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Therapeutic Controlled Release Strategies for Human Osteoarthritis

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Osteoarthritis is a progressive, irreversible debilitating whole joint disease that affects millions of people worldwide. Despite the availability of various options (non-pharmacological and pharmacological treatments and therapy, orthobiologics, and surgical interventions), none of them can definitively cure osteoarthritis in patients. Strategies based on the controlled release of therapeutic compounds via biocompatible materials may provide powerful tools to enhance the spatiotemporal delivery, expression, and activities of the candidate agents as a means to durably manage the pathological progression of osteoarthritis in the affected joints upon convenient intra-articular (injectable) delivery while reducing their clearance, dissemination, or side effects. The goal of this review is to describe the current knowledge and advancements of controlled release to treat osteoarthritis, from basic principles to applications in vivo using therapeutic recombinant molecules and drugs and more innovatively gene sequences, providing a degree of confidence to manage the disease in patients in a close future.

1. The Joint and Osteoarthritis: The Disease, Current Treatments, and Emerging Concepts

1.1. The Normal Joint

The knee joint is a highly specialized organ composed of different tissues with crosstalks, including the hyaline articular cartilage that covers the subchondral bones of the opposing bone ends (osteochondral unit), supporting the skeletal structures and providing for shock absorption, the synovium and a synovial cavity-filling synovia, a fluid that lubricates and nourishes the joint, the menisci that transmit weight-bearing forces and increase joint stability, tendons and ligaments that control the motion of the joint, and a fibrous capsule that stabilizes and insulates the entire joint for protection and self-equilibrium[1] (**Figure 1**).

The articular cartilage is a highly hydrated (80% water content), multilayered avascular and aneural, hypoxic (< 5% depending on the depth) tissue with a low hydraulic permeability whose biomechanical properties depend on the zonal, structural, and functional organization i) of the components of the extracellular cartilage matrix (ECM) and ii) of the articular chondrocytes displaying specific phenotypes and gene expression patterns in the superficial, middle, and deep (calcified) zones to the subchondral bone.[2] The hyaline cartilage is separated from the calcified cartilage by the basophilic tidemark.[3] The dense ECM network (95–98% of cartilage wet weight) produced and degraded by the articular chondrocytes in a tightly controlled physiological balance (homeostasis) is composed of small molecular weight (MW) ions and of macromolecular compounds mainly proteoglycans (compressive stiffness), type-II collagen (tensile strength; 85–90% of the collagens that also include small amounts of type-VI/-IX/-XI/-XIV collagen as well as type-I/-X collagen), and other noncollagenous proteins (biglycan, hyaluronan, perlecan),[2b,c,h,m,4] the balance of which is critical to the spatial and temporal organization of the ECM.[4a] The resident articular chondrocytes present at low densities in the adult cartilage (< 2%). Embedded in their matrix, including in their narrow pericellular matrix (PCM), they form biomechanically-responsive chondrons,[4h,5] displaying a stable phenotype, with a low potential for proliferation (post-mitotic vitality) and low metabolic activities (minimal ECM turnover),[2b,c,k,m,n,c,6] and limited abilities for self-regeneration.[7] The vascularized, highly organized subchondral bone containing a type-I collagen and nanohydroxyapatite matrix and exhibiting self-healing abilities is located below the deep (calcified) zone of the articular cartilage and separated from it by the undulating cement line.[1a,8] It is divided into two distinct anatomic entities, the subchondral bone plate and the subarticular spongiosa (subchondral trabecular bone) that dynamically modify their characteristics by bone remodeling throughout growth and life via different properties according to the mechanical loads.[3b,8] Although the shape and architecture of the bone may be modified in physiological conditions, the amount of bone removed by the osteoclasts (resorption) relative to that formed by the osteoblasts is balanced to maintain the bone mass.[3b,7a,8,9] The vascularized synovium (synovial membrane with fibroblast-

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adhm.202402737

DOI: 10.1002/adhm.202402737

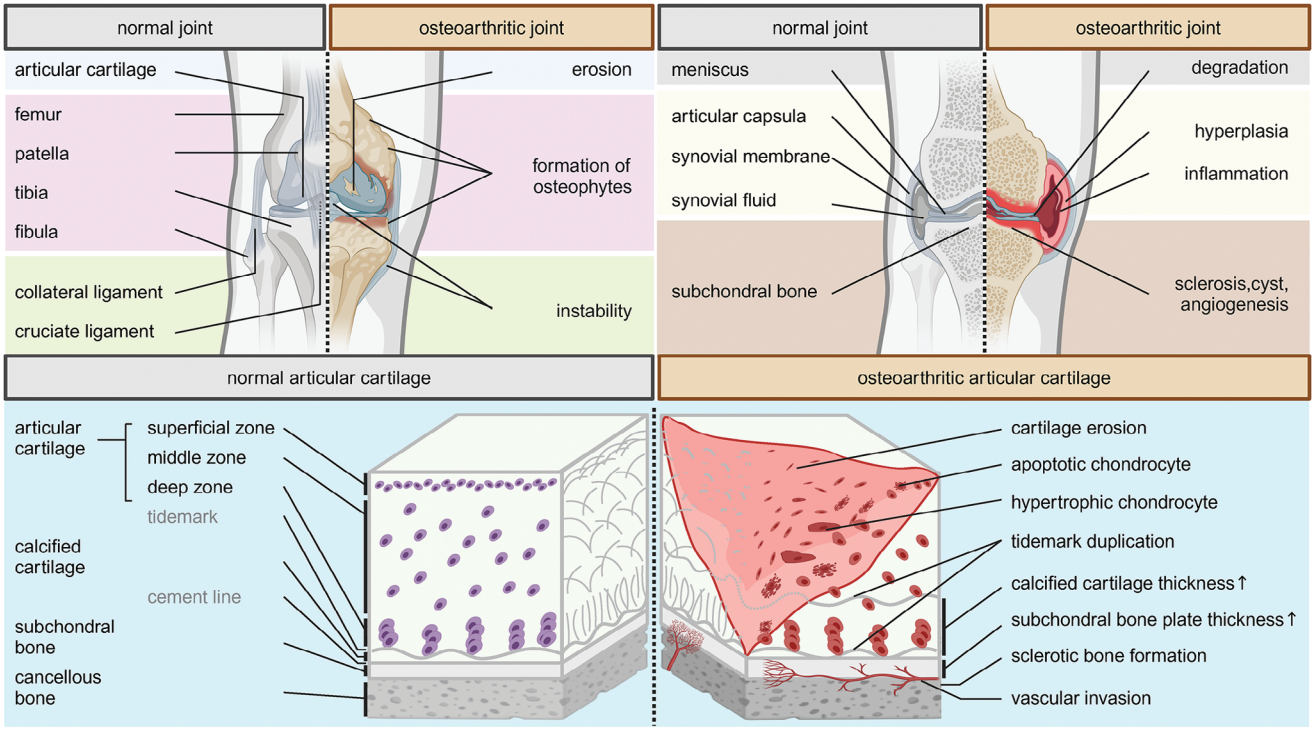

Figure 1. Representation of normal and osteoarthritic knee joints and tissues. The anatomical representation of the knee joint (top panels) and the schematic composition of the osteochondral unit (bottom panels) are illustrated for normal (left panels) and osteoarthritic (right panels) knee joints, tissues, and zones (created with BioRender).

like synoviocytes – FLS – and macrophage-like synoviocytes – MLS; synovial space with the synovial fluid) provides the joint cavity and the avascular articular cartilage with lubricating agents among which hyaluronic acid (HA) and lubricin produced by the FLS also for shock absorption and with plasma-derived nutrients while shaping and maintaining the synovial ECM (proteoglycans, collagens, fibronectin, tenascin, laminin).[10] The meniscus, a semi-circular tissue that transmits weight-bearing forces in the joint, increases its stability and supports its nutrition, lubrication, and proprioception, is a fibrocartilaginous structure composed of fibrochondrocytes predominantly embedded in a type-I collagen matrix with to some extent proteoglycans and type-II collagen.[11] This connective tissue is divided into a peripheral, vascularized red-red zone (2/3) that can heal in response to injury, an intermediate red-white zone, and a central, avascular white-white zone (1/3) with poor healing ability.[11] Tendons and ligaments are other connective tissues that stabilize the joint and play crucial roles in kinematics as dense, cable-like structures primarily made of type-I collagen in fiber bundles, with also other collagens (type-III/-IV/-V/-VI collagen), elastin, fibronectin, and proteoglycans, overall surrounded by a vascularized sheath, with a limited ability for self-healing.[12]

1.2. Osteoarthritis: The Pathological Joint

Osteoarthritis (OA) is a highly prevalent, progressive complex whole joint degenerative disease affecting 7.6% of the world population (≈595 million individuals worldwide)[13] and the leading cause of disability and reduced quality of life in globally aging individuals.[14] Major clinical OA symptoms typically involve chronic pain, reduced function, and stiffness. Structural alterations include changes in all affected tissues. Deformities and other signs of bony dysfunctions are detectable on radiographs (joint space narrowing, osteophytes, subchondral bone cysts). Signs of acute inflammation (local warmth, soreness, joint effusion) may be present in every stage.[14h,k,l,n,u,v,z,aa,15] OA is associated with distinct phenotypes sharing differences in etiology and underlying pathobiological and pain mechanisms, whose clinical manifestations reflect structural and functional consequences.[14s,u,v,16] The increasing availability of magnetic resonance imaging (MRI) data including using delayed gadolinium-enhanced MRI of the cartilage (dGEMRIC)[17] and of advanced biomarkers (including by multiomics, nanotheranostics, single-cell RNA-Seq, and biosensors) together with the support of machine learning technologies[17b,g,18] to detect particular OA characteristics and stages expand the possibilities of distinguishing between potential disease subtypes, diagnosis, and treatments of OA, especially at early phases.[19]

