

ADVANCED REVIEW

Management of osteoarthritis: From drug molecules to nano/micromedicines

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Abstract

With the change in lifestyle and aging of the population, osteoarthritis (OA) is emerging as a major medical burden globally. OA is a chronic inflammatory and degenerative disease initially manifesting with joint pain and eventually leading to permanent disability. To date, there are no drugs available for the definitive treatment of osteoarthritis and most therapies have been palliative in nature by alleviating symptoms rather than curing the disease. This coupled with the vague understanding of the early symptoms and methods of diagnosis so that the disease continues as a global problem and calls for concerted research efforts. A cascade of events regulates the onset and progression of osteoarthritis starting with the production of proinflammatory cytokines, including interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α ; catabolic enzymes, such as matrix metalloproteinases (MMPs)-1, -3, and -13, culminating into cartilage breakdown, loss of lubrication, pain, and inability to load the joint. Although intra-articular injections of small and macromolecules are often prescribed to alleviate symptoms, low residence times within the synovial cavity severely impair their efficacy. This review will briefly describe the factors dictating the onset and progression of the disease, present the current clinically approved methods for its treatment and

Abbreviations: AC, articular cartilage; ACLT, anterior cruciate ligament transection; ADAMTs, a disintegrin and metalloproteinase with thrombospondin motifs; Agg, proteoglycan aggrecan; AMSCs, adipose tissue-derived mesenchymal stem cells; BA, betamethasone acetate; BMP-7, bone morphogenetic protein 7; BMSCs, bone marrow tissue-derived mesenchymal stem cells; BP, betamethasone sodium phosphate; Ca²⁺, divalent calcium ions; Cl⁻, monovalent chloride anions; CLX-Lip, Celecoxib liposomes; COX-2, cyclooxygenase 2; DEX, dexamethasone; DMOADs, disease modifying osteoarthritis drugs; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DTT, dithiothreitol; ECM, extracellular matrix; FGF-18, fibroblast growth factor 18; HA, hyaluronic acid or hyaluronan; hAMSCs, efficacy human amniotic mesenchymal stem cells; HSPC, hydrogenated L- α -phosphatidylcholine; IA, intra-articular; IGF-1, insulin-like growth factor 1; Ihh, Indian Hedgehog siRNA; IL, interleukin; L, lesion; MD, molecular dynamics; MF, medial femur; MLV, multilamellar vesicles; MM, medial meniscus; MMPs, matrix metalloproteinases; MMx, medial meniscectomy; MRI, magnetic resonance imaging; MSCs, mesenchymal stem cells; MT, medial tibia; MW, molecular weight; Na⁺, monovalent sodium cations; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOS, nitric oxide synthase; OA, osteoarthritis; PAMAM, polyamidoamine; PC, phosphatidylcholine-based lipids; PCL, poly(caprolactone); PEA, poly(ester amide); PEG, poly(ethylene glycol); PGE2, prostaglandin E2; PGR4, lubricin; PGs, aggrecan proteoglycans; PL, phospholipid; PLGA, poly(lactic-co-glycolic acid); PPS, poly(propylene sulfide); PRP, platelet-rich plasma; PTOA, post-traumatic osteoarthritis; S/O/W, solid-in-oil-in-water; sCT, salmon calcitonin; SF, synovial fluid; siRNA, short interference RNA; SUV, small unilamellar vesicles; TA, triamcinolone acetate; TH, triamcinolone hexacetone; TNF, tumor necrosis factor.

Martina Di Francesco and Agnese Fragassi contributed equally to this study.

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diagnosis, and finally elaborate on the main challenges and opportunities for the application of nano/micromedicines in the treatment of osteoarthritis. Thus, future treatment regimens will benefit from simultaneous consideration of the mechanobiological, the inflammatory, and tissue degradation aspects of the disease.

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cartilage protection, inflammation, intra-articular delivery, joint health, microparticle

1 | INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis that simultaneously affects the lives of elderly people as well as young individuals suffering post traumatic injuries (Loeser et al., 2016). This chronic inflammatory disease can potentially influence any articular joints, but knees, hands, feet, and fingers are more affected. OA is a complex disease affecting the whole joint, in which subchondral sclerosis, synovial membrane inflammation, and enzymatic degradation of the extracellular matrix (ECM) concomitantly have a pivotal role. These processes result in the progressive degeneration of cartilage. OA represents the main source of joint pain and its progression can be associated with functional loss and, eventually, permanent disability (Martel-Pelletier et al., 2016). The 2017 Global Burden of Disease Study reports that over 300 million people are affected by OA, with a higher prevalence in women and elderly individuals (Safiri et al., 2020). In addition to age, other modifiable and non-modifiable risk factors can promote OA including obesity, lack of exercise, genetic predisposition, and bone density (Loeser et al., 2016; Martel-Pelletier et al., 2016; Shaik et al., 2018). Considering its high incidence and negative outcomes, OA is associated with an enormous economic burden on national healthcare and society (Cross et al., 2014; Vos et al., 2012). It has been predicted that the economic burden of OA in the US only could be close to \$200 billion/year by 2030 (Colombo et al., 2021). Indeed, the aging of the world's population will inevitably contribute to increase the incidence of this disease thus requiring more research efforts to identify effective and definitive therapies.

Several pharmacological and non-pharmacological approaches, either individually or in combination, are currently used for managing this widespread disease and public health issue. Nowadays, pharmacological treatments are mostly limited to alleviate the symptoms, such as pain, stiffness and swelling, rather than reversing and curing the disease. In general, an ideal OA drug therapy should revert the damage to joint structures, reduce pain, inflammation, and improve or restore joint function. Yet, no approved disease modifying osteoarthritis drugs (DMOADs) are available for clinical use. Considering the localized nature of the disease, the direct injection of the medication into the joint cavity is frequently prescribed, as it reduces possible side effects associated with drug systemic exposure. However, intra-articularly (IA) injected drugs are often rapidly removed from the joint space through venules and lymphatic vessels located in the synovium (Brown et al., 2019; Edwards, 2011; Gerwin et al., 2006; Kumar & Sharma, 2020). Increasing the residence time of therapeutic agents within the joint represents a big challenge in the management of OA. This goal could be effectively addressed by the application of nano/microtechnologies to create local drug depots directly at the target site thus reducing the frequency of administrations while improving patient compliance with the treatment (Kou et al., 2019). Also, considering the multiple pathological processes involved in the OA development, different pathways could be simultaneously targeted using nano/microtechnologies capable to precisely deploy different therapeutic molecules (Kass & Nguyen, 2021). In this review, after briefly introducing the physiopathology of osteoarthritis, clinically approved IA treatments, the most recent and promising preclinical intervention strategies will be described and critically analyzed.

2 | THE ARCHITECTURE AND BIOLOGICAL STRUCTURE OF THE JOINT

Main structural and biological components of joints are the cartilage, the synovial fluid (SF) and the synovium. Articular cartilage is a thin layer (in human joints, hips and knees, ~1–3 mm in thickness; Frisbie et al., 2006; Malda

et al., 2013) that covers the ends of the bones in diarthrodial joints. It is a uniquely complex tissue devoid of blood vessels, lymphatics or nerves and it adsorbs a wide range of mechanical loads and impacts, facilitating a virtually friction-free movement. Highly specialized cells, the chondrocytes, sparsely distributed within this matrix are involved in the homeostasis of this complex tissue (Figure 1). The articular tissue is composed predominantly of hyaluronic acid or hyaluronan (HA), collagen fibrils (mostly type II collagen with some type IX and XI collagen), aggrecan proteoglycans (PGs), and other macromolecules, which are continuously synthesized by chondrocytes (Eyre et al., 2006; Freeman, 1979). HA is a linear high molecular weight (6500–10,900 kDa, Table 1) anionic polymer constituted by repeating disaccharide units of D-glucuronic acid and D-N-acetylglucosamine attached by β (1–4) and β (1–3) glycosidic bonds (Altman et al., 2015; Gupta et al., 2019; Moreland, 2003; Tamer, 2013). HA acts as a major component of the ECM keeping the articular cartilage hydrated and creates the backbone for PGs of the ECM (Gupta et al., 2019). In this way, it protects the cartilage and blocks the loss of PGs from the cartilage matrix into the synovial space, maintaining the physical form of the ECM. The cartilage is lubricated by the components of SF that fills the synovial space. The three key components of the SF are HA, the glycoprotein lubricin, and phosphatidylcholine (DPPC) (Figure 1). Due to its viscoelastic properties, SF acts as a protective barrier between the bone ends as well as a biochemical pool for nutrients and regulatory cytokines (Tamer, 2013). Hence, HA is responsible for both joint lubrication and shock absorption. The joint cavity filled by the SF is lined by the synovium, a specialized connective tissue. Its main function is the maintenance of SF volume and composition, by producing lubricin and HA. Through the SF and together with subchondral bone, the synovium also provides nutrition to the articular cartilage (Mathiessen & Conaghan, 2017). It is composed of two portions: a layer of cells (intima) and the underlying tissue (subintima). The first one contains type B synoviocytes and fibroblasts. These cells display distinct physico-chemical properties and are responsible for the overall maintenance of the SF and the articular cavity (Hascall & Laurent, 1997). The outer layer—subintima—consists of three types of connective tissues: fibrous (dense collagenous type), adipose (found essentially in fat pads), and areolar (loose collagenous type; Mathiessen & Conaghan, 2017).

