use of advanced DDSs, such as liposomes, lipid nanoparticles, and composite systems, has contributed to enhanced stability, targeted delivery, and prolonged retention of these therapeutics in the joint space. Active targeting strategies have shown a clear

advantage over passive targeting; however, more research is necessary to investigate the efficiency of these strategies in physiologically relevant conditions. Importantly, OA has been recognized as a "serious disease" with an "unmet medical need" for therapies that could "potentially change its natural course to prevent long-term disability" by the FDA [142] because of the increased mortality owed to a sedentary lifestyle in presence of a walking disability [143]. This label opens up accelerated paths to develop solutions for OA.

Some critical aspects should not be underestimated when developing nanomedicine formulations for local administration: (i) differently from dosage forms meant for oral intake or subcutaneous administration, therapeutics via the IA route require the support of healthcare professionals. Reduced clearance of the DDS in the joint space is pivotal to ensure higher patient compliance; (ii) despite the great advance of lipid-based nanomedicine during the COVID-19 pandemic, their manufacture is still not as widespread as conventional dosage forms such as tablets and solutions for injections and their specific regulatory framework is still being defined at the European and US level by dedicated working groups and task forces. This implies that even the most successful DDS at the preclinical stage may additionally require the optimization of several manufacturing process parameters such as shear force, pressure, pH, temperature, batch-size-related hold times, lyophilization parameters, and sterilization approach, and this further optimization may affect the performance of lipid-based nanomedicines; (iii) the lack of proper biorelevant compendial assays to test the pharmaceutical quality of DDS for IA route makes the early product development particularly challenging. 3-D bioprinted osteochondral tissue or chondrospheres stand out as the most promising OA model aimed at bridging cell-free assays and in vivo studies but assessing drug release profiles and lubrication properties of lipid DDS using those systems is not trivial; (iv) appropriate experimental models of OA are required to accurately translate preclinical results into possible therapeutic benefit in humans and this is particularly true for nanomedicine, for which the translational knowledge gap is still substantial.

Looking ahead, the development of multifunctional DDSs that can deliver combinations of therapeutics, such as RNA molecules and small molecule DMOADs, may provide synergistic effects and improved OA treatment outcomes. A crucial aspect of advancing OA therapy is the design of long-acting systems that resist rapid clearance from the joint space. Particle size and targeting ability are critical factors in achieving this goal, as they can enhance the localization of DDSs to synovial tissues and prolong their therapeutic effect. Additionally, combining cartilage lubrication properties that reduce cartilage wear with sustained drug delivery has shown promise in animal models. While it is crucial to advance novel DDSs into human clinical trials for OA treatment, comparative analysis between these innovative systems and current standard treatments, like oral and topical NSAIDs as well as IA corticosteroids, is essential. These head-to-head comparisons are vital for assessing the effectiveness, safety, and cost-efficiency of new DDSs. If these novel systems prove superior in these aspects, they could potentially redefine first and second-line treatment regimens for OA, offering a promising and cost-efficient approach to managing the condition. Such comprehensive data would significantly inform clinical decision-making and shape the future of OA therapy. However, the urgency for such comparisons might be less for DDSs encapsulating drugs with unique mechanisms of action, such as small-molecule DMOADs or RNA therapeutics. These treatments may offer substantial potential for patients unresponsive to or unable to tolerate NSAIDs or corticosteroids. Therefore, although they should eventually be compared with standard therapies, their unique benefits could warrant expedited clinical exploration. By pushing the boundaries of DDS innovation, we can strive towards harnessing the full potential of lipid-based DDSs for IA administration in OA therapy.

CRediT authorship contribution statement

Gregor Bordon – Conceptualization, Visualization, Writing - Original Draft. **Francis Berenbaum** – Writing – Review and Editing. **Oliver Distler** – Writing – Review and Editing. **Paola Luciani** – Conceptualization, Project administration, Supervision, Validation, Writing – Review and Editing.

Declaration of Competing Interest

Gregor Bordon and **Oliver Distler** declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. **Francis Berenbaum** is founder and CMO of 4Moving Biotech and has consulted for 4P Pharma, AstraZeneca, Cellprothera, Grunenthal, GSK, Medivir, Novartis, Pfizer, Lilly, Servier. **Paola Luciani** has consulted and received research funding from Lipoid GmbH, Sanofi-Aventis Deutschland and DSM Nutritional Products Ltd.

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