OA involves multiple structural features such as the progressive degeneration of the articular cartilage together with alterations in the subchondral bone, the generation of osteophytes, an inflammation of the synovium, and the degeneration of the meniscus and of tendons and ligaments[1a,2b,g,i,j,l–n,14a,b,f,h,l,n,p,u,v,20] (Figure 1). OA is a multifactorial disease involving a variety of host, environmental, biomechanical, and biochemical factors (age, obesity, sex, gender, genetic abnormalities, joint instability,

muscle weakness, peripheral neuropathy, repetitive stress injury, pathological loading/stress, joint malalignment, inflammation, signaling and growth/senescent pathways)[14f,l,n,t,z,ab,15h,16b,20m,21] leading to an irreversible joint malfunction due to the limited ability of joint tissues for self-repair that markedly further decline with age.[20i,21f,22] This is particularly evident in the articular cartilage where the chondrocytes undergo irremediable phenotypic changes in response to the pathological OA joint environment, with a disruption of the normal post-mitotic state leading to a senescence-associated secretory phenotype with increased catabolic activities (matrix-degrading enzymes such as matrix metalloproteinases – MMP-3, -9, -13 – and A Disintegrin and Metalloproteinase with Thrombospondin Motifs – ADAMTS4, ADAMTS5), cell clustering, hypertrophy-like maturation, calcification, and vascular invasion with nerve growth that ultimately contribute to the destruction of the cartilage and its ECM, with the pathological presence of ECM degradation products that may further contribute to local inflammation.[1a,2m,n,14l,n,v,20k,m,21c,23] The subchondral bone is also remodeled in OA, with increased thickness (especially in the calcified cartilage zone) and density of the subchondral bone plate and subchondral spongiosa while vascular invasion occurs in the calcified zone and the histological tidemark is being duplicated.[1a,8,14n,u,v,20k,24] Other pathological changes include subchondral bone alterations among which bone sclerosis, the formation of osteophytes (at the margins of the articular cartilage) and subchondral cysts, and the presence of microedema, microcracks, and microbleeding.[1a,8,14u,v,20k,24] These alterations are linked to a shift in the osteoblast phenotype, with increased cell proliferation and a modified matrix composition and abnormal mineralization, with overproduction of type-I collagen (homotrimeric alpha1, i.e., $(\alpha 1)_3$ form) exhibiting a lower affinity for calcium than that of $(\alpha 1)_2$ $\alpha 2$ type-I collagen, of alkaline phosphatase activity, interleukin 6 – IL-6, IL-8, osteocalcin, osteopontin, MMP-13, and Wingless and Int-1 (Wnt) signaling pathway.[24d,25] Alterations of the joint capsule and synovial inflammation resulting in synovitis are also features of OA, with synovium hypertrophy, hyperplasia, increased vascularity, higher synovial lining cell numbers, and infiltration of mononuclear cells such as lymphocytes and macrophages and excessive production of inflammatory agents (mediators like reactive oxygen species – ROS, nitric oxide – NO, prostaglandin E_2 – PGE_2, advanced glycation end products – AGEs; cytokines and chemokines such as IL-1β, tumor necrosis factor alpha – TNF-α, IL-6, IL-8, IL-10, IL-15, IL-17, granulocyte-macrophage colony-stimulating factor – GM-CSF; adipokines including adiponectin, leptin, and visfatin; neuropeptides like the nerve growth factor – NGF, substance P) and of MMPs (MMP-1, -3, -9, -13) and ADAMTS (ADAMTS4, ADAMTS5) that all ultimately contribute to cartilage degradation and joint malfunction.[14n,v,21c,x,23a,25d,26] Meniscus injuries also considerably contribute to the global pathology of the OA knee joint, associated with cell clustering, loss of matrix components, and with an up-regulation of inflammatory cytokines (IL-1β, TNF-α), damage-associated molecular patterns (DAMPs), and MMPs (MMP-1, -3, -9, -13) and ADAMTS (ADAMTS4, ADAMTS5).[11a,c,14n,27] Tendons and ligaments also undergo degeneration in response to inflammation in OA, with reduced cellularity, disorganization of the collagen fibers, and impaired expression of specific markers like scleraxis and alpha-smooth muscle actin (α-SMA).[14n,28]

1.3. Osteoarthritis: Current Treatments, Emerging Options

The complexity of OA as a multifactorial, whole joint disease with distinctive features occurring upon its gradual progression from early to severe (end) stages[14m,n,p,ab,15b,29] makes it a particularly challenging disorder to durably and effectively treat in the global population. An effective therapeutic approach for OA would need to take into account the various tissues affected in the joint of the patient as well as the patient's own characteristics (age, sex, gender, weight, activity, comorbidities, symptoms, and disease severity, etc) in order to restore the OA joint in its full structural and functional (biomechanical) integrity.

Current OA treatments include non-pharmacological management (education, self-management, weight loss, exercise, physical therapy, strength training, load relief), pharmacological treatments and drug therapy (analgesics: paracetamol, acetaminophen, opioids; non-steroidal anti-inflammatory drugs – NSAIDs – as cyclooxygenase – COX – inhibitors: diclofenac – DCF, ibuprofen, ketoprofen, naproxen, celecoxib; glucocorticoids: steroidal anti-inflammatory agents, corticosteroids and corticoids like triamcinolone acetonide – TCA – and dexamethasone – dex; viscosupplementation: HA, glucosamine, chondroitin sulfate – CS; slow-acting drugs in OA – SADOAs: diacerein, rhein, methotrexate; hydroxychloroquine; IL-1 receptor antagonist – IL-1Ra: anakinra; IL-1α and -β inhibitors: canakinumab, ABT-981; TNF antagonists: adalimumab, etanercept, infliximab; inducible NO synthase – iNOS – inhibitor: cindunistat; NGF antagonists: tanezumab, fulranumam, fasinumab; ADAMTS inhibitors: M6495, GLPG1972/S201086; GM-CSF inhibitors: GSK3196165 antibody; Wnt signaling pathway inhibitors: lorecivivint SM04960; transient receptor potential vanilloid – TRPV – channel inhibitors and antagonists: CNTX-4975, lopain, GSK1016790A; cathepsin K inhibitors: MIV-711; bisphosphonates; vitamin D; metformin; growth factors: bone morphogenetic protein 7 – BMP-7, fibroblast growth factor 18 – FGF-18 – sprifermin, parathyroid hormone – PTH: teriparatide; kartogenin – KGN; senolytic agents: UBX0101, fisetin), orthobiologics (blood derivatives: platelet-rich plasma – PRP, super-activated platelet lysate – sPL, bone marrow aspirate concentrate – BMAC; cell-based materials: bone-marrow-derived mesenchymal stromal cells – BM-MSCs, adipose-derived stem cells – ASCs, secretome, extracellular vesicles – EVs, exosomes – Exos), and ultimately surgical interventions (debridement, marrow stimulation techniques, osteotomy, joint arthroplasty, endoprosthesis).[14v,w,aa,ab,29b,30] However, none of these drugs or treatments thus far have been fully capable of preventing, arresting, or even delaying the progression of the disease nor of reliably restoring a complete, normal joint in OA patients or have been abandoned, mostly due to complications, adverse effects, and contra-indications,[14r,30ah,31] showing the critical need for new treatments and disease-modifying anti-OA drugs (DMOADs) that are not available yet.[29b,32] Limitations of the current OA treatments may be due to the difficulty of the provided agents to penetrate dense tissues in order to reach their targets, their dissemination to non-target locations, and/or their rapid clearance that may necessitate to use potentially harmful/cytotoxic repeated injections and/or higher doses.[30y,ar,33]

In this regard, emerging options for OA may be based on strategies controlling the release of bioactive compounds

(recombinant drugs, gene therapy sequences) from injectable delivery systems originating from the field of tissue engineering to overcome the pharmacokinetic limitations of the therapeutic agent[33e,34] and enable a sustained treatment of OA by spatiotemporally and safely enhancing the intrinsic mechanisms of remodeling and repair in OA while avoiding a repeated use of agents at high doses that may be deleterious to the joint.[33e,35] In the following chapters, we describe the principles of therapeutic controlled release from the perspective of applications for the treatment of human OA, highlighting the currently employed biomaterials and therapeutic agents in relevant settings in vivo and discussing the most innovative strategies to support the durable and safe effects of the systems on OA joint tissue remodeling and regeneration.

2. Therapeutic Controlled Release Applications for Osteoarthritis

2.1. Therapeutic Controlled Release: Principles

Therapeutic controlled release is based on the manipulation of materials that are biocompatible and biodegradable, without the generation of deleterious (toxic, immunogenic) degradation products, initially used in tissue engineering procedures[34a,36] to deliver recombinant molecules with short pharmacological half-lives (minutes to hours) as a means to improve their bioavailability and therapeutic effects in a target in a spatiotemporal manner.[37] A controlled release system may therefore be composed of a biomaterial as a delivery platform for one or multiple therapeutic agents (recombinant molecules or gene sequences) with specific loading capabilities and interactions between these two components (affinity, electrostatic interactions, hydrophobic association, conjugation, immobilization/tethering, physical and chemical interactions, micro-/encapsulation, etc) that may influence each other via the physicochemical properties of the agent(s) and the structural characteristics of the biomaterial[34c,38] (**Figure 2**).

The controlled release of a therapeutic candidate allows for its fine-tuned, tailored delivery at functionally effective levels with a low frequency of administration to maintain their concentration, availability, and/or retention in a particular target in response to various parameters and stimuli including time, location, and environment (e.g., pH, temperature, oxygen, ionic strength, light, osmosis, catalysts, ultrasounds (US), inflammatory/biochemical/mechanical environment, enzymes, etc) while reducing potentially adverse effects due to repeated dosing.[37c,39] Release may occur upon degradation of the biomaterial or via substrate delivery from the biomaterial.

The release profile (efficacy, kinetics) of a therapeutic agent from a controlled release system (reservoir)[40] generally includes i) its rapid (burst) release near the surface of the platform (phase I), ii) a slow (controlled) release phase of the agent (phase II), and iii) its fast release phase together with the degradation of the platform (phase III).[41] The whole process is regulated by the rate of diffusion/dissolution of the agent(s) from the biomaterial and by the rate of degradation of the biomaterial by surface erosion and bond cleavage depending on its properties (MW, crystallinity, elasticity/deformability, ability to form pores, glass transition temperature – Tg, solubility – hydrophilicity/hydrophobicity, etc)[34a,36a,37a,39a,41b,42] via complex mechanisms (network degradation, solvent/chemical activation, ion exchange, osmosis/swelling, deformation, stimulus-responsiveness, etc) and may be predicted and even elucidated with the help of mathematical models of release kinetics to provide guidance in the design of optimal systems.[43]

2.2. Therapeutic Controlled Release: Applications in Osteoarthritis

While controlled release strategies have great potential for applications in a progressive disorder such as OA,[18l,33f,34g–i,35a,44] their implementation needs to take into account the complex intra-articular biochemical and biomechanical environment of the joint at various stages of the disease, with multiple affected tissues and cells and with the presence of the ECM in specific zones.[33e,34c,45]

The choice of the delivery platform for a successful application in OA is therefore critical regarding the architecture and properties of the biomaterial that must be adapted to formulate and deliver the treatment compound(s) in the affected joint environment via effectively controlled release processes. Biomaterials employed as therapeutic controlled release systems may be composed of natural, highly biocompatible polymers (collagen, fibrin, gelatin, silk fibroin, keratin, chitosan, CS, HA, cellulose, alginate, etc) and/or of synthetic, reproducible polymers (polyethylene glycol – PEG, polypropylene glycol – PPG, poly(lactic acid) – PLA, poly-glycolic acid – PGA, poly(lactide-co-glycolic acid) – PLGA, polyvinyl alcohol – PVA, poloxamers/poloxamines, poly(ϵ-caprolactone) – PCL, polyurethane – PU, etc).[18d,l,33f,h,34g–i,k,37c,44b,d,46] Systems employed as controlled delivery platforms can be used in the form of microparticles (MPs)/microspheres (0.1–100 µm) and nanoparticles (NPs)/nanospheres (1–100 nm) that also include dendrimers (repetitively branched molecular systems), micelles (self-assembling amphiphilic systems at a critical micelle concentration – CMC – and that may further form gels by undergoing sol-to-gel transition at increased temperature and depending on polymer concentration), and liposomes (aqueous-core systems with a lipid bilayer), cell-derived phospholipid bilayer vesicles (30–1000 nm) involved in cell-cell communication such as Exos (30–200 nm), hydrogels, solid scaffolds, and hybrid scaffolds.[18d,l,33f,h,34g,i,k,37c,44b,d,46] Hydrogels formed using hydrophilic polymers under mild fabrication conditions offer powerful systems for OA because of their high water contents mimicking the ECM environment of the articular cartilage, their high biocompatibility and lack of immunogenicity, inflammatory responses, and thrombogenicity, their safe degradation, and their low mechanical properties relative to solid scaffolds. Solid scaffolds are highly porous systems, allowing for the fine release of therapeutic compounds from mechanically stable systems adapted to the functional properties of the articular cartilage. Hybrid scaffolds are based on the association of hydrogels with solid scaffolds and might combine the properties of each of these systems. Biomaterials may further be modified in order to improve the targeting effects of the therapeutic agent(s) in a specific affected joint tissue. This is particularly critical in intra-articular delivery strategies that aim at reaching a precise location (like