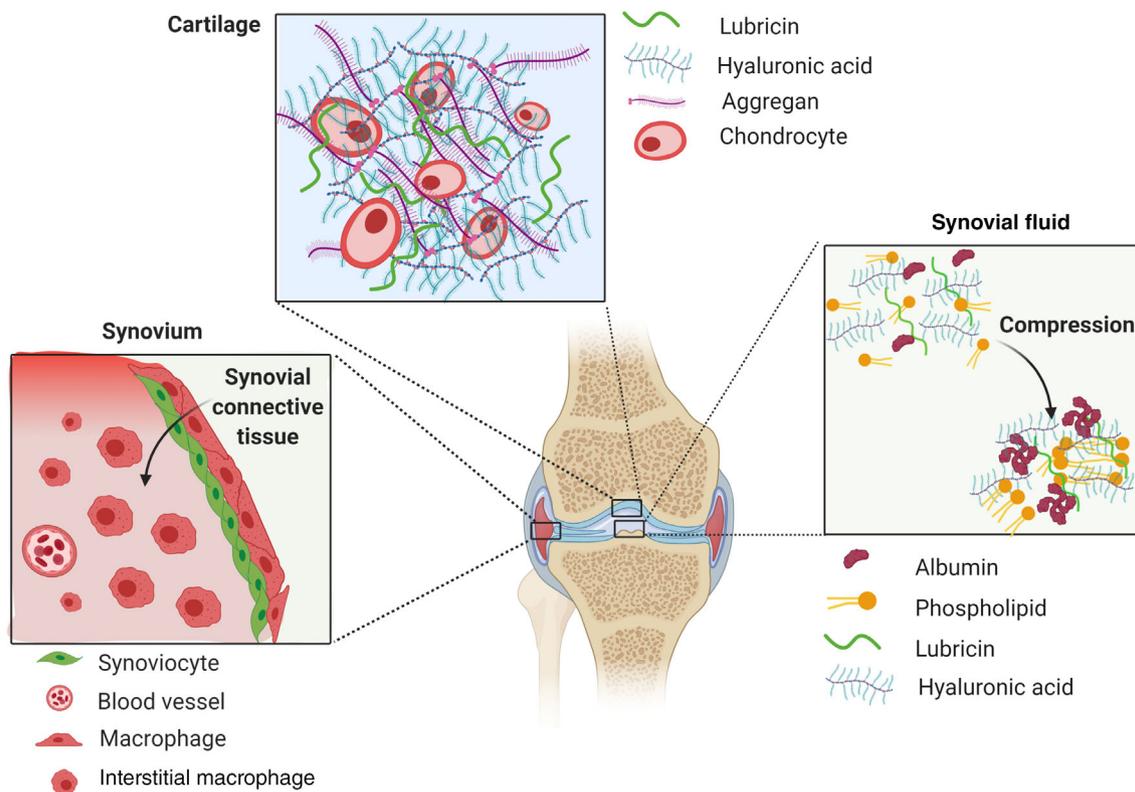


FIGURE 1 The knee joint. Schematic representation of the components of the knee articular joint, highlighting its cellular and molecular components

3 | PHYSIOPATHOLOGY OF OSTEOARTHRITIS

While OA pathogenesis is still to be completely elucidated, biological (breakdown and repair of joint cartilage) and mechanical (wear-and-tear and biolubrication) processes are clearly documented to trigger disease progression (Martel-Pelletier et al., 2016).

Under physiological conditions, cartilage homeostasis (normal cycle of breakdown and repair under mechanical stress) is maintained by the dynamic remodeling of ECM (Figure 1). Differently, during OA progression, alteration of the joint tissue metabolism (molecular derangement) followed by anatomic and/or physiologic derangements, such as reduction of proteoglycans concentration, inflammation, and cartilage degradation facilitates the irreversible tissue disintegration (Loeser et al., 2016; Maldonado & Nam, 2013). Also, a traumatic joint injury or joint hypermobility can induce an inflammatory response by synoviocytes and chondrocytes. They can release proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , in the SF of the affected joint. Proinflammatory cytokines induce the production of some catabolic enzymes by chondrocytes, such as matrix metalloproteinases (MMPs)-1, -3, and -13, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and -5 (aggrecanases-1 and -2). It is evident that MMP-13 is one of the key enzymes in OA progression, degrading the primary cartilage component, collagen type II. The activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) induces the release of other elements, such as nitric oxide (NO), cyclooxygenase 2 (COX-2), nitric oxide synthase (NOS), and prostaglandin E2 (PGE2), which lead to the disruption of the chondrocytes. All these events together with the products of ECM degradation induce an inflammatory response that triggers the OA degenerative cycle, until complete tissue destruction (Goldring & Otero, 2011; Lee et al., 2013; Loeser et al., 2016; Maldonado & Nam, 2013; Martin & Buckwalter, 2006). Also, they induce an alteration of both structure and function of the lymphatic system (Han et al., 2020; Shi et al., 2014). Under pathological conditions HA helps to prevent invasion of inflammatory cells into the joint space (Moreland, 2003). In the early stage of OA, the presence of proinflammatory cytokines in SF promotes a progressive HA decrease in concentration and molecular weight (MW) (2700–4500 kDa, Table 1) (Falcone et al., 2006; Weigel et al., 1986). In particular, it is reported that the production of proinflammatory cytokines IL-1 and TNF- α by rabbit synovial membrane cells stimulates expression of HA synthetase which may contribute to the fragmentation of HA under inflammatory conditions (Tanimoto et al., 2001). A progressive degeneration of the mechanical and viscoelastic properties occurs because of HA physico-chemical alterations in the SF, thus leading to significant pain, loss of function and erosion of articular surface (Gupta et al., 2019; Mathieu et al., 2009; Moreland, 2003).

Biolubrication in synovial articular joints results from the synergistic action among multiple biomolecules, including glycoproteins (e.g., lubricin), HA, and phospholipids (Figure 2). The articular cartilage surface is covered by hydrated stacks of phospholipid (PL) membranes that help reduce the friction with the opposing surface. Ex-vivo lubrication studies conducted by Pickard et al. on bovine articular cartilage revealed that, while lipids play a role in reducing the coefficient of friction under dynamic loading, proteins had a more significant effect in longer periods of static loading (Pickard et al., 1998). The lowest coefficient of friction was found when PGR4 (lubricin) was adsorbed on a soft layer composed of hyaluronan (HA) and collagen type II (Majd et al., 2014; Seror et al., 2015). Lubricin interacts with collagen type II on the outer surface of the cartilage. Hyaluronan is partially entrapped on the superficial zone of the cartilage where it forms complexes with phosphatidylcholines, after being immobilized by proteoglycan-4 PRG4, and in part protrude outside. Within the cartilage tissue and onto its surface, HA also interacts with the proteoglycan Aggrecan (Agg), a macromolecule composed of a protein backbone with grafted highly negatively charged glycosaminoglycan chains of chondroitin sulfate and keratan sulfate. As HA-Agg aggregates cannot be alone responsible for the

TABLE 1 Human synovial fluid (SF)

Parameter	Normal	OA
Volume (mL)	0.5–2.0	>3.5
Temperature (°C)	~34	>36
Viscosity (mPa s)	>300	<300
Total protein (g/100 mL)	10–30	15–35
HA MW (kDa)	6500–11,000	2700–4500

Note: Physico-chemical and biological features of SF under normal and OA conditions (Gerwin et al., 2006; Zaffagnini et al., 1996). Abbreviations: HA, hyaluronic acid; MW, molecular weight.

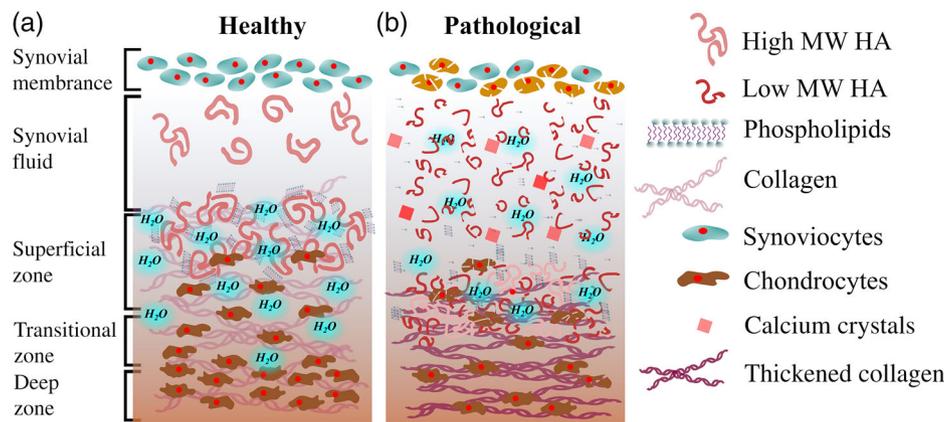


FIGURE 2 Molecular components involved in the biolubrication of the joint. Schematic representation of the arrangement of different components within the articular joint under normal physiological (a) and pathological (b) conditions. The part figures (a) and (b) illustrates the process of dehydration, shrinking of the collagenous cartilage surface, degradation of HMW HA into proinflammatory LMW HA in the SF and loss of chondrocyte and synoviocytes in the diseased tissue

characteristic low friction of synovial joints at physiological loads, additional components, such as phospholipids, are indeed expected to contribute significantly (Seror et al., 2012). Along this line, the combined effect of different molecular weights HA chains and liposomes on lubrication was systematically studied ex-vivo in human cartilage model and in-vivo in a rabbit model of osteoarthritis (Forsey et al., 2006; Kawano et al., 2003). It was suggested that the HA would aid in the fluid lubrication occurring at low-loading conditions while the phospholipids would contribute toward the boundary lubrication prevailing at high-loading conditions. The effect of dehydration and changes in the morphology of the constituents of the cartilage and the synovial cavity under normal and pathological conditions is schematically shown in Figure 2. The viscosity of water under confined conditions, as in between two sliding membranes, dramatically increases upon dehydration. However, the shear friction coefficient remains moderately low due to an increased repulsion between the two opposing surfaces as they become closer (Leng & Cummings, 2005; Schlaich et al., 2017). Incidentally, molecular dynamics (MD) simulations represent an ideal tool to elucidate the mechanisms regulating surface friction between biological layers, as extensively documented in the open literature (Chatterjee et al., 2020). High MW HA is assumed to possess a random coil and semi-stiff conformation under physiological conditions. However, the ionic strength, ion binding affinity and pH can affect HA structure as the coil would shrink or expand depending on the ion type and charge density. Specifically, kosmotropic ions (e.g., Na^+ , Ca^{2+}) would favor intramolecular HA interaction and the ordering of water (“salting out” effect), whereas chaotropic ions (e.g., K^+) would destabilize the water structure and promote HA solubilization (“salting in” effect). Interestingly, ion channels appear to be upregulated in early OA and the concentration of ions in the osteoarthritic SF is generally higher than under healthy conditions. For instance, an up to 60% enrichment in calcium has been documented in OA *versus* healthy joints (Jubeck et al., 2008). This is relevant as HA physical crosslinking mediated by ionic and hydrophobic interactions and chains entanglement influence its organization and mechanical strength and therefore the resulting coefficient of friction (Majd et al., 2014). Specifically, under healthy conditions, highly reactive oxygen-derived free radicals (ROS), normally produced at low levels, are involved in the HA catabolism within the joint. As the ROS concentration increases, following injury or aging, HA degradation accelerates and tend to stimulate joint inflammation (Day & Carol, 2005; Vuorio et al., 2017). Persistent oxidative stress and unbalanced HA degradation decreases the average HA MW, thus further triggering the inflammatory cascade and altering lubrication (Band et al., 2015). The interaction of low MW HA with a lipid bilayer was also investigated by MD simulations. The diminished lubrication under high loads was attributed to a weaker attachment of the shorter compared with the longer HA chains to the cartilage surface, leading to their easier removal along with the PC lipids attached to them by the sliding friction (Figure 2). Notably, the pathological SF contains a greater amount of phospholipids compared with the healthy conditions (Kosinska et al., 2013).

4 | DIAGNOSTIC TOOLS IN OSTEOARTHRITIS

Imaging and early detection of joint degeneration are key in improving disease prognosis and therapy follow-up. The gold standard to diagnose and stratify patients in terms of OA severity is radiographic investigation. Conventional

radiographic imaging is widely available, economical, and well accepted by patients, although it uses ionizing radiation. On the other hand, Magnetic Resonance Imaging (MRI) is used only to visualize inflammatory lesions in joints and periarticular regions that cannot be observed with X-ray. Notably, a MRI scan can cost up to \$4000 and require almost 2 h, while X-ray imaging costs on average less than \$100 and lasts a few seconds (“MRI vs. X-ray”; Diffen LLC, 2021). For this reason, X-ray will continue to be a cornerstone in OA diagnosis despite its severe limitations. In the early stages of OA, X-ray detects subchondral sclerosis or subchondral cysts and the joint space narrowing (Braun & Gold, 2012). Kinds et al. assessed the diagnosis of knee OA comparing clinical *versus* radiological diagnosis (Kinds et al., 2011). This study showed that there was less than 10% agreement between the two diagnostic methods. The main reason is due to the projectional nature of the radiographs: the low number of acquired images and their projectional views reduces the ability to accurately detect OA (Duncan et al., 2006). Sakellariou et al. suggested that weight-bearing and posteroanterior and lateral views should be acquired to improve the diagnostic power of X-ray in OA (Sakellariou et al., 2017). Certainly, the combination of radiographic techniques with clinical diagnosis and more sophisticated imaging modalities (MRI sonography, scintigraphy) could improve even further OA diagnosis (Zhang et al., 2010). Specifically, MRI can discriminate between soft and hard tissues and properly visualize different biological structures within the joint. Furthermore, when a contrast agent is injected during MR imaging, synovitis can be diagnosed via joint effusion analysis (Guermazi et al., 2012; Roemer et al., 2010). The most common MRI contrast agents used for imaging synovitis are Intravenous gadolinium (Magnevist [gadopentetate dimeglumine; Bayer HealthCare Pharmaceuticals, Bayer Schering Pharma AG, Berlin, Germany] or Omniscan [gadodiamide; GE Healthcare, New Jersey]), that are administered at a dose of 0.2 mL (0.1 mmol)/kg body weight (Guermazi et al., 2011). However, to date, MRI alone cannot improve the early detection of knee OA, but it remains a powerful research tool to characterize the biological structure–pain relationship and provide insights into the progression of structural changes (Hunter et al., 2015). More methodologically robust studies are needed to explore the value of imaging, and possibly multimodal imaging, in the early diagnosis and management of OA.

5 | OA TREATMENTS VIA SMALL MOLECULES

The therapeutic approaches currently available in the clinic for OA management are mostly focused on alleviating the symptoms. The localized nature of the disease offers the opportunity to deliver drugs IA reducing potential systemic side effects and allowing the use of molecules with low bioavailability (Evans et al., 2014; Wehling et al., 2017). However, this administration route is associated with different challenges, such as the risk of infection, swelling, inflammation, and the requirement of a trained personnel (Charalambous et al., 2003; Chen et al., 2002; Cheng & Abdi, 2007). Importantly, the rapid clearance of the injected drugs from the joint space is a major limitation to localized therapies (Aigner & Söder, 2006; Wehling et al., 2017). As such, increasing the drug dwelling time within the joint to reduce the number of injections represents the biggest challenge in the development of novel IA OA therapies. Conventional palliative therapies act on pain and inflammation using analgesics and corticosteroids, and on biolubrication proving viscoelastic supplements, as the injection of exogenous HA (Hunter, 2011).

5.1 | Reduction of OA pain and inflammation

Several drugs, belonging to a wide range of different pharmacological classes, are used for the treatment of OA inflammation and pain. Oral analgesics are used as first line therapy. Among them, acetaminophen is preferred because of its low cost and safety profile (Kolasinski et al., 2020). However, when acetaminophen cannot manage the symptoms anymore, more potent drugs need to be used including non-steroidal anti-inflammatory drugs (NSAID), such as Ketorolac, and COX-2 inhibitors, such as Diclofenac, Ibuprofen, Celecoxib, and Rofecoxib (Bannuru et al., 2019). Eventually, when these potent anti-inflammatory molecules fail to control pain and inflammation, opioids are considered. Multiple and severe side effects, such as gastrointestinal, cardiovascular, renal, and central nervous system complications, are associated with the chronic oral uptake of these drugs (Hochberg et al., 2012; Steinmeyer et al., 2018; W. Zhang, Ouyang, et al., 2016). Glucocorticoids is another important pharmacological class of drugs used for OA treatment. They are mostly administered IA and include methylprednisolone acetate, triamcinolone acetate (TA), betamethasone acetate (BA) and betamethasone sodium phosphate (BP), triamcinolone hexacetonide (TH), and dexamethasone (DEX). They exhibit a complex biological activity, involving anti-inflammatory and immunosuppressive effects, that blocks the

production of proinflammatory cytokines, leukocyte recruitment and activation. The IA injection of glucocorticoids presents rare side effects, such as infection at the site of injection and loss of bone density, but the main limitation is their rapid clearance leading to short term effect on OA associated pain (Hepper et al., 2009).