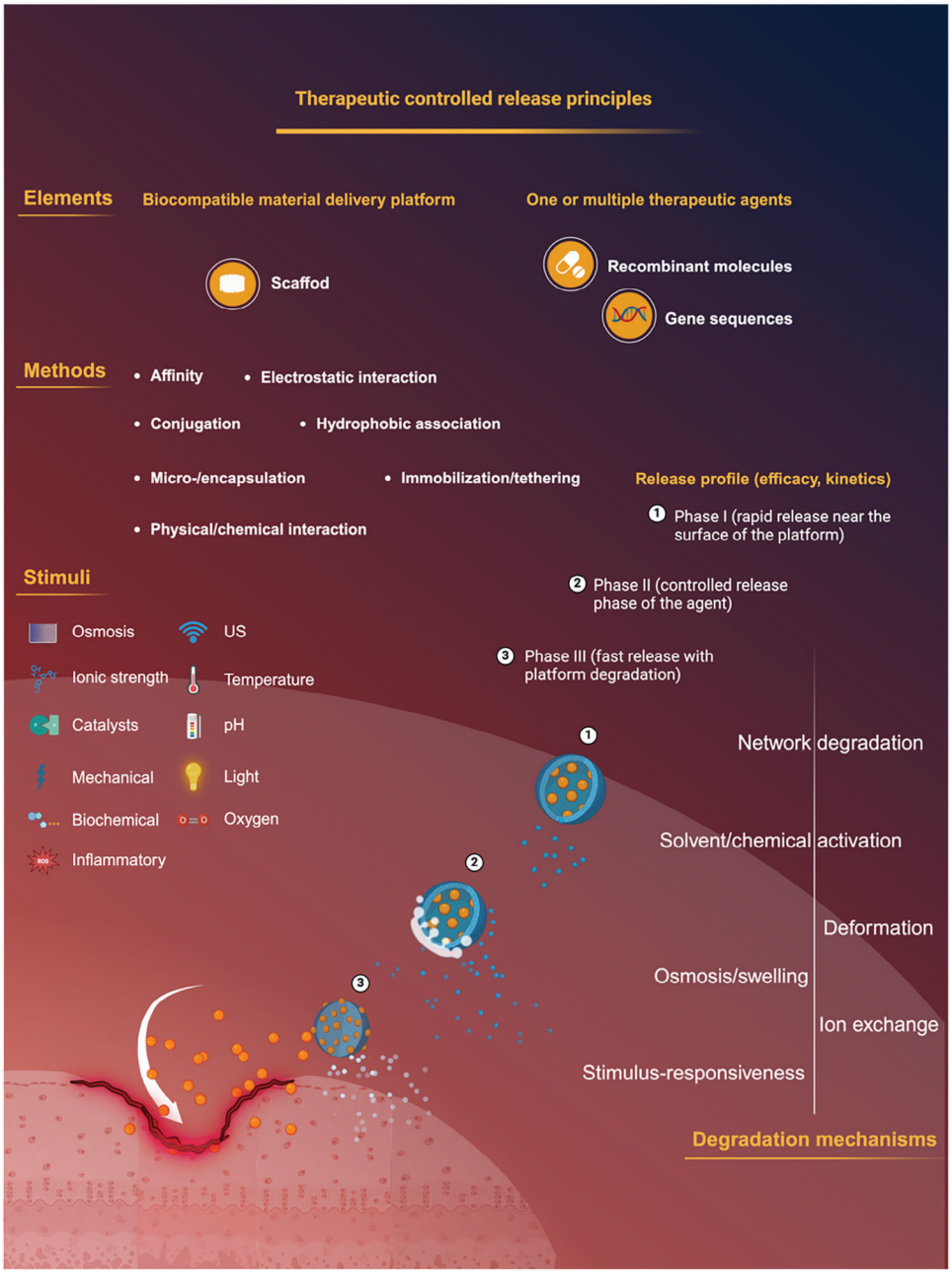

Figure 2. Principles of therapeutic controlled release. Therapeutic controlled release involves 1) a biocompatible material and one (or more) therapeutic agent(s) (elements), with 2) specific interactions (methods) and release in response to 3) various parameters (stimuli) upon 4) specific steps of material degradation (degradation mechanisms), leading to release profiles in three phases (phase I: rapid agent release; phase II: slow, controlled release of the agent; phase III: fast agent release with material degradation) (created with BioRender).

the OA articular cartilage) when the therapeutic platform and agent(s) need to penetrate through the synovium membrane acting as a barrier and be transported into the joint space to reach target cells embedded in their ECM before being potentially cleared.[33a,b,d–i] Biomaterials may also be functionalized as "smart" therapeutic controlled delivery systems by generating stimuli-responsive platforms capable of releasing therapeutic agent(s) in response to particular single or multiple joint- and OA-associated stimuli and other types of triggers including oxygen, inflammation, enzymatic and biochemical factors, mechanical loading, pH, temperature, ionic strength, light, osmosis, catalysts, US, and electric and magnetic fields.[33f,36f,39b,47]

Therapeutic agents for OA delivered via biocompatible materials that could be conveniently injected (and potentially forming in situ) in affected joints classically include recombinant molecules but they can be also more innovatively derived from genetic (DNA, RNA) materials carried by shuttles or vectors[48] as gene therapy, genome engineering (especially

using the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) system), and epigenetic therapy[18v,30bq,33e,49] combined with tissue engineering tools[46c,50] may have a strong potential to stably manage the long-term progression of OA, offering protection to the cargos (genes and vectors) against detrimental host responses (toxicity, immunogenicity) potentially raised when applying gene vectors on themselves in the absence of biomaterial.[29b,51] Gene vectors include nonviral carriers (plasmids, liposomes, polymers, dendrimers, peptides, nucleic acid/ligand complexes, etc)[49u] and virus-derived constructs such as adenoviral, herpes simplex viral (HSV), retro-/lentiviral, and recombinant adeno-associated viral (rAAV) vectors[52] that may be either encapsulated in the controlled release system by loading during its fabrication or incorporated/immobilized in the preformed controlled release system.

2.2.1. Controlled Release of Recombinant Molecules for OA In vivo

A variety of recombinant molecules have been provided via controlled release strategies to relevant models of OA in vivo, including NSAIDs, corticosteroids, glucocorticoids, viscosupplementation, SADOAs, drugs targeting inflammation, oxidation, autophagy, senolysis, catabolism, regeneration, orthobiologics, pleiotropic gas, and bioactive ions (**Table 1** and **Figure 3**). While controlled release of anti-inflammatory mediators and/or viscosupplementation may be favored in the early stages of the disease, a sequential release of these drugs with factors displaying anti-oxidative, anti-apoptotic, and pro-anabolic activities together with agents regulating macrophage polarization may be needed to address synovial swelling, pain, vascular invasion, osteophyte formation, and irreversible cartilage degradation in the next and later OA stages.[44c,53]

NSAIDs: NSAIDs decrease the production of inflammatory prostaglandins by inhibiting COX-1 or COX-2 activities, reducing pain caused by inflammation.[54,55b,56–59] Several NSAIDs have been applied in OA models in vivo using controlled release systems, among which lornoxicam,[54] DCF,[55] naproxen,[56] celecoxib,[57] etoricoxib,[58] and flurbiprofen[59] using MPs and microspheres,[54,55f,b,c,f] NPs, nanospheres, nanocapsules, and liposomes,[55b,c,e,57a,d,58] cavitand,[59] and gels/hydrogels.[55d,56,57e]

For instance, the controlled delivery of lornoxicam via PLGA microspheres led to enhanced cartilage repair in a papain OA model in rats for 4 weeks[54a] while its application using chitosan/triphosphate microspheres reduced inflammation in monosodium iodoacetate (MIA)-induced OA in rats for 3 weeks.[54b] Administration of DCF via collagen (Col)/lipid MPs,[55a] Col/HA/soybean phosphatidylcholine (SPC)/dipalmitoyl phosphatidylethanolamine (DPPE) liposomes,[55b] or poloxamer 407 (P407)/HA hydrogel[55d] reduced inflammation and enhanced cartilage repair in MIA-induced OA in rats for 17 days to 3 weeks, while it decreased osteophyte formation and inflammation and afforded cartilage protection in rat models of surgical OA (destabilization of the medial meniscus – DMM; anterior cruciate ligament transection – ACLT) for 4–8 weeks when using mesoporous silica (MS)/poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) nanospheres,[55e] methacrylate gelatin (GelMA)/dopamine methacrylamide (DMA)/2-methacryloyloxyethyl phosphorylcholine (MPC) microspheres,[55f] and pluronic 127 (PF127)/chitosan oligosaccharide (COS) nanospheres.[55c] The delivery of naproxen via a gelatin/dextran/HA hydrogel reduced inflammation and afforded cartilage protection in collagenase-induced OA in rabbits for 3 weeks.[56] Application of celecoxib using SPC/cholesterol (CLS)/HA liposomes[57a] and polyester amide (PEA) microspheres[57b,c] led to pain relief, reduced inflammation, and afforded cartilage protection in rabbit and rat models of surgical OA (ACLT; medial meniscectomy – MMx) for 2–16 weeks while it had similar effects in MIA-induced OA in rats for 3 weeks via a hyaluronan nanocapsules[57d] and P407/Gantrez S97 (GS97)/alginate/polyvinylpyrrolidone (PVP)/HA gel[57e] and in chronic OA in dogs for 8 weeks via PEA microspheres.[57f] Finally, the delivery of etoricoxib[58] and of flurbiprofen[59] using PLGA/PEG NPs[58] or zwitterion-modified cavitand (CV-2)[59] reduced inflammation[59] and afforded cartilage protection and repair[58,59] in rat models of surgical OA (ACLT or ACLT, medial collateral ligament transection – MCLT, medial meniscal transection – MMT) for 8–12 weeks.[58,59]

Corticosteroids: Corticosteroids reduce the production of inflammatory cytokines, phospholipase A2 (PLA2), prostaglandins, and leukotrienes by inhibiting the p38/mitogen-activated protein kinase (MAPK) signaling pathway while inducing the apoptosis of immune cells.[60]

TCA, the most commonly used, approved corticosteroid,[61–65] has mostly been employed in controlled release strategies to target in vivo models of OA, promoting pain relief in patients with knee OA for up to 26 weeks via delivery in a hyaluronan hydrogel[62] and in PLGA microspheres (FX006 formulation),[63] reducing inflammation in collagenase-induced OA in rats for 7 weeks using PEA microspheres,[64] and affording cartilage protection in MIA-induced OA in mice and in rats for up to 8 weeks via dextran sulfate and poly(organophosphazene) NPs.[65]

Glucocorticoids: Glucocorticoids inhibit the production of IL-1β, PGE_2, and TNF-α and impact that of IL-6, MMP-3, -9, and -13, and of pain-related mediators while triggering the anti-inflammatory macrophage M2 phenotype.[56,57e,66b,67,68b] Controlled release systems have been applied to OA models in vivo essentially to deliver dex using microspheres and microplates,[66] NPs, nanosheets, and liposomes,[55b,67] and gels/hydrogels.[56,57e,68]

Notably, pain relief has been evidenced in patients with knee OA for 24 weeks when receiving dex via a formulation of TLC599 liposomes.[67h] The benefits of dex have further been reported in MIA-induced OA in rats[55b,57e,66c,67c] and in mice,[66a,67e,f] reducing inflammation for 17 days using Col/HA liposomes[55b] and for 3 weeks using either a P407/GS97/alginate/PVP/HA gel[57e] or ROS-responsive PLGA microspheres,[66a] reducing bone erosion for 5 weeks using ROS-responsive polyphenol-poloxamer 188 (PP188) NPs,[67e] enhancing cartilage repair for 4–5 weeks using polythioketal urethane (PTKU) NPs[67c] or PEG/PCL/N1-(4-boronobenzyl)-N3-(4-boronobenzyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium (TSPBA)/GelMa (collagen II-targeting WYRGRL peptide) microspheres,[66c] and affording cartilage protection for up to 5 weeks using either a P407/GS97/alginate/PVP/HA gel,[57e] ROS-responsive PLGA microspheres,[66a] PP188 NPs,[67e]

Table 1. Controlled release of recombinant molecules for OA in vivo.

Family	Molecules	Biomaterials	OA models	Species, Patients	Effects	References
NSAIDs	lornoxicam	PLGA MPs	papain	rats	cartilage repair (4 weeks)	[54a]
		chitosan/tripolyphosphate microspheres	MIA	rats	reduced inflammation (3 weeks)	[54b]
	DCF	Col/lipid MPs	MIA	rats	reduced inflammation (18 days)	[55a]
		Col/HA/SPC/DPPE liposomes			reduced inflammation (17 days)	[55b]
		P407/HA hydrogel			cartilage repair (3 weeks)	[55d]
		MS/PMPC nanospheres	DMM	rats	reduced osteophyte formation, cartilage protection (4 weeks)	[55e]
		GelMA/DMA/MPC microspheres			reduced inflammation, cartilage protection (8 weeks)	[55f]
		PF127/COS nanospheres	ACLT, DMM	rats	reduced inflammation, cartilage protection (8 weeks)	[55c]
	naproxen	gelatin/dextran/HA hydrogel	collagenase	rabbits	reduced inflammation, cartilage protection (3 weeks)	[56]
	celecoxib	SPC/CLS/HA liposomes	ACLT, MMx	rabbits	pain relief, cartilage protection (2 weeks)	[57a]
		PEA microspheres		rats	pain relief, reduced inflammation, cartilage protection (12/16 weeks)	[57b,c]
		hyaluronan nanocapsules	MIA	rats	reduced inflammation, cartilage protection (3 weeks)	[57d]
		P407/GS97/alginate/PVP/HA gel			reduced inflammation, cartilage protection (3 weeks)	[57e]
		PEA microspheres	chronic OA	dogs	pain relief, reduced inflammation (8 weeks)	[57f]
	etoricoxib	PLGA/PEG NPs	ACLT	rats	cartilage repair (12 weeks)	[58]
	flurbiprofen	CV-2	ACLT, MCLT, MMT	rats	reduced inflammation, cartilage protection (8 weeks)	[59]
Corticosteroids	TCA	hyaluronan hydrogel	knee OA	patients	pain relief (26 weeks)	[62]
		PLGA microspheres (FX006)			pain relief (12–24 weeks)	[63a–d]
		PEA microspheres	collagenase	rats	reduced inflammation (7 weeks)	[64]
		dextran sulfate NPs	MIA	mice	cartilage protection (3 weeks)	[65a]
		poly(organophosphazene) NPs		rats	cartilage protection (8 weeks)	[65b]
Glucocorticoids	Dex	TLC599 liposomes	knee OA	patients	pain relief (24 weeks)	[67h]
		Col/HA liposomes	MIA	rats	reduced inflammation (17 days)	[55b]
		PTKU NPs			cartilage repair (4 weeks)	[67c]
		P407/GS97/alginate/PVP/HA gel			reduced inflammation, cartilage protection (3 weeks)	[57e]
		PEG/PCL/TSPBA/GelMA (WYRGRL) microspheres			cartilage repair (5 weeks)	[66c]
		ROS-responsive PLGA microspheres		mice	reduced inflammation, cartilage protection (3 weeks)	[66a]
		ROS-responsive PP188 NPs			reduced bone erosion, cartilage protection (5 weeks)	[67e]
		TK/PEG (DWRVIIPPRPSA) NPs			cartilage protection (4 weeks)	[67f]
		chitosan-modified MoS_2 nanosheets	papain	mice	cartilage protection (4 weeks)	[67a]
		PEG/pPAD NPs		rats	reduced inflammation, cartilage protection (3 weeks)	[67d]
		gelatin/dextran/HA hydrogel	collagenase	rabbits	reduced inflammation, cartilage protection (3 weeks)	[56]
		HA hydrogel	ACLT	rats	reduced inflammation, cartilage protection (12 weeks)	[68a]
		hollow copper sulfide NPs			reduced inflammation, cartilage protection (4 weeks)	[67g]

(*Continued*)

Table 1. (Continued)

Family	Molecules	Biomaterials	OA models	Species, Patients	Effects	References
		PEG/4MAL/PLGA NPs	PTOA	mice	reduced osteophyte formation, cartilage protection (2 weeks)	[67b]
		PLGA/PVA microplates			reduced inflammation, cartilage protection (4 weeks)	[66b]
		chitosan/glycerin hydrogel	DMM	mice	pain relief, cartilage protection (11 weeks)	[68b]
Viscosupplementation	HA	p(HPMAm-lac)/PEG hydrogel	collagenase	mice	reduced inflammation, cartilage protection (3 weeks)	[69a]
		PLGA NPs	DMM	mice	reduced osteophyte formation, cartilage protection (5 weeks)	[69b]
	CS	PF127/HA hydrogel	DMM	mice	reduced osteophyte formation, cartilage protection (7 weeks)	[70]
SADOAs	diacerein	CS/lipid NPs	MIA	rats	reduced inflammation (12 weeks)	[71a]
		PF127/P407/PPG/soybean oil hydrogel			cartilage protection (3 weeks)	[72]
		PLGA NPs			reduced inflammation, cartilage protection (9 weeks)	[71c]
	rhein	P407 NPs	MIA	rats	reduced inflammation, cartilage protection (8 weeks)	[71b]
Drugs (inflammation)	HCQ	ferritin (WYRGRL/GPLGVRGC) nanocages	papain	mice	reduced inflammation (6 weeks)	[73a]
		HA-MA/SA (GPLGVRGC) microspheres	MIA	rats	reduced inflammation, cartilage protection (4 weeks)	[73b]
	IL-1Ra	ELP depots	PTOA	mice	reduced inflammation, cartilage protection (8 weeks)	[74a]
		PLGA microspheres	ACLT	rats	reduced inflammation, cartilage protection (5 weeks)	[74b]
	IL-36Ra	PLGA/PEG/PLGA hydrogel	DMM	mice	cartilage protection (8 weeks)	[74c]
	etanercept	Col/chitosan/hydroxyapatite porous scaffold	collagenase	mice	cartilage protection (5 weeks)	[75]
	$sPLA_2i$	PC/DOTAP/DSPE/PEG NPs	DMM	mice	reduced inflammation, cartilage protection (16 weeks)	[76]
	MK-8722	PLGA/PEG NPs	collagenase	mice	cartilage protection (2 weeks)	[77]
	resolvin D1	DOTAP/DSPE/PEG liposomes	DMM	mice	reduced inflammation and osteophyte formation (12 weeks)	[78]
	adenosine	PC/PEG NPs	ACLT	rats	cartilage protection (8 weeks)	[79a]
		PC/soybean oil/CLS/glycerin liposomes		rats, mice	cartilage protection (8 weeks)	[79b]
	fluvastatin	PLGA microspheres	ACLT	rabbits	cartilage protection (6 weeks)	[80a]
	simvastatin	gelatin hydrogel	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[80b]
	curcumin	gelatin/silk fibroin microspheres	MIA	rats	reduced inflammation (8 weeks)	[81a]
		PEG micelles		mice	cartilage protection (4 weeks)	[81c]
		chitosan/HA NPs	ACLT	rats	reduced inflammation, cartilage protection (4 weeks)	[81b]
		MOF NPs	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[81d]
	sulforaphane	PLGA microspheres	ACLT	rats	cartilage protection (8 weeks)	[82]
	TMP	PLGA microspheres	papain	rats	reduced inflammation, cartilage protection (4 weeks)	[83]
	TTS	DGME/OMG/POE/PEG hydrogel	papain	rabbits	reduced inflammation (4 weeks)	[84]
	clodronate	liposomes	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[85]

(*Continued*)

Table 1. (Continued)

Family	Molecules	Biomaterials	OA models	Species, Patients	Effects	References
	hesperetin	$Gd_2(CO_3)_3$/PDA/PEG (DWRVIIPPRPSA) NPs	ACLT	mice	cartilage protection (8 weeks)	[86a,b]
	EGCG	gelatin/HA hydrogel	ACLT	mice	cartilage protection (4 weeks)	[87]
	celastrol	HMS/chitosan NPs	MIA	rats	cartilage protection (6 weeks)	[88]
	psoralidin	PEOz/PCL (WYRGRL/GPLGVRGC) nanomicelles	papain	mice	cartilage protection (6 weeks)	[89]
	protocatechuic acid	MOF/HA NPs	ACLT	rats	reduced inflammation (8 weeks)	[90]
	bilirubin	MOF/MPDA (WYRGRL) NPs	ACLT	rats	reduced inflammation, cartilage protection (6 weeks)	[91]
	andrographolide	MS/PAA NPs	ACLT	rats	reduced inflammation, cartilage protection (8 weeks)	[92]
	pioglitazone	dodecylamine/HA (WYRGRL) nanomicelles	DMM	rats	cartilage protection (6 weeks)	[93]
	sulfasalazine	HA gel formulation	MIA	rats	reduced inflammation, cartilage protection (9 weeks)	[94]
	icariin	tannic acid NDs	MIA	rats	reduced inflammation, cartilage protection (9 weeks)	[95]
	BTZ	ROS-responsive mPEG NPs	MMT	mice	reduced inflammation, cartilage protection (12 weeks)	[96]
Drugs (oxidation)	CAT/SMT	ZIF-8 NPs	ACLT	rats	cartilage protection (4 weeks)	[97]
	astaxanthin	ROS-responsive HPMDA/PEG NPs	ACLT	mice	reduced inflammation, cartilage protection (6 weeks)	[98]
	CORMs	POSS-G_3-Lys peptide dendrimer/FA/HA nanogel	MIA	rats	cartilage protection (3 weeks)	[99]
	rebamipide	PEG/PDLLA and PLGA NPs	MIA	rats	reduced inflammation, cartilage protection (8 weeks)	[100]
	EPA	gelatin hydrogel	DMM	mice	reduced inflammation (8 weeks)	[101]
	SOD	PEG/PBD/PPO NPs	DMM	mice	cartilage protection (12 weeks)	[102]
	liquiritin	CS/alginate/HSPC/DSPE/PEG hydrogel	DMM	rats	reduced osteophyte formation, cartilage protection (10 weeks)	[103]
Drugs (autophagy)	rap	LIPUS/DSPC liposomes	spontaneous OA	guinea pigs	cartilage protection (8 weeks)	[104b]
		gelatin hydrogel	DMM	mice	reduced inflammation, cartilage protection (10 weeks)	[104a]
		PLGA/PVA MPs			reduced inflammation, cartilage protection (8 weeks)	[104d]
		MOF/MPDA (WYRGRL) NPs	ACLT	rats	reduced inflammation, cartilage protection (6 weeks)	[91]
		HSPC/CLS/octadecylamine/HA liposomes			reduced osteophyte formation, cartilage protection (4 weeks)	[104c]
		ROS-responsive HPMDA/PEG NPs		mice	reduced inflammation, cartilage protection (6 weeks)	[98]
	met	ferritin nanocages	papain	mice	cartilage protection (6 weeks)	[105]
	sinomenium	GelMA/chitosan hydrogel	ACLT	mice	cartilage protection (8 weeks)	[106]
	cordycepin	chitosan/HA hydrogel	ACLT	mice	cartilage protection (8 weeks)	[107]
	urolithin A	DSPE/PEG/HA (WYRGRL) liposomes	DMM	rats	reduced osteophyte formation, cartilage protection (8 weeks)	[108]
Drugs (senolysis)	quercetin	PEG/PA hydrogel	ACLT	rats	pain relief, reduced inflammation, cartilage protection (12 weeks)	[109a]
		DSPE/PEG/CX3 NPs	DMM	mice	cartilage protection (4 weeks)	[109b]
	dasatinib	DSPE/PEG/CX3 NPs	DMM	mice	cartilage protection (4 weeks)	[109b]