5.2 | Reduction of cartilage breakdown

Several drugs have been identified for their ability to inhibit cartilage degeneration, promoting its repair, but none of them have been translated to clinical practice yet (Matthews & Hunter, 2011). These include growth factors, such as insulin-like growth factor 1 (IGF-1), fibroblast growth factor 18 (FGF-18), and bone morphogenetic protein (BMP) 7. These molecules act by stimulating cartilage growth to prevent further degradation and loss of chondrocytes. Even upon IA injection, these molecules are rapidly cleared from the joint, limiting their clinical translation. Thus, strategies for improving their retention in the cartilage are needed (Hunter et al., 2010; Miller et al., 2010; Onuora, 2014). For example, a simple fusion of IGF-1 with heparin-binding domain was sufficient to prolong the joint retention time of 7 days in a rat model of OA (Loffredo et al., 2014). The proteases responsible for progressive cartilage degradation have been evaluated as another potential pharmacological target. In particular, the inhibition of MMP-13, a key enzyme in the degradation of collagen type II, could block cartilage degradation and slow down the disease progression (Li et al., 2011). Nevertheless, the clinical use of MMP inhibitors has been limited by dose and duration due to musculo-skeletal side effects (Krzeski et al., 2007). In order to overcome these limitations, MMP-13 short interference RNA (siRNA) has been examined as an alternative strategy to efficiently inhibit the expression of MMP-13. However, naked siRNA application in-vitro and in-vivo is limited by poor intracellular uptake and rapid enzymatic degradation. These limitations can be overcome by using chemically modified siRNAs or nanoparticles, as discussed later (Akagi et al., 2014; Bedingfield, Colazo, Yu, et al., 2021; Gao et al., 2011). Finally, biologic agents, such as monoclonal antibodies against inflammatory cytokines, such as IL-1 β (canakinumab) and TNF (infliximab, adalimumab), and other anti-IL-1 or anti-TNF agents (anakinra, etanercept), have been considered to reduce cartilage breakdown. Unfortunately, clinical trials have lacked evidence of either sustained benefit or effective cartilage targeting (Evans et al., 2014).

6 | OA TREATMENTS VIA MACROMOLECULES (VISCOSUPPLEMENTATION)

The intra-articular IA injection of HA represents another well-established strategy for the local pain and inflammation management in OA. Balazs and Denlinger demonstrated that the beneficial effects of the IA injected HA are mostly associated with the partial restoration of the SF rheological properties (Balazs & Denlinger, 1993). Also, the IA injection of HA has the potential to reduce joint structure deterioration in the early stage of the disease by acting on multiple pathways (Çubukçu et al., 2005). Exogenous HA interferes with the production of NO, superoxide, hydroxyl radicals, suppresses MMP and ADAMT, and can protect chondrocytes and synoviocytes from apoptosis. This improves endogenous HA and PGs synthesis, both preventing cartilage degradation and promoting its regeneration (Gupta et al., 2019). In addition, exogenous HA also alleviates joint pains by modulating nerve impulses and nerve sensitivity (Goldberg & Buckwalter, 2005; Gupta et al., 2019; Moreland, 2003).

Several HA formulations have been developed for OA treatment, as listed in Table 2, presenting different molecular structures and weights (Bannuru et al., 2011; Bowman et al., 2018; Miller & Block, 2013). Specifically, exogenous HA are characterized by linear or cross-linked molecular structures, or combination thereof, to increase the dwelling time and improve shock-absorbing properties (Iannitti et al., 2012; Watterson & Esdaile, 2000). As per the molecular weight, it tends to be higher than 500 kDa, as multiple studies have demonstrated that hyaluronan fragments of low MW can trigger inflammatory processes (Cyphert et al., 2015).

The biological activity of exogenous HA with different MW was investigated in several preclinical studies (Ghosh et al., 2005; Shimizu et al., 1998; Smith & Ghosh, 1987). The first study conducted by Smith and Ghosh on different cell lines of human synovial fibroblasts from OA patients demonstrated that the addition of exogenous HA stimulated the HA synthesis in human synovial cell lines. A maximum effect was observed for exogenous HA MW ranging between 500 and 4000 kDa, while no effect was reported for MW lower than 500 kDa and a reduced effect was measured for MW higher than 4700 kDa. Thus, intermediate MW HA appears to be more effective in promoting endogenous HA biosynthesis, possibly due to their optimal binding to HA receptors on synovial fibroblast cells derived from an

TABLE 2 FDA-approved injectable HA viscosupplementation products (Bowman et al., 2018; Lee et al., 2006)

Product	Molecular weight (kDa)	Dose (mg)	Frequency	Crosslinking
Hyalgan®	500–730	20 (5 doses)	Weekly	No
Supartz FX™	620–1170	25 (5 doses)	Weekly	No
Monovisc®	1000–2900	88 (1 dose)	Once	Yes
Orthovisc®	1000–2900	30 (3–4 doses)	Weekly	No
Hyruan Plus®	3000	20 (3 doses)	Weekly	No
Euflexaa	2400–3600	20 (3 doses)	Weekly	No
Synivisc®	6000	16 (3 doses)	Weekly	Yes
Durolane®	100,000	60 (1 dose)	Once	No
Gel-one®	∞	30 (1 dose)	Once	Yes
Synivisc-One®	∞	48 (1 dose)	Once	Yes

osteoarthritic joint (Smith & Ghosh, 1987). Also, studies conducted on preclinical OA model demonstrated that injection of HA, with a MW range between 500 and 1000 kDa, lead to a partial restoration of synovial cell metabolism and normalization of HA biosynthesis (Ghosh & Guidolin, 2002). Although the correlation between HA MW and its therapeutic activity in-vitro and in preclinical animal models (Antonacci et al., 2012; Mori et al., 2002; Schmidt et al., 2007) was clearly documented, these results were not replicated in clinical settings. Different clinical trials were conducted to understand the relationship between the IA injection of exogenous HA and OA pain (Gigis et al., 2016; V. Karatosun et al., 2005; Karlsson et al., 2002; Lee et al., 2006; Testa et al., 2021; Wobig et al., 1999). However, the results of these trials were often contradictory: some clinical studies demonstrated the advantages of using high MW HA (Bayramoğlu et al., 2003; Kotevoglou et al., 2006; Tıkız et al., 2005), while others did not confirm this hypothesis (DeGroot III et al., 2012; Ghosh & Guidolin, 2002; V. Karatosun et al., 2005; J. Karlsson et al., 2002; Vitanzo Jr & Sennett, 2006). In conclusion, there is no consensus on the advantage of injecting IA low versus high MW HA for OA treatment.

In the attempt to resurrect the clinical use of HA, several preclinical (Dong et al., 2013; Euppayo et al., 2017; Karakurum et al., 2003; Z. Zhang, Wei, et al., 2016) and clinical (Bannuru et al., 2009; Bellamy et al., 2006; de Campos et al., 2013; Lee et al., 2011; Ozturk et al., 2006; Petrella et al., 2015) studies have been conducted to investigate possible synergism of exogenous HA with anti-inflammatory drugs. It was reported that the symptoms are relieved starting a few weeks after the first administration of HA and lasts from 6 to 12 months (Bannuru et al., 2009; Bannuru et al., 2011; Bellamy et al., 2006; Davalillo et al., 2015; Tammachote et al., 2016). The benefits of this combination therapy stay as an active clinical investigation field.

Some of these trials consistently demonstrated an improvement in pain relief and faster analgesic effect for the IA injection of HA and anti-inflammatory drugs as opposed to the sole IA administration of HA (de Campos et al., 2013; Lee et al., 2011; Ozturk et al., 2006; Petrella et al., 2015). For example, it was observed a significant improvement in terms of pain in knee OA in the group that received both ketorolac, a NSAID, and HA as compared with the HA alone within 16 weeks of follow-up (Lee et al., 2011). Similar outcomes were also obtained for the combination of TA, a glucocorticoid, with Orthovisc® (Ozturk et al., 2006). It was demonstrated that this combination showed a more rapid pain relief than HA alone, displaying a beneficial effect during the first year post-treatment. In conclusion, it appears that HA combined with corticosteroid should be preferred to HA alone for the treatment of patients with knee OA.

7 | OA TREATMENT VIA NANO/MICROMEDICINES

Studies at the molecular level reveals that the biolubrication process in the synovial joints involve a complex interplay of proteins, sugars, and lipids where only one component is unable to emulate the process. In order to overcome the challenges of conventional treatment, it is necessary to simultaneously achieve longer lubrication of the diseased joint; improve the residence time of administered drugs; and, in advanced conditions, achieve regeneration of the degraded cartilage. Lipid-based nanoparticles have been studied to investigate into the possibility of using them as lubricants, while nanoparticles and microparticles derived from dendrimers, polymers and biopolymers have been utilized to improve the residence time of therapeutics. Currently, tissue regeneration strategies are also being considered in order

to recover the diseased and lost cartilage. Different strategies have been explored using specialized nanoparticles like cationic and targeted nanoparticles, microparticles or microgels and stimuli-responsive hydrogels to increase the dwelling time and the therapeutic efficacy as summarized in Figure 3.

7.1 | Lipid-based nano/microparticles in biolubrication

As previously mentioned, HA would aid in the fluid lubrication and static load bearing capacity while phospholipids would contribute toward the boundary lubrication. Three different treatment formulation consisting of (i) 2000 kDa HA (high MW), (ii) 800 kDa (medium MW), and (iii) a combination of 2000 kDa HA with 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) liposomes were studied simultaneously. In three different experimental groups, these were administered by IA injections in the anterior cruciate and medial collateral ligament transection induced OA rabbit model (Kawano et al., 2003). Histological analysis of the articular cartilage post-treatment showed that there was no significant regeneration of the diseased cartilage in the groups treated with HA alone but the combined treatment group (HA + liposomes) showed a significantly less damaged cartilage. Moreover, different kind of phosphatidylcholine-based (PC) liposomal formulations, including small unilamellar vesicles (SUV) of size <100 nm and multilamellar vesicles (MLV) >800 nm, with transition temperatures ranging from -21°C to 74°C were studied in an ex-vivo human sourced cartilage-on-cartilage apparatus (Sivan et al., 2010). Interestingly, it was observed that MLV were more efficient lubricants than SUV. The most effective lubrication was achieved when 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) was used with a transition temperature slightly below body temperature. The study also highlighted the need for hydration and high compressibility as a criterion to achieve effective lubrication. The same group also developed a MLV composed at a molar ratio of 0.6:1.0 DMPC:DPPC with a diameter of ~ 3 μm (Verberne et al., 2010). The comparative study concluded that the MLV was a more efficient lubricant and induced less wear in comparison to cartilage lubricated with inflamed SF. More recent studies focused on understanding the

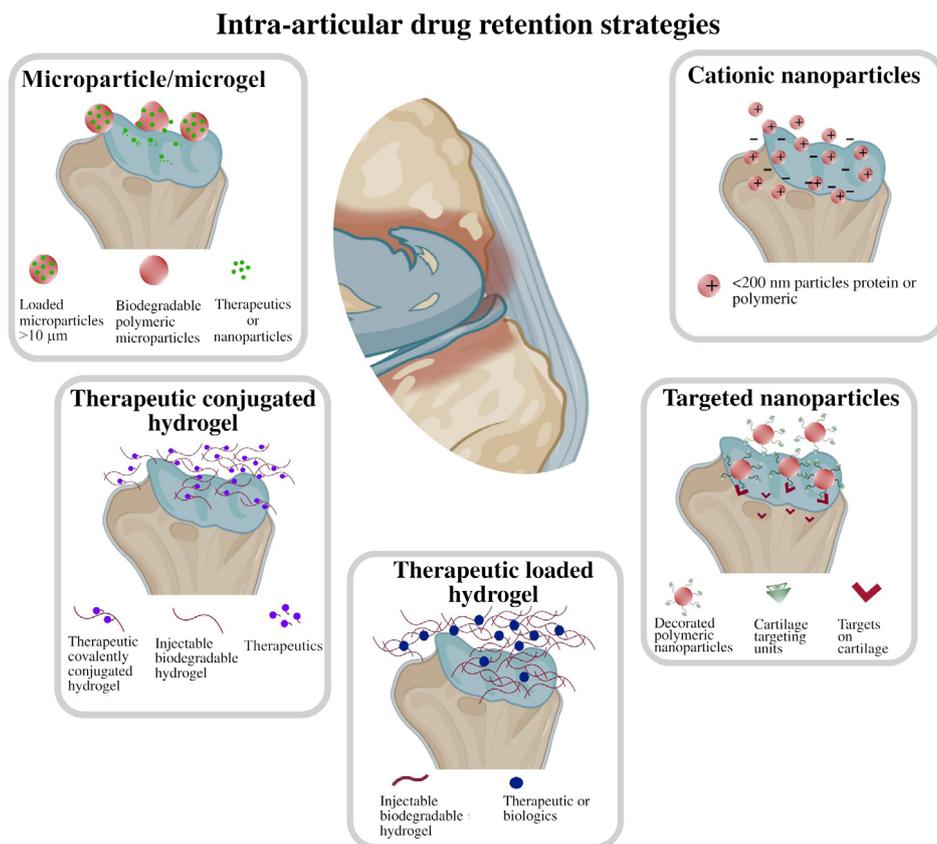


FIGURE 3 Pictorial representation of different strategies at the molecular, nano, and microscale for improving the IA residence time of small molecules

actual association between HA and vesicles made out of DPPC measured the coefficient of friction using colloidal AFM probe technique (Wang et al., 2013). The association structures formed at the interface of a supported lipid bilayer of DPPC and DPPC liposomes and HA in bulk solution were sufficiently stable. The low coefficient of friction and high load bearing capacity of such composite layers highlighted its lubricating property. A significantly low coefficient of friction of 0.01 was found when DPPC was added as the last adsorbed component, for pressures significantly above what is encountered in healthy joints. Similarly, Klein et al. have studied SUV composed of hydrogenated L- α -phosphatidylcholine (HSPC) lipid of 65 nm and it was suggested as a boundary-lubricating agent (Goldberg et al., 2011). Surface force balance studies were conducted to study the normal and shear forces operating under high loading conditions and found that extremely low coefficient of frictions, at pressures comparable to that in healthy joints. It was proposed that at the highest pressures the surfaces approached to a “hard-wall” repulsion at a separation $\sim 21 \pm 2$ nm, which corresponds to four bilayers arising from the two flattened liposome layers. Furthermore, using similar technique HA was immobilized on the mica surface and MLV composed of DPPC and HSPC was added to the surface (Seror et al., 2015). The synergistic effect of the lubrication at the interface resulted in a coefficient of friction of 0.001 at 100 atm. The study further emphasized that the HA attached to the collagen surface of the cartilage plays a major role in the process of lubrication together with lipid bilayers (Seror et al., 2015).

7.2 | Nanoparticles and liposomes in IA drug delivery

In the context of OA in addition to lubrication it is often challenging to achieve prolonged drug residence in the synovial joint. As described earlier, the cartilage is primarily composed of a dense network of PGs which are highly anionic in nature. In order to circumvent the problem of therapeutic loss through the synovial vasculature and lymphatic system, nanoparticles and microparticles have emerged with significant promise. In this context, *ex vivo* studies using bovine cartilage was used to study the role of size and charge on the cartilage penetration propensity of solutes (Bajpayee et al., 2014). Solute sizes ranging from 0.8 to 16 nm of various charges were considered and it was found that avidin, with a hydrodynamic radius of about 7 nm and cationic charge under physiological conditions, had the highest penetration ability, while neutravidin having the same size but with neutral charge was found to localize at the surface of the cartilage.

Subsequently, preclinical studies have investigated the IA administration of siRNA loaded solid cationic lipid nanoparticles (~ 67 nm) derived out of Dlin-KC2-DMA (cationic lipid), DPPC, C16 ceramide-mPEG2000 and cholesterol (Wang et al., 2018; Zhang et al., 2014). The therapeutic efficacy of Indian Hedgehog (Ihh) siRNA involved in the differentiation and maturation of chondrocytes was studied *in vivo* in rats following IA injections every 2 weeks for 10 weeks. The histological analysis clearly demonstrated that the liposomal delivery system was associated with an increase of collagen type II and a down regulation of proinflammatory factors like MMP-13, collagen type X, and Runx2 compared with the free siRNA. Thus, these studies clearly demonstrated the advantage and the problems associated with cationic nanoparticles. The drug delivery system was more efficient in reaching the chondrocytes and delivering the drug into cells, however the system was also associated with the problem of frequent injection. With the similar idea of achieving deep cartilage penetration and to increase the residence time of the therapeutic agent, IGF-1 was conjugated to the amine terminal of polyamidoamine (PAMAM) dendrimers (~ 10 nm in size) where the end was functionalized with variable molar ratios of poly(ethylene glycol) (PEG) in order to control surface charge (Figure 4; Geiger et al., 2018). As a result of this conjugation, the drainage of the particles through the lymphatic and vascular system was reduced. The small size along with the cationic charge of the conjugates led to significantly higher penetration into the cartilage and significantly increased the residence time of drug in the articular region. The activity of the conjugate was studied *in vivo* in OA rat model and it was found that the conjugate reduced loss of aggrecans and chondrocytes 4 weeks post-IA injection, while no effect was observed for the unconjugated IGF-1. The possible conjugation of cartilage matrix-binding ligands to NPs was also recently reported for siRNA delivery against MMP-13 using polymeric micelles (~ 100 nm) with anti-collagen II antibody conjugated to the corona (Bedingfield, Colazo, Yu, et al., 2021). The effect of the conjugation of the antibody on the enhancement of the retention time of the nanoparticle was studied in a load-induced mouse model of post-traumatic osteoarthritis (PTOA). However, also in this case IA injections were performed once per week that is an intensive dosing regimen and it would benefit from methods that could further prolong the residence time of the cargo.