(*Continued*)

Table 1. (Continued)

Family	Molecules	Biomaterials	OA models	Species, Patients	Effects	References
Drugs (catabolism)	dox	HA hydrogel	MMx	rabbits	cartilage protection (2 weeks)	[110]
	NSC23766	chitosan/HA microspheres	ACLT	mice	cartilage protection (8 weeks)	[111]
	114810	HA hydrogel	ACLT	rats	cartilage protection (8 weeks)	[112]
	adavivint	PLGA/CM NPs	ACLT	rats/dogs	cartilage protection (4/20 weeks)	[113]
	chidamide	PLGA microcapsules	ACLT	rats	cartilage protection (8 weeks)	[114]
	BI-4394	TG-18 hydrogel	ACLT	rats	cartilage protection (5 weeks)	[115]
Drugs (regeneration)	FGF-2	gelatin microspheres	ACLT	rabbits	cartilage protection (10 weeks)	[116a]
	PTH(1-34)	PLGA microspheres	papain	rats	cartilage protection (5 weeks)	[116b]
	BMP-2	PlnD1/HA microgels	papain	mice	cartilage protection (2 weeks)	[116c]
		graphene oxide flakes	ACLT	rats	cartilage protection (4 weeks)	[116d]
	IGF-I	pGlu/pArg nanoplexes	ACLT, MMx	rats	reduced inflammation, cartilage protection (4 weeks)	[116e]
		PAMAM/PEG nanocarriers			cartilage protection (4 weeks)	[116f]
	TGF-α	PEG/PCL/PLL/DSPE NPs	DMM	mice	cartilage protection (3 weeks)	[116g]
	FGF-18	CS/PLEL/EPL NPs	ACLT	mice	reduced inflammation, cartilage protection (8 weeks)	[116h]
	KGN	GelMA/PCL/PEG/TSPBA (WYRGRL) hydrogel	MIA	rats	cartilage repair (5 weeks)	[66c]
		chitosan NPs/MPs	ACLT	rats	cartilage protection (14 weeks)	[117a]
		PLGA/PEG/PLGA gel		rabbits	reduced inflammation, cartilage protection (3 weeks)	[117e]
		PLGA/PDA/PEG (EPLQLKM) NPs		rats	cartilage protection (12 weeks)	[117g]
		PLA nanocrystals	DMM	mice	cartilage protection (8 weeks)	[117c]
		GelMA/lecithin/CLS microgels		rats	reduced osteophyte formation, cartilage protection (8 weeks)	[117f]
		PF127/COS nanospheres	ACLT, DMM	rats	reduced inflammation, cartilage protection (8 weeks)	[55c]
		PU/PEG NPs			cartilage protection (12 weeks)	[117d]
		PEG/HA micelles	ACLT, MMx	rats	cartilage protection (8 weeks)	[117b]
		CV-2	ACLT, MCLT, MMT	rats	reduced inflammation, cartilage protection (8 weeks)	[59]
	atsttrin	E_5C porous network gel	ACLT	rabbits	cartilage repair (8 weeks)	[118]
	berberine	chitosan NPs	ACLT, MMx	rats	cartilage repair (10 weeks)	[119]
	3,4,6-O-Bu 3 GalNAc	PLGA microspheres	MMT	rats	reduced inflammation, cartilage protection (4 weeks)	[120]
	cassic acid	PF127/CS nanoreservoirs	MIA	rats	reduced inflammation, cartilage protection (8 weeks)	[121]
Orthobiologics	PRP	gelatin hydrogel	ACLT	rabbits	reduced inflammation, cartilage protection (10 weeks)	[122a]
		P407/HA hydrogel	MIA	rats	reduced inflammation, cartilage protection (5 weeks)	[122b]
		BSA/MnO_2/HA hydrogel			cartilage protection (4 weeks)	[122c]
	sPL	PLGA/chitosan/gelatin microspheres	ACLT, DMM	rats	cartilage protection (12 weeks)	[123]
	EVs, Exos	(iMSC-EVs) DA HA/PEG hydrogel	ACLT, MMx	rats	cartilage protection (5 weeks)	[124]
		(SMSC-EVs) PLEL hydrogel	MCLT, MMT	rats	reduced inflammation, cartilage protection (24 weeks)	[125]
		(AC-Exos) PF127/HA hydrogel	DMM	rats	reduced inflammation, cartilage protection (12 weeks)	[126]
		(UCMSC-Exos) CLS/PEG/HA (DWRVIIPPRPSA) gel	ACLT	rats	cartilage protection (8 weeks)	[127]
		(BM-MSC-Exos/LRRK2-IN-1) GelMA (WYRGRL) hydrogel	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[128]
		(ASC-Exos) hyaluronan MPs	DMM	mice	cartilage protection (8 weeks)	[129]

(*Continued*)

Table 1. (Continued)

Family	Molecules	Biomaterials	OA models	Species, Patients	Effects	References
Pleiotropic gas	H_2	H_2-CBN@GelDA hydrogel	MIA	rats	reduced inflammation, cartilage protection (4 weeks)	[131b]
		H-Si/GelMA fibers			reduced inflammation, cartilage repair (1 week)	[131d]
	H_2S	H_2S/GYY-4137 donor	MCLT, MMT	rats	reduced inflammation, cartilage protection (6 weeks)	[130d, 131a]
			DMM	mice	reduced inflammation (8 weeks)	[131c]
Bioactive ions	Mg^{2+}	MoS_2@PDA-Mg@PSB nanosheets	MIA	mice	reduced inflammation, cartilage protection (8 weeks)	[133]
		MgO&SA@PLGA microspheres	MMT	rats	cartilage protection (4 weeks)	[134]
	Cu^{2+}	Cu-BGC scaffolds	PTOA	rabbits	reduced inflammation, cartilage protection (12 weeks)	[135]
	Fe^{2+}/Fe^{3+}	Fe^{2+}/Fe^{3+}/type-II collagen hydrogel	PTOA	rats	reduced inflammation, cartilage protection (12 weeks)	[136]

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SADOAs, slow-acting drugs in OA; OA, osteoarthritis; DCF, diclofenac; TCA, triamcinolone acetonide; dex, dexamethasone; HA, hyaluronic acid; CS, chondroitin sulfate; HCQ, hydroxychloroquine; IL-1Ra, interleukin-1 receptor antagonist; IL-36Ra, interleukin-36 receptor antagonist; $sPLA_2i$, secretory phospholipase A2 inhibitor; MK-8722, activator of AMPK; AMPK, 5′-adenosine monophosphate-activated protein kinase; TMP, tetramethylpyrazine; TTS, 3,5,4′-trimethoxy-trans-stilbene; EGCG, epigallocatechin-3-gallate; BTZ, bortezomib; CAT, catalase; SMT, S-methylisothiourea hemisulfate salt; CORMs, CO release molecules; EPA, eicosapentaenoic acid; SOD, superoxide dismutase; rap, rapamycin; met, metformin; dox, doxycycline; NSC23766, Rac1 inhibitor; Rac1, Ras-related C3 botulinum toxin substrate 1; Ras, rat sarcoma virus; 114810, ADAMTS-5 inhibitor; ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; BI-4394, MMP-13 blocker; MMP-13, matrix metalloproteinase 13; FGF-2; basic fibroblast growth factor; PTH(1-34), parathyroid hormone (1-34); BMP-2, bone morphogenetic protein 2; IGF-I, insulin-like growth factor I; TGF-α, transforming growth factor alpha; FGF-18, fibroblast growth factor 18; KGN, kartogenin; 3,4,6-O-Bu 3 GalNAc, tri-butanoylated N-acetyl-D-galactosamine analog; PRP, platelet-rich plasma; sPL, super-activated platelet lysate; EVs, extracellular vesicles; Exos, exosomes; H_2, hydrogen gas; H_2S, hydrogen sulfide; Fe^{2+}/Fe^{3+}, ferrous/ferric ions; PLGA, poly(lactide-co-glycolic acid); MPs, microparticles; Col, collagen; SPC, soybean phosphatidylcholine; DPPE, dipalmitoyl phosphatidylethanolamine; P407, poloxamer 407; MS, mesoporous silica; PMPC, poly(2-methacryloyloxyethyl phosphorylcholine); GelMA, methacrylate gelatin; DMA, dopamine methacrylamide; MPC, 2-methacryloyloxyethyl phosphorylcholine; PF127, pluronic F127; COS, chitosan oligosaccharide; CLS, cholesterol; PEA, polyester amide; GS97, Gantrez S97; PVP, polyvinylpyrrolidone; PEG, polyethylene glycol; NPs, nanoparticles; CV-2, zwitterion-modified cavitand; PTKU, polythioketal urethane; PCL, poly(ϵ-caprolactone); TSPBA, N1-(4-boronobenzyl)-N3-(4-boronobenzyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium; WYRGRL, collagen II-targeting peptide; ROS, reactive oxygen species; PP188, polyphenol-poloxamer 188; TK, thioketal linker; MoS_2, molybdenum disulfide; pPAD, phenylboronic acid; 4MAL, four-arm maleimide; PVA, polyvinyl alcohol; p(HPMAm-lac), poly(hydroxypropyl methacrylamide lactate); PPG, polypropylene glycol; GPLGVRGC, MMP-13-cleavable peptide; HA-MA, methacrylated HA; SA, sulfonated azocalix[4]arene; ELP, ϵ-poly-L-lysine; PC, phosphatidyl choline; DOTAP, 1,2-dioleoyl-3-trimethylammonium propane; DSPE, distearyl phosphatidylethanolamine; MOF, metal-organic framework; DGME, diethylene glycol monoethyl ether; OMG, oleoyl macrogolglyceride; POE, polyoxyethylene; Gd, Gadolinium; PDA, polydopamine; DWRVIIPPRPSA, cartilage-targeting peptide; HMS, hollow mesoporous silica; PEOz, poly(2-ethyl-2-oxazoline); MPDA, mesoporous polydopamine; PAA, pH-responsive polyacrylic acid; NDs, nanodiamonds; mPEG, monomethoxy PEG; ZIF-8, zeolitic imidazolate framework-8; HPMDA, 1,2,4,5-cyclohexanetetracarboxylic dianhydride; POSS-G_3-Lys, POSS core-based generation 3 PLL; POSS, polyhedral oligomeric silsesquioxane; PLL, poly-L-lysine; FA, folic acid; PDLLA, poly(D,L-lactide); PBD, polybutadiene; PPO, poly(propylene oxide); HSPC, hydrogenated soybean phosphatidylcholine; LIPUS, low-intensity pulsed US; US, ultrasounds; DSPC, CLS, octadecylamine, 1, 2-distearoyl, L-α-phosphatidylcholine; PA, poly(alanine); CX3, CX3 aptamer; CM, chondrocyte membrane; TG-18, triglycerol monostearate; PlnD1, perlecan domain 1; pGlu, poly(glutamic acid); pArg, poly(arginine); PAMAM, amine terminal polyamidoamine; PLEL, poly(D, L-lactide)-poly(ethylene glycol)-poly(D, L-lactide); EPL, ϵ-poly-L-lysine; EPLQLKM, BM-MSC-targeting peptide; BM-MSCs, bone marrow-derived MSCs; MSCs, mesenchymal stromal cells; PLA, poly(lactic acid); PU, polyurethane; E_5C, recombinant protein block polymer with five repeats of elastin-like polypeptide (E) and a coiled-coil domain of COMP; COMP, cartilage oligomeric matrix protein; BSA, bovine serum albumin; MnO_2, molybdenum disulfide; iMSCs, induced MSCs; SMSCs, synovium MSCs; DA, Diels-Alder crosslinking; AC, articular chondrocytes; UCMSCs, umbilical cord-derived MSCs; LRRK2-IN-1, inhibitor of LRRK2; LRRK2, leucine-rich repeat kinase 2; ASCs, adipose-derived stem cells; CBN, calcium boride nanosheets; GelDA, dopamine-grafted gelatin; H-Si, hydrogen-silicon; GYY4137, morpholin-4-ium 4 methoxyphenyl(morpholino) phosphinodithioate; PSB, zwitterionic polysulfobetaine; MoS_2@PDA-Mg@PSB, MoS2-based nanozyme sequentially modified with Mg^{2+}-doped polydopamine and zwitterionic polysulfobetaine; MgO, magnesium oxide; SA, stearic acid; BGC, bioactive glass-ceramics; MIA, monosodium iodoacetate; DMM, destabilization of the medial meniscus; ACLT, anterior cruciate ligament transection; MMx, medial meniscectomy; MCLT, medial collateral ligament transection; MMT, medial meniscal transection; PTOA, post-traumatic OA.

or thioketal linker (TK)/PEG (cartilage-targeting DWRVIIP-PRPSA peptide) NPs.[67f] Similar effects were associated with the use of dex in a papain OA model in mice[67a] and in rats[67d] for 3–4 weeks, affording cartilage protection via chitosan-modified molybdenum disulfide (MoS_2) nanosheets[67a] and a PEGylated/phenylboronic acid (pPAD)/HA hydrogel that also reduced inflammation,[67d] as also noted in collagenase-induced OA in rabbits for 3 weeks using a gelatin/dextran/HA hydrogel.[56] Finally, controlled delivery of dex was also beneficial in rat[67g,68a] and mouse[66b,67b,68b] models of surgical OA (ACLT, post-traumatic OA – PTOA, DMM), with pain relief for 11 weeks using a chitosan/glycerin hydrogel,[68b] reduced inflammation and osteophyte formation and afforded cartilage protection for up to 12 weeks using either a HA hydrogel,[68a] hollow copper sulfide NPs,[67g] PEG/four-arm maleimide (4MAL)/PLGA NPs,[67b] or PLGA/PVA microplates.[66b]

Viscosupplementation: Viscosupplementation improves joint lubrication, helps to distribute loads across joint surfaces, and provides synovial fluid with antinociceptive and anti-inflammatory effects.[69,70] HA acts by binding to the CD44 receptor, a cell-surface glycoprotein on articular cells, inhibiting the production of IL-1β, PGE_2, and MMPs[69a] while increasing heat shock protein 70 (HSP70) direct analgesia by masking joint nociceptors.[69b] CS exerts anti-inflammatory activities by target-

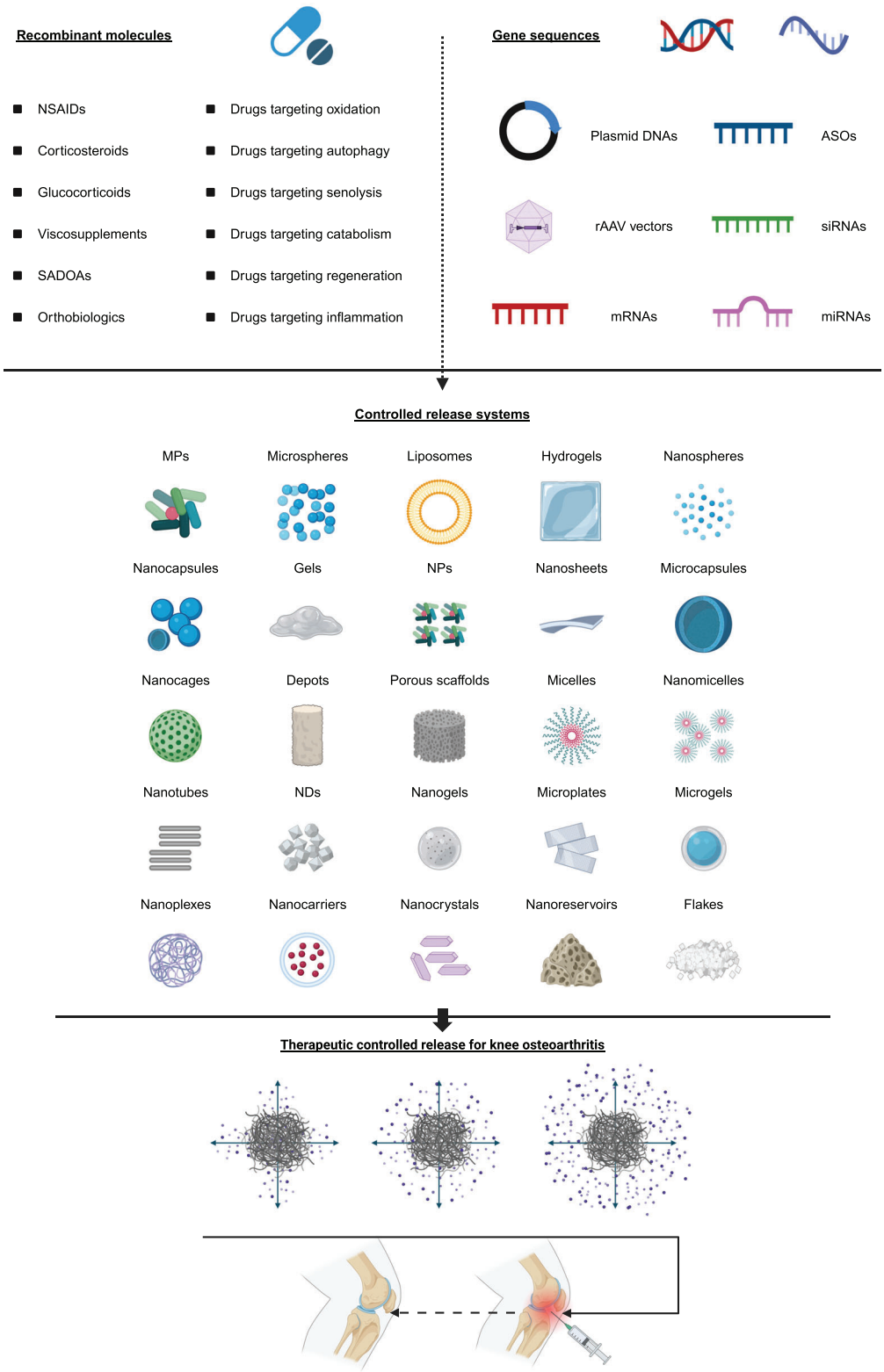

Figure 3. Controlled release systems for osteoarthritis. Recombinant molecules (top left) and gene sequences (top right) have been applied to relevant models of OA in vivo using various controlled release systems (middle) supporting over time cargo release as convenient injectable therapies for human OA (bottom). Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SADOAs, slow-acting drugs in OA; OA, osteoarthritis; DNA: deoxyribonucleic acid; ASO: antisense oligonucleotide; rAAV, recombinant adeno-associated virus; siRNA, small interfering RNA; RNA, ribonucleic acid; mRNA, messenger RNA; miRNA, microRNA; MPs, microparticles; NPs, nanoparticles; NDs, nanodiamonds (created with BioRender).

ing the complement protein 5 (C5) and regulating the complement system activated by a series of serine proteases in OA.[70]

HA[69] and CS[70] have been administered in OA models in vivo via controlled release strategies, reducing inflammation and affording cartilage protection in collagenase-induced OA in mice for 3 weeks using a poly(hydroxypropyl methacrylamide lactate) (p(HPMAm-lac))/PEG hydrogel[69a] and reducing osteophyte formation and affording cartilage protection in mouse models of surgical OA (DMM) for 5–7 weeks using either PLGA NPs[69b] or a PF127/HA hydrogel.[70]

SADOAs: SADOAs inhibit the production of IL-1β, MMPs, and transforming growth factor beta 1 and 2 (TGF-β1, TGF-β2) while increasing that of anti-inflammatory IL-4 and IL-10 by regulating the MAPK and nuclear factor kappa B (NF-κB) signaling pathways.[71,72]

SADOAs have been reported to effectively reduce inflammation for 8–12 weeks[71] and afford cartilage protection for 3–9 weeks[71b,c,72] in MIA-induced OA in rats using CS/lipid,[71a] PLGA,[71c] or P407[71b] NPs or a PF127/P407/PPG/soybean oil hydrogel.[72]