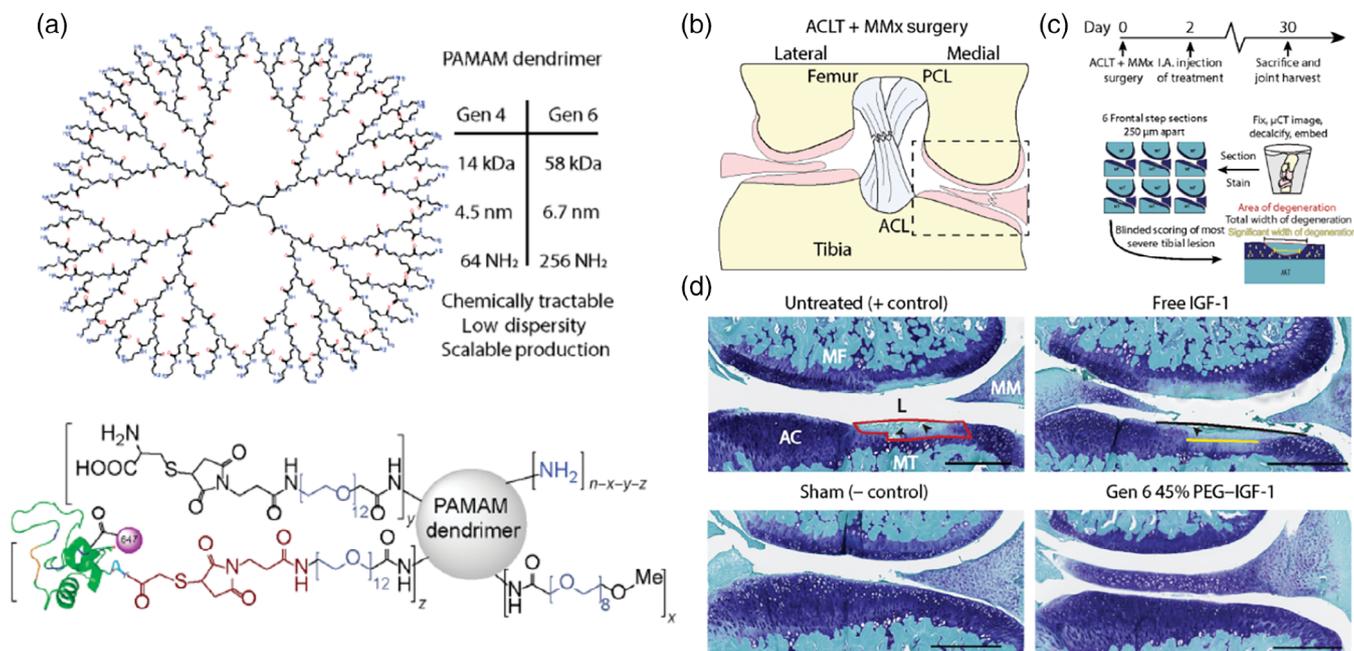


FIGURE 4 Therapeutic efficacy of insulin-like growth factor 1 (IGF-1) conjugated polyamidoamine (PAMAM) dendrimers. (a) Chemical structure and characteristics of PAMAM dendrimers (Gen 4 shown); (b) schematic representation of a rat knee frontal section illustrating the ACLT (anterior cruciate ligament transection) + MMx (medial meniscectomy) surgery. Dotted lines show the primary zone of lesion formation; (c) schematic of surgery timeline and tissue processing procedures. IA, intra-articular; (d) representative toluidine blue/fast green stained frontal sections of the medial femur and tibia. Area of degeneration outlined in red. Total and significant widths of degeneration are outlined in black and yellow, respectively. Matrix loss shown as black arrowheads. AC, articular cartilage; L, lesion; MF, medial femur; MT, medial tibia; MM, medial meniscus. Scale: 500 μm (Reprinted with permission from Geiger et al. (2018))

7.3 | Microparticles and microgels

In addition to using charge-based binding and cartilage targeting agents to enhance the residence time of therapeutics, larger particles, or microparticles have also been considered. The long residence time of these systems makes them particularly suitable for the delivery of drug conjugates with cartilage-penetrating behavior to form a long-term drug depot in the joint. These can be engineered into a large range of size and shape and these larger particles are also resistant to lymphatic and vascular drainage. Recently, approved by FDA, Zilretta[®] is a poly(lactic-co-glycolic acid) (PLGA) based microparticle formulation designed to release an anti-inflammatory drug TA after IA injections. The system features a monolithic PLGA microparticle system loaded with crystals of TA where the size ranges from 20 to 100 μm and it is fabricated by solid-in-oil-in-water (S/O/W) emulsion technique. The system not only extended the residence time of the corticosteroid in the IA region, but also it reduced the blood drug concentration thereby reducing systemic exposure of other organs (Bodick et al., 2015). The success of the system lies in its simplicity and this made similar PLGA-based systems attractive for future clinical applications. Recently, our research group has developed an injectable PLGA-based microparticle system using a top-down approach where the size, shape and mechanical properties of the particles can be tuned independently (Di Francesco et al., 2021). These microparticles were loaded with another FDA approved corticosteroid, DEX, for OA management and the ability to reduce joint structural changes by sustained release of the drug was studied in-vivo in mouse model of overload injury-associated PTOA. The reduction in the proinflammatory factors was studied over a time period of 1 month. Interestingly, in addition to the therapeutic efficacy of the composite system, the microparticle system *per se* was found to have a therapeutic efficacy. It was hypothesized that the unique flat shape and mechanical property of the particles complementarily aided in the process of lubrication (Figure 5; Di Francesco et al., 2021). Additionally, the same particles were used for delivering matrix metalloproteinase 13 (MMP-13) interfering RNA loaded nanoparticles (siMMP13-NPs) in the same animal model (Bedingfield, Colazo, Di Francesco, et al., 2021). In particular, the authors demonstrated that the combination of siRNA NPs with microparticles (siMMP13-NPs loaded μPLs) significantly increased the residence time in the joint compared with the free NPs. Also, the gene silencing effect of siMMP13-NPs loaded μPLs in-vivo was maintained for 28 days after a single IA injection, thereby reducing all the