Drugs Targeting Inflammation: These drugs reduce the actions of inflammatory mediators like IL-1β, IL-6, IL-36, TNF-a, secreted PLA2 (sPLA2), MMP-1, -2, -3, and -13, and ADAMTS-5 by targeting the NF-κB and 5′-adenosine monophosphate-activated protein kinase (AMPK) signaling pathways, scavenging cytotoxic oxygen free radicals, shifting the pro-inflammatory M1 macrophage phenotype to the anti-inflammatory M2 macrophage phenotype, and increasing the expression of genes associated with cell proliferation.[73–96] Anti-inflammatory drugs have broadly been employed in a variety of OA models in vivo using different controlled release systems, including hydroxychloroquine (HCQ),[73] IL receptor antagonists (IL-1Ra, IL-36Ra),[74] etanercept,[75] a sPLA2 inhibitor (sPLA$_2$i),[76] MK-8722 (an activator of AMPK),[77] resolvin D1,[78] adenosine,[79] statins (fluvastatin, simvastatin),[80] curcumin,[81] sulforaphane,[82] tetramethylpyrazine (TMP),[83] 3,5,4′-trimethoxy-trans-stilbene (TTS),[84] clodronate,[85] hesperetin,[86] epigallocatechin-3-gallate (EGCG),[87] celastrol,[88] psoralidin,[89] protocatechuic acid,[90] bilirubin,[91] andrographolide,[92] pioglitazone,[93] sulfasalazine,[94] icariin,[95] and bortezomib (BTZ, a proteasome inhibitor)[96] via depots,[74a] microspheres,[73b,74b,80a,81a,82,83] nanocages, nanodiamonds (NDs), NPs, nanomicelles, and liposomes,[73a,76–79,81b–d,85,86,88–93,95,96] hydrogels,[74c,80b,87,94] and porous scaffolds.[75]

For instance in papain OA models, TMP reduced inflammation and afforded cartilage protection in rats for 4 weeks via PLGA microspheres,[83] HCQ[73a] and TTS[84] reduced inflammation in mice[73a] and in rabbits[84] for 4–6 weeks using ferritin (collagen II-targeting WYRGRL peptide/MMP-13-cleavable GPLGVRGC peptide) nanocages[73a] and a diethylene glycol monoethyl ether (DGME)/oleoyl macrogolglyceride (OMG)/polyoxyethylene (POE)/PEG hydrogel,[84] and psoralidin afforded cartilage protection in mice for 6 weeks via poly(2-ethyl-2-oxazoline) (PEOz)/PCL (collagen II-targeting WYRGRL peptide/MMP-13-cleavable GPLGVRGC peptide) nanomicelles.[89] In MIA-induced OA models, HCQ,[73b] curcumin,[81a,c] sulfasalazine,[94] and icariin[95] reduced inflammation and afforded cartilage protection in rats[73b,81a,94,95] and in mice[81c] for 4–9 weeks using methacrylated HA (HA-MA)/sulfonated azocalix[4]arene (SA) (MMP-13-cleavable GPLGVRGC peptide) microspheres,[73b] gelatin/silk microspheres,[81a] PEG micelles,[81c] an HA gel formulation,[94] and tannic acid NDs[95] while celastrol afforded cartilage protection in rats for 6 weeks using hollow mesoporous silica (HMS)/chitosan NPs.[88] In collagenase-induced OA models, etanercept[75] and MK-8722[77] afforded cartilage protection in mice for 2–5 weeks using Col/chitosan/hydroxyapatite porous scaffolds[75] and PLGA/PEG NPs.[77] In a surgical PTOA model, an IL-1Ra reduced inflammation and afforded cartilage protection in mice for 8 weeks using ϵ-poly-L-lysine (ELP) depots.[74a] In surgical ACLT models, an IL-1Ra,[74b] curcumin,[81b] bilirubin,[91] and andrographolide[92] reduced inflammation and afforded cartilage protection in rats[74b,81b,91,92] for 4–8 weeks using PLGA microspheres,[74b] chitosan/HA NPs,[81b] metal-organic framework (MOF)/mesoporous polydopamine (MPDA) (collagen II-targeting WYRGRL peptide) NPs,[91] and MS/pH-responsive polyacrylic acid (PAA) NPs.[92] Also in ACLT models, adenosine,[79] Fluvastatin,[80a] sulforaphane,[82] hesperetin,[86] and EGCG[87] afforded cartilage protection in rats,[79,82] in mice,[79b,86,87] and in rabbits[80a] for 4–8 weeks via phosphatidyl choline (PC)/PEG NPs,[79a] PC/soybean oil/CLS/glycerin liposomes,[79b] PLGA microspheres,[80a,82] Gadolinium ($Gd_2(CO_3)_3$)/polydopamine (PDA)/PEG (cartilage-targeting DWRVIIPPRPSA peptide) NPs,[86] and a gelatin/HA hydrogel,[87] while protocatechuic acid reduced inflammation in rats for 8 weeks via MOF/HA NPs.[90] In surgical DMM models, a sPLA$_2$i,[76] simvastatin,[80b] clodronate,[85] and curcumin[81d] reduced inflammation and afforded cartilage protection in mice for 8–16 weeks using PC/1,2-dioleoyl-3-trimethylammonium propane (DOTAP)/distearyl phosphatidylethanolamine (DSPE)/PEG NPs,[76] a gelatin hydrogel,[80b] liposomes,[85] and MOF NPs.[81d] Also in DMM models, an IL-36Ra[74c] and pioglitazone[93] afforded cartilage protection in mice[74c] and in rats[93] for 6–8 weeks via a PLGA/PEG/PLGA hydrogel[74c] and dodecylamine/HA (collagen II-targeting WYRGRL peptide) nanomicelles,[93] while resolvin D1 reduced inflammation and osteophyte formation in mice for 12 weeks using DOTAP/DSPE/PEG liposomes.[78] In a surgical MMT model, BTZ reduced inflammation and afforded cartilage protection in mice for 12 weeks using ROS-responsive monomethoxy PEG (mPEG) NPs.[96]

Drugs Targeting Oxidation: These drugs decrease the ROS levels, and inhibit the release of IL-1β, IL-6, TNF-α, MMP-3 and -13, COX-2, NO synthase (NOS), and heme oxygenase-1 (HO-1) by reducing the p38/MAPK, NF-κB, and toll-like receptor (TLR-2) signaling pathways while shifting the M1 to the M2 macrophage phenotype.[97–103]

Several anti-oxidative drugs have been employed in surgical models of OA, showing therapeutic benefits in vivo. In surgical ACLT models, catalase (CAT)/S-methylisothiourea hemisulfate salt (SMT)[97] and astaxanthin[98] reduced inflammation[98] and afforded cartilage protection[97,98] in rats[97] and in mice[98] for 4–6 weeks using either zeolitic imidazolate framework-8 (ZIF-8) NPs[97] or ROS-responsive 1,2,4,5-cyclohexanetetracarboxylic dianhydride (HPMDA)/PEG NPs.[98] In MIA models, CO release molecules (CORMs)[99] and rebamipide[100] reduced inflammation[100] and afforded cartilage protection in rats for 3–8 weeks via a polyhedral oligomeric silsesquioxane

core-based generation 3 poly-L-lysine (POSS-G_3-Lys) peptide dendrimer/folic acid (FA)/HA nanogel[99] and PEG/poly(D, L-lactide) (PDLLA) and PLGA NPs.[100] In surgical DMM models, eicosapentaenoic acid (EPA),[101] superoxide dismutase (SOD),[102] and liquiritin[103] reduced inflammation and osteophyte formation[101,103] and afforded cartilage protection[102,103] in mice[101,102] and in rats[103] for 8–12 weeks using gelatin[101] or CS/alginate/hydrogenated soybean phosphatidylcholine (HSPC)/DSPE/PEG hydrogel[103] and PEG/polybutadiene (PBD)/poly(propylene oxide) (PPO) NPs.[102]

Drugs Targeting Autophagy: These drugs tackle autophagy and mitophagy by suppressing the mammalian target of rap (mTOR) signaling pathway, activating the AMPK and sirtuin 1 (SIRT1)/coactivator 1 alpha (PGC-1α) signaling pathways, and inhibiting the expression of ADAMTS-5 and MMP-1 and -13 via the NF-κB signaling pathway while shifting the M1 to the M2 macrophage phenotype.[91,98,104–108] Various drugs affecting autophagy have been successfully employed to target OA in vivo, including rapamycin (rap),[91,98,104] metformin (met),[105] sinomenium,[106] cordycepin,[107] and urolithin A[108] via MPs,[104d] nanocages, NPs, and liposomes,[91,98,104b,c,105,108] and hydrogels.[104a,106,107]

For instance, the controlled delivery of rap afforded cartilage protection in a model of spontaneous OA in guinea pigs for 8 weeks via low-intensity pulsed US (LIPUS)/DSPC liposomes.[104b] In surgical DMM models, rap reduced inflammation and afforded cartilage protection in mice for 8–10 weeks using either a gelatin hydrogel[104a] or PLGA/PVA MPs.[104d] In surgical ACLT models, rap reduced inflammation and osteophyte formation and afforded cartilage protection in rats[91,104c] and in mice[98] for 4–6 weeks with MOF/MPDA (collagen II-targeting WYRGRL peptide)[91] and ROS-responsive HPMDA/PEG[98] NPs and with HSPC/CLS/octadecylamine/HA liposomes.[104c] In a papain OA model, met afforded cartilage protection in mice for 6 weeks using ferrition nanocages,[105] while sinomenium[106] and cordycepin[107] had similar effects in surgical ACLT models in mice for 8 weeks using GelMA/chitosan[106] or chitosan/HA[107] hydrogels and urolithin A in a surgical DMM model in rats also for 8 weeks together with reduced osteophyte formation via DSPE/PEG/HA (collagen II-targeting WYRGRL peptide) liposomes.[108]

Drugs Targeting Senolysis: These drugs induce FLS apoptosis, protect articular chondrocytes from oxidative stress, target senescent synovial cells, and reduce the expression of TNF-α, IL-1β, MMP-3, and pro-apoptotic caspase 3.[109]

Quercetin[109] and dasatinib[109b] have been reported to promote pain relief and reduce inflammation[109a] and to afford cartilage protection[109] in models of surgical OA (ACLT, DMM) in rats[109a] and in mice[109b] for 4–12 weeks using a PEG/poly(alanine) (PA) hydrogel[109a] and DSPE/PEG/CX3 aptamer (CX3) NPs.[109b]

Drugs Targeting Catabolism: These drugs reduce the expression of MMP-13 and ADAMTS-5 by inhibiting the Wnt and NF-κB signaling pathways.[110–115]

Doxycycline (dox),[110] NSC23766 (an inhibitor of Rac1, a rat sarcoma virus – Ras – related C3 botulinum toxin substrate 1),[111] the 114810 agents (an inhibitor of ADAMTS5),[112] adavivint,[113] chidamide (a histone deacetylase inhibitor),[114] and BI-4394 (an MMP-13 blocker)[115] were described for their ability to afford cartilage protection in surgical models of OA in rabbits with MMx[110] and in mice,[111] in rats,[112–115] and in dogs[113] with ACLT for 2–20 weeks using HA[110,112] and triglycerol monostearate (TG-18)[115] hydrogels, chitosan/HA microspheres,[111] PLGA/chondrocyte membrane (CM) NPs,[113] and PLGA microcapsules.[114]

Drugs Targeting Regeneration: These drugs suppress the terminal differentiation of articular chondrocytes while promoting the synthesis of ECM compounds, the activation of the anti-inflammatory M2 macrophage phenotype, and the stimulation of the KGN frees core-binding factor beta (CBF-β)/runt-related transcription factor 1 (RUNX1), NF-κB, Wnt/β-catenin, and TNF receptor 2 (TNFR2) signaling pathways for chondroprotection.[55c,59,116–121] Regenerative drugs have been applied to OA models in vivo among which a variety of growth factors (FGF-2 and -18), PTH(1-34), BMP-2, insulin-like growth factor I (IGF-I), transforming growth factor alpha (TGF-α),[116] KGN,[55c,59,66c,117] atsttrin,[118] berberine,[119] tri-butanoylated N-acetyl-D-galactosamine analog (3,4,6-O-Bu 3 GalNAc),[120] and cassic acid[121] via flakes,[116d] MPs and microspheres,[116a,b,117a,120] NPs, nanospheres, nanoplexes, nanocarriers, nanocrystals, nanoreservoirs, and micelles,[55c,116e–h,117a–d,g,119,121] CV-2,[59] and gels/hydrogels.[66c,116c,117e,f,118]