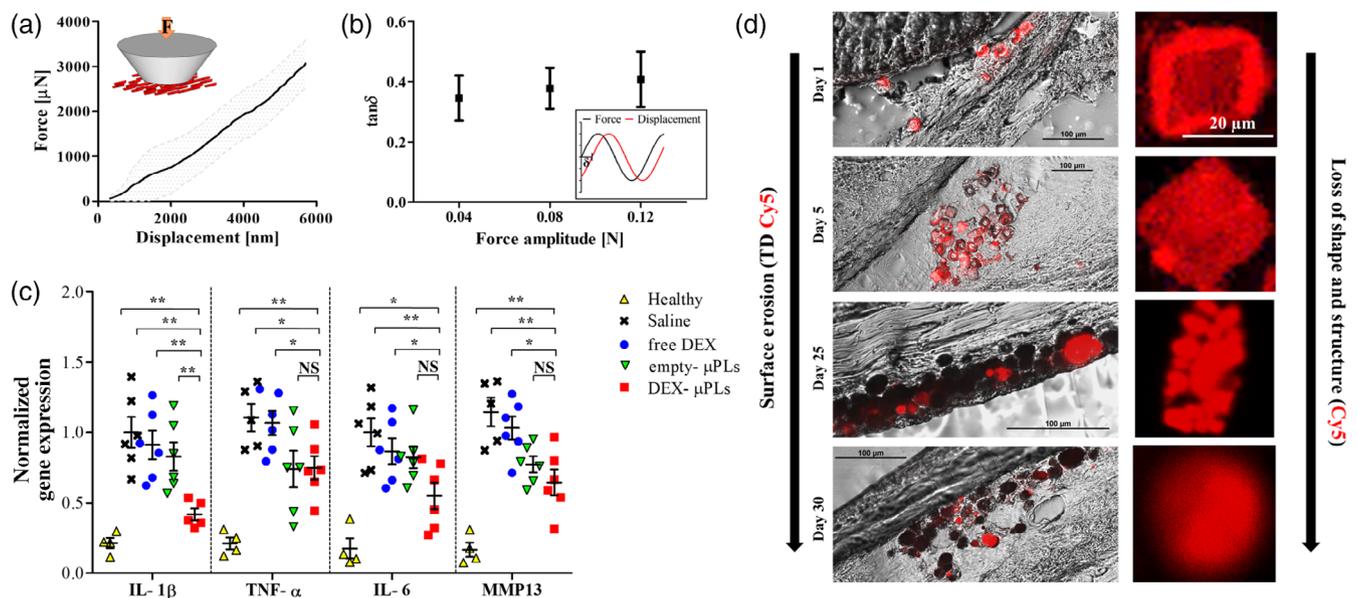


FIGURE 5 Therapeutic efficacy of dexamethasone loaded PLGA microplates. (a) Force–displacement curve for a flat punch indentation experiment on μ PLs (average curve and standard deviation). In the inset, a schematic of the experimental setup is provided. (b) Mechanical damping of μ PLs upon cyclic loading (frequency 5 Hz) as a function of the force oscillation amplitude. In the inset, a schematic of the testing routine highlights the phase angle δ -dissipation parameter. Results are presented as the average \pm SD ($n = 3$). (c) In-vivo expression of IL-1 β , TNF- α , IL-6, and MMP-13 measured by TaqMan qPCR (for each treatment groups $n = 6$, while for the healthy group $n = 4$). Statistical analysis via one-way ANOVA (GraphPad Prism 8), corrected for multiple comparisons by controlling the false discovery rate with a two-stage, step-up Benjamini–Krieger–Yekutieli method: * $p < 0.05$, ** $p < 0.01$, while no significant differences are indicated on the graphs as NS. (d) The $\times 20$ images zoomed in on Cy5- μ PLs within a mouse model of PTOA at days 1, 5, 25, and 30. Microplates are seen in the joint for up to 30 days with surface erosion evident by loss of fluorescence (heterogenous) in a significant number of individual Cy5- μ PLs at days 25 and 30 as compared with days 1 and 5. Cy5- μ PLs at days 1 and 5 have a consistent square shape and structure meanwhile Cy5- μ PLs at days 25 and 30 have lost this morphology. In all images on the right scale bar = 100 μ m. TD, transmission detector (Reprinted with permission from Di Francesco et al. (2021))

problems associated with MMP-13 activities in the progression of the disease itself (Bedingfield, Colazo, Di Francesco, et al., 2021). Different polymers including chitosan or synthetic materials like PEG, poly(caprolactone) (PCL), and poly(propylene sulfide) (PPS) have been utilized to develop similar slow releasing platforms. Inflamed joints are particularly characterized by elevated protease levels and with the objective of using this environment as a trigger to release therapeutics from amino acid based poly(ester amide) (PEA) has emerged as a promising polymer. Microparticles with an average diameter of 22 μ m derived from PEA was utilized to load corticosteroid TA in order to reduce the repeated administrations (Rudnik-Jansen et al., 2017). The efficacy of TA and PEA loaded TA was studied in an OA rat model. The residence time of the PEA microparticles in healthy rat joints or joints with mild collagenase-induced OA was specifically monitored by loading near infrared marker NIR780-iodide where injected microspheres showed retention of up till 70 days. Simultaneously, the microparticle system was associated with lower peak serum levels of TA than free drug. Subsequently, the same group also studied the efficacy of PEA *versus* PLGA microparticles of similar average diameter loaded with TA (Rudnik-Jansen et al., 2019). The efficacy was studied in rats induced with synovitis flares at days 0, 14, and 28. While all the formulations significantly reduced joint swelling, only the PEA system showed an effective anti-inflammatory activity after the second and the third flare and extended the release to 3 months.

With the objective of simultaneously achieving longer residence time and cushioning effect, microgels have also been used for the treatment of OA. Recently, injectable microgels were synthesized using 4-arm PEG-Maleimide functionalized with a cartilage or synoviocyte-binding peptide. A droplet based microfluidic system was employed for the fabrication of microparticles with an average size of 50 μ m loaded with PLGA nanoparticles with an average size of 200 nm. The cartilage-targeting peptide in combination with the large size of the particle increased the retention time of the construct, while the PLGA nanoparticle was used to load a hydrophilic drug model, such as rhodamine. The retention of the particles in the joint space for at least 3 weeks was studied using a PTOA rat model. Additionally, all microgel formulations were found to be localized in the synovial membrane and significantly increase the IA retention

time of a considered drug model (Mancipe Castro et al., 2020). Indeed, the nested drug delivery system comprising nanoparticles distributed within targeted microgels allows one to reduce the frequency of IA administrations for both molecular therapeutic agents and nanoparticles. A similar “mechanical pillow” was developed where a 4-arm PEG Malemide was crosslinked with 50% non-degradable dithiothreitol (DTT) and 50% MMP-degradable peptide crosslinker (GCRD-VPMSMRGGDRCG, VDM) to obtain a “on-demand” soft release system (Holyoak et al., 2019). The system was also incorporated with PLGA nanoparticles loaded with DEX, which were essentially released by collagenase action and not by mechanical loading of the system. The disease modifying capacity of the system was studied in an OA mouse model and 2 weeks postinjection, both NP-loaded hydrogels and hydrogels alone significantly reduced osteophyte size compared with non-hydrogel-treated groups.

7.4 | Hydrogel and combination therapies

Although all the above discussed systems are associated with some advantages, the current research is more focused on combining these systems to achieve better disease outcomes. On one hand, studies were conducted to study the combined lubrication effect of hydrogel and liposomes on the other hand hydrogels were combined with anti-inflammatory drugs and mesenchymal stem cells to simultaneously address the problem of inflammation, drug residence, and tissue damage. In this section, we will briefly discuss some of the concepts, preclinical and clinical studies on the possible combination therapies.

In order to unravel the mechanisms underlying the possible use of hydrogels and hydrogel liposome combination to achieve biolubrication, an extensive study was conducted using MLV immobilized on different hydrogel matrices. In order to create a cartilage-like lubrication system, small amounts of MLV were incorporated within the gel matrix to form microreservoirs inside the hydrogel matrix (Figure 6). The lubrication effect of MLV obtained using DMPC and HSPC both on the surface of the gel as well as incorporated within the gel was studied in synthetic polymeric systems like polymethacrylamide, poly(HEMA-*co*-methacrylic acid), poly(acrylic acid-*co*-dimethacrylamide), and biopolymer like cross-linked gelatin methacrylate with different hydration conditions. The frictional pattern was studied using a tribometer and a significant reduction in the friction was found in all the systems incorporating MLVs within the hydrogel

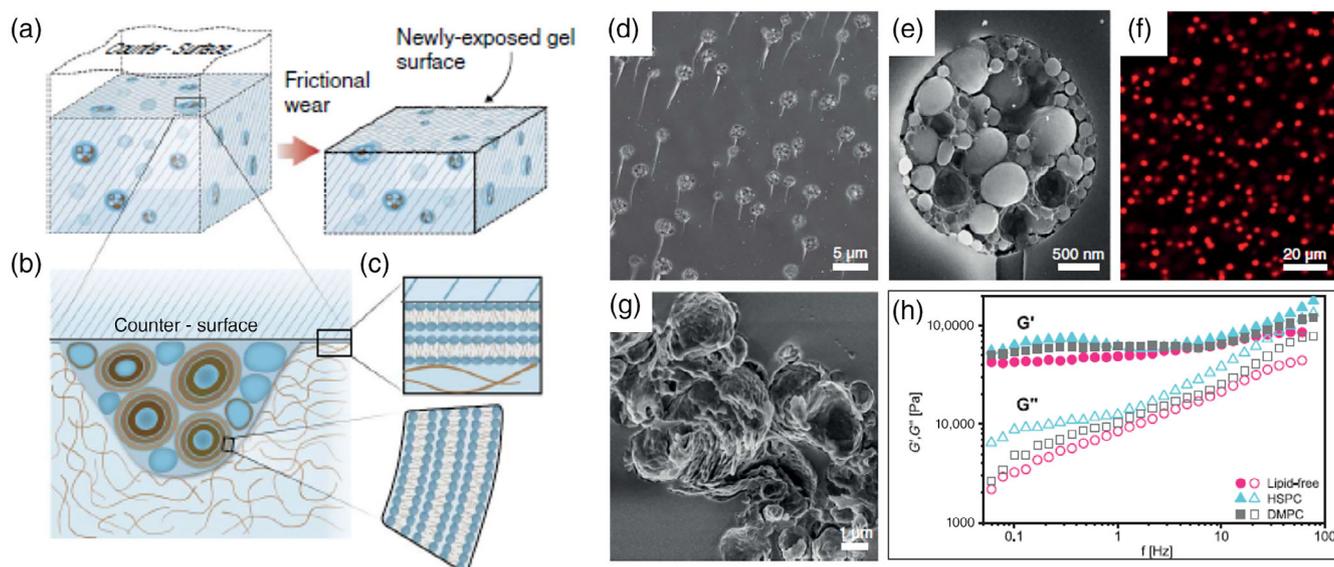


FIGURE 6 Mechanical properties of lipid-incorporated hydrogels. (a) Schematic representation of the self-lubricating lipid-incorporated hydrogels. The surface of the hydrogel, incorporating lipids as vesicles in microreservoirs; (b) and (c) wears away because of friction, additional microreservoirs of lipid are exposed. This ensures boundary layers of lipids form on the surfaces, leading to friction reduction via the hydration lubrication mechanism; (d) characterization of lipid-incorporating hydrogels; (e) a single microreservoir from (d) at larger magnification; (f) confocal microscopy section of the hydrogel incorporating fluorescently labeled DMPC vesicles, showing the lipid microreservoir distribution; (g) freeze-fracture surface of the gel incorporating HSPC vesicles; (h) storage and loss moduli of lipid-free and lipid-incorporating pHEMA gels (Reprinted with permission from Lin et al. (2020))

matrix. The authors explained this observation by considering that hydrogels containing the MLV dispersed within the matrix functioned as microreservoirs of lipids and formed a molecularly thin lubricating layer on the surface. Almost 99% reduction in the friction and wear was achieved in the case of (pHEMA) hydrogel containing MLVs composed of PC lipids. Thus, the study provides a possible way of achieving continuous lubrication by the simple use of hydrogel in combination with PC lipids (Lin et al., 2020). In the context of combination therapies as discussed above the hydrogel matrix of HA has often been utilized as a matrix to increase the drug residence in the IA region. Based on the idea of increasing the IA drug residence time, preclinical studies have also been conducted where salmon calcitonin (sCT) was covalently conjugated to HA and the chondroprotective effect of the conjugate was studied by IA administration in the anterior cruciate ligament transection (ACTL) rabbit model. sCT is a polypeptide-based hormone which potentially lowers the concentration of calcium and phosphate groups and improve the therapeutic outcome by directly targeting the bone and cartilage degradation. In the study, three injections of sCT/HA-sCT once a week were administered, with the first injection at 10 days after surgery. It was observed that both the systems significantly reduced the loss of the superficial layer and erosion of the cartilage and imparted protective effects against the OA-like degenerative changes in the articular cartilage, but the HA-sCT was more potent than the bare sCT (Mero et al., 2014). Dong et al. reported similar observations when Celecoxib liposomes (CLX-Lip) were developed to improve OA therapy and to reduce CLX associated cardiovascular adverse effects. The CLX-Lip was embedded in HA gel in order to prove their synergistic effect in ACLT rabbit model. In fact, they demonstrated that a single IA injection of HA or CLX-Lip was not able to inhibit cartilage degeneration, while their combination showed significant improvement after 14 days postinjection (Dong et al., 2013).

Moreover, many studies reported the possible combination of HA with other injectable agents, such as platelet-rich plasma (PRP) for OA treatment (Andia & Abate, 2014; Chen et al., 2014; Lana et al., 2016). Commonly, PRP is a concentrated cocktail of growth factors derived from whole blood. It is well known that PRP can promote ECM production, inhibit inflammation and increase chondrogenesis in cartilage (Wu et al., 2011). Preclinical studies involved the combined use of sulfated polysaccharide fucoidan with gelatin and HA derived hydrogel systems with PRPs to achieve the slow release of growth factors in a surgical rabbit model of OA (Lu et al., 2019). Kon et al. proved its clinical efficacy by demonstrating a statistically significant improvement of clinical scores in 100 OA knee patients after three IA PRP injections (Kon et al., 2010). Based on these evidences, the combination of PRP and HA could have the synergistic effect on the two components: on one side, PRP should promote chondrogenesis, while, on the other, HA should act on the biomechanical aspect (Andia & Abate, 2014; Chen et al., 2014; Lana et al., 2016). In a recent study conducted by Lana et al., the efficacy of IA injection of PRP plus HA *versus* the use of two single components in the treatment of mild and moderate OA knee was compared. Their results demonstrated that the use of PRP plus HA produces better outcome than HA alone up to 1 year and PRP alone up to 3 months (Lana et al., 2016).

In the recent years, adipose tissue-derived mesenchymal stem cells (AMSCs) and bone marrow tissue-derived mesenchymal stem cells (BMSCs) have also been utilized for the treatment of OA. Sato and coworkers investigated how the IA injection of mesenchymal stem cells (MSCs) suspended in HA solution promoted the regeneration of cartilage tissue in a Hartley strain guinea pig spontaneous model of OA. Five weeks post-transplantation, a higher amount of type II collagen around both residual chondrocytes and transplanted MSCs was reported in MSCs plus HA group compared with other groups. So, they concluded that HA scaffold improved regeneration of MSCs by promoting their cell-binding and proliferative effects (Sato et al., 2012). In 2016, a study investigated the therapeutic efficacy of IA injection of MSCs and HA in ACLT rabbit model. They found that MSCs plus HA IA injection suppressed the OA progression in the knee joint of mature rabbits significantly better than IA HA injection alone. This was detected already 6 weeks after treatment when MSCs were well-engrafted into both femoral and tibial cartilage (Chiang et al., 2016). Also, similar therapeutic efficacy was reported in OA beagle model. In 2018, Li et al. demonstrated that IA injection of BMSCs and HA improved cartilage defects in OA beagle model. Their report showed promising improvement with BMSCs plus HA in cartilage defects compared with those in the other two treatment groups HA alone and saline. Based on these results, they concluded the efficacy of BMSCs plus HA rather than HA in promoting the formation of cartilage-like tissue (Li et al., 2018). Moreover, Wang et al. proved the efficacy of HA plus MSCs for the treatment in OA knee of rat model. They demonstrated the improvement of regenerative activity of IA injection efficacy human amniotic mesenchymal stem cells (hAMSCs) when combined with HA in rat OA models. They concluded that the presence of HA enhances all the activities of hAMSCs, modulating cytokines secretion (Wang et al., 2020).

In addition to IA treatment by injections, similar approaches were investigated for the treatment of articular defects using a combination of scaffold and cells by direct implantation into the lesion. Kuroda et al. conducted the first clinical trial using the scaffold-cells combination in 2007. They evaluated the ability of a collagen scaffold loaded with

autologous MSCs to promote tissue regeneration of medial femoral condyle articular cartilage in an athlete, demonstrating the formation of a hyaline-like cartilage and the improvement of clinical symptom after 1 year (Kuroda et al., 2007). Some examples of scaffold-cells combination in OA human patients were reported (Lamo-Espinosa et al., 2016; Park et al., 2017). For instance, in 2016, Lamo-Espinosa et al. demonstrated a cartilage regeneration over the subchondral bone after 12 weeks of a single IA injection BMSCs combined with HA. They concluded that this combination is a safe and effective strategy for biomechanical and functional management of OA knee (Lamo-Espinosa et al., 2016). Indeed, the result of another clinical trial has strengthened more the potential of this combination. In particular, Park et al. reported that a single IA injection of Cartistem (a combination of HA hydrogel and with human umbilical cord blood-derived MSCs) is able to promote the maturing tissue repair at 12 weeks and reduction of symptoms at 24 weeks, both of which remained stable over 7 years of follow-up (Park et al., 2017). Recently, a clinical trial is recruiting people for testing the efficacy of a HA based scaffold (size: 2×2 cm or 5×5 cm) embedded with BMSCs in the treatment of symptomatic cartilage defects of the knee (Shah et al., 2021). In conclusion, combined treatment strategies could be an effective way to explore in order to improve the management of OA.

8 | CONCLUSION

OA is a chronic disabling inflammatory disease that affects a growing percentage of the worldwide population where the degenerative cascade leads to the manifestation of pain and progresses toward permanent disability. In spite of its prevalence, there is no well-defined treatment regimen, DMOADs, or methods for early diagnosis for the treatment of this chronic disease. One of the first clinically approved therapy to treat OA was the IA injection of HA to regain lubrication of the affected joint. However, several clinical trials revealed that although this approach may provide temporary relief, it is also associated with several limitations.

Low residence time of IA injected agents and the biological complexity of the disease, calling for combinatorial rather than monotherapies, are major hurdles in the process of developing a definitive cure for OA. At this juncture, future therapies based on nano/microparticles in combination with biologics, like PRPs and stem cells, could make the difference by simultaneously addressing the problems of joint lubrication, drug dwelling time, and ECM remodeling by chondrocyte replacement. The combination of hydrogels with other nanoparticles or corticosteroid-based therapeutics for prolonged release is another promising direction but still at an initial stage and requires extensive studies to reach the clinical standards. Additionally, evolution of the treatment design into a combination therapy might allow to overcome the drawbacks of previously rejected therapeutic targets. In summary, designing clinically efficient treatment for OA is a multiscale challenge of growing relevance, which requires complementary and combination efforts of different scientific approaches.

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AUTHOR CONTRIBUTIONS

Martina Di Francesco: Conceptualization (equal); writing – original draft (equal). **Agnese Fragassi:** Conceptualization (equal); writing – original draft (equal). **Martina Pannuzzo:** Supervision (equal); writing – original draft (equal). **Miguel Ferreira:** Supervision (equal); writing – original draft (equal). **Sayanti Brahmachari:** Writing – original draft (equal); writing – review and editing (equal). **Paolo Decuzzi:** Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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