Interestingly, PTH(1-34)[116b] and BMP-2[116c] afforded cartilage protection in papain-induced OA models in rats[116b] and in mice[116c] for 2–5 weeks using PLGA microspheres[116b] and perlecan domain 1 (PlnD1)/HA microgels.[116c] Besides, KGN[66c] and cassic acid[121] reduced inflammation[121] and afforded cartilage protection[66c,121] in MIA-induced OA in rats for 5–8 weeks via a GelMA/PCL/PEG/TSPBA (collagen II-targeting WYRGRL peptide) hydrogel[66c] and PF127/CS nanoreservoirs.[121] In surgical ACLT models, FGF-2 and -18,[116a,h] BMP-2,[116d] KGN,[117a,e,g] and atsttrin[118] reduced inflammation[116h,117e] and afforded cartilage protection and repair[116a,d,h,117a,e,g,118] in rats,[117a,g] in mice,[116h] and in rabbits[116a,117e,118] for 4–14 weeks using gelatin microspheres,[116a] graphene oxide flakes,[116d] CS/poly(D, L-lactide)-poly(ethylene glycol)-poly(D, L-lactide) (PLEL)/ϵ-poly-L-lysine (EPL) NPs,[116h] chitosan NPs/MPs,[117a] PLGA/PDA/PEG (BM-MSC-targeting EPLQLKM peptide) NPs,[117g] a PLGA/PEG/PLGA gel,[117e] and a recombinant protein block polymer with five repeats of elastin-like polypeptide (E) and a coiled-coil domain of cartilage oligomeric matrix protein (COMP, i.e., C) (E_5C) porous network gel.[118] In surgical DMM models, TGF-α[116g] and KGN[117c,f] reduced osteophyte formation[117f] and afforded cartilage protection[116g,117c,f] in rats[117f] and in mice[116g,117c] for 3–8 weeks via PEG/PCL/poly-L-lysine (PLL)/DSPE NPs,[116g] PLA nanocrystals,[117c] and GelMA/lecithin/CLS microgels.[117f] In surgical ACLT and DMM models, KGN reduced inflammation and afforded cartilage protection in rats for 8–12 weeks using PF127/COS nanospheres[55c] and PU/PEG NPs.[117d] In surgical ACLT and MMx models, IGF-I,[116e,f] KGN,[117b] and berberine[119] reduced inflammation[116e] and afforded cartilage protection[116e,f,117b,119] in rats for 4–10 weeks via poly(glutamic acid) (pGlu)/poly(arginine) (pArg) NPs,[116e] amine terminal polyamidoamine (PAMAM)/PEG nanocarriers,[116f] PEG/HA micelles,[117b] and chitosan NPs.[119] In surgical ACLT, MCLT, and MMT models, KGN reduced inflammation and afforded cartilage protection in rats for 8 weeks using CV-2.[59] Finally, in surgical MMT models, 3,4,6-O-Bu 3

GalNAc reduced inflammation and afforded cartilage protection in rats for 4 weeks via PLGA microspheres.[120]

Orthobiologics: Orthobiologics are composed of various growth factors, cytokines, and gene sequences including microRNAs (miRNA) and messenger RNAs (mRNA) that promote cell proliferation and ECM production while modulating cell catabolism via the Wnt, AMPK, protein kinase B (PKB/AKT), extracellular signal-regulated kinase (ERK), mTOR, and tumor protein p53 signaling pathways and shifting the M1 to the M2 macrophage phenotype.[122–129]

PRP[122] and sPL[123] were reported to reduce inflammation[122a,b] and to afford cartilage protection[122,123] in models of OA in rabbits with surgical ACLT[122a] and in rats with MIA-induced OA[122b,c] or with ACLT and DMM[123] for 4–12 weeks using gelatin,[122a] P407/HA,[122b] and bovine serum albumin (BSA)/molybdenum disulfide (MnO_2)/HA[122c] hydrogels or PLGA/chitosan/gelatin microspheres.[123] EVs from induced MSCs (iMSCs)[124] or synovium MSCs (SMSCs)[125] and Exos from articular chondrocytes,[126] umbilical cord-derived MSCs (UCMSCs),[127] BM-MSCs loaded with LRRK2-IN-1 (an anti-inflammatory inhibitor of the leucine-rich repeat kinase 2 – LRRK2),[128] and ASCs[129] were shown to reduce inflammation[125,126,128] and to afford cartilage protection[124–129] in models of surgical OA in rats[124–127] and in mice[128,129] with ACLT,[124,127] MMx,[124] MCLT,[125] MMT,[125] or DMM[126,128,129] for 5–24 weeks using Diels-Alder crosslinked (DA) HA/PEG,[124] a PLEL hydrogel,[125] PF127/HA,[126] CLS/PEG/HA (cartilage-targeting DWRVIIPPRPSA peptide),[127] and GelMA (collagen II-targeting WYRGRL peptide)[128] hydrogels or hyaluronan microparticles.[129]

Pleiotropic Gas: Hydrogen (H_2) and hydrogen sulfide (H_2S) gases exert chondroprotective and anti-pyroptotic effects, protect against ECM degradation, and reduce the expression of IL-1β, IL-6, MMP-13, PGE_2, NO, ROS, and HO-1 by quenching ROS and reactive nitrogen species (RNS) via the activation of the transcription factor nuclear factor erythroid-derived 2-like 2 (Nrf-2) while inhibiting the NF-κB, ERK, and MAPK signaling pathways and reducing the M1 phenotype.[130]

H_2 and H_2S were reported to reduce inflammation[130d,131] and to afford cartilage protection[130d,131a,b,d] in rats with MIA-induced OA[131b,d] or with surgical MCLT or MMT[130d,131a] and in mice with surgical DMM[131c] for 1–8 weeks using a calcium boride nanosheet (CBN) with a dopamine-grafted gelatin (GelDA) hydrogel (H_2-CBN@GelDA),[131b] silicon (Si) with GelMA fibers (H-Si/GelMA),[131d] and the morpholin-4-ium 4 methoxyphenyl(morpholino) phosphinodithioate (GYY-4137) donor.[130d,131a,c]

Bioactive Ions: Mg^{2+}, Cu^{2+}, and ferrous/ferric ions (Fe^{2+}/Fe^{3+}) reduce the expression of TNF-α, IL-6, and MMP-13, by reducing the NF-κB and Wnt/β-catenin signaling pathways while increasing the phosphatidylinositol 3-kinase (PI3K)/AKT and MAPK signaling pathways.[132]

Mg^{2+} was shown to reduce inflammation[133] and to afford cartilage protection[133,134] in mice with MIA-induced OA[133] and in rats with surgical MMT[134] for 4–8 weeks using MoS2-based nanozyme sequentially modified with Mg^{2+}-doped polydopamine (PDA) and zwitterionic polysulfobetaine (PSB) (MoS_2@PDA-Mg@PSB) nanosheets[133] and magnesium oxide (MgO) with stearic acid (SA) PLGA microspheres.[134] Cu^{2+}[135] and Fe^{2+}/Fe^{3+}[136] were reported to reduce inflammation and afford cartilage protection in rabbits[135] and rats[136] with surgical PTOA for 12 weeks using bioactive glass-ceramics (BGC)[135] and a type-II collagen hydrogel.[136]

2.2.2. Controlled Release of Gene Sequences for OA In vivo

A variety of genetic sequences have also been provided via controlled release strategies to relevant models of OA in vivo, including plasmid DNAs, rAAV vectors, and mRNAs as well as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and miRNAs for gene silencing and regulation (**Table 2** and Figure 3). Like for recombinant molecules, anti-inflammatory gene sequences may be used in early OA followed by a sequential use of genes coding for anti-oxidative, anti-apoptotic, pro-anabolic, and repolarizing factors.[137]

Plasmid DNAs: Plasmid DNAs coding for an IL-1Ra,[137] a cytokine response modifier A (CrmA),[138] GDF-5,[139] or for CRISPR/Cas9 with a single guide RNA targeting MMP-13 (sgMMP-13) or FGF-18 (sgFGF-18)[140] were reported to reduce inflammation[138,140b] and to afford cartilage protection[137–140] in models of surgical OA in rats with ACLT[138,140b] or with DMM[140a] and in rabbits with MCLT[137] or with ACLT, MCLT, and MMT[139] for 2–12 weeks using chitosan or chitosan/HA NPs,[137,138] chitosan/HA/CS nano-microspheres,[139] chondrocyte-affinity peptide (CAP)-Exo liposomes,[140a] or a CAP-Exo/methacrylic anhydride-modified hyaluronic acid (HAMA) hydrogel.[140b]

rAAV Vectors: rAAV vectors carrying sequences for the cartilage-specific transcription factor sex-determining region Y-type high mobility group box 9 (SOX9) that activates the production of ECM compounds (type-II collagen, proteoglycans)[141] or IGF-I[142] were shown to reduce inflammation[141] and to afford cartilage protection[141,142] in models of surgical PTOA in minipigs for 4–52 weeks using a PF127[142] or alginate hydrogel.[141]

mRNAs: mRNAs coding for the RUNX1[143] or for the activating transcription factor 5 (ATF5)[144] afforded cartilage protection in models of surgical OA in mice with MCLT and MMx[143] and in rats with DMM[144] for 4–12 weeks using PEG-polyamino acid (poly{N-[N′-(2-aminoethyl)-2-aminoethyl]aspartamide}) block copolymer (PAsp DET)/polyamino acid (poly(N-{N′-[N′′-(2-aminoethyl)-2-aminoethyl]-2-aminoethyl}aspartamide) block copolymer (TET) (PEG-PAsp DET/TET) nanomicelles[143] and a PLGA-PEG-PLGA/Exos from BM-MSCs hydrogel.[144]

ASOs: An ASO directed against IL-1β was reported to reduce inflammation and to afford cartilage protection in a model of surgical OA in mice with DMM for 12 weeks using a gold nanorod (Au NR)/HA hydrogel.[145]

siRNAs: A variety of siRNAs have been applied in OA models using controlled release systems, targeting the hypoxia-inducible factor 2 alpha (Hif-2α),[81d,146] $NF\text{-}_{K}B$,[147] the Indian hedgehog (Ihh),[148] the neurogenic locus notch homolog protein 1 (Notch1),[149] the cytosolic subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (p47phox),[150] the isoform of the sarcoma tyrosine kinase (Src) homology and collagen A (shcA) adaptor protein family (p66shc),[151] periostin,[152] MMP-13,[153] the cyclin-dependent kinase inhibitor 2A (p16INK4a),[154] the Jumonji domain-containing protein

Table 2. Controlled release of gene sequences for OA in vivo.

Family	Genes	Biomaterials	OA models	Species	Effects	References
Plasmid DNAs	IL1-Ra	chitosan NPs	MCLT	rabbits	cartilage protection (2 weeks)	[137]
	CrmA	chitosan/HA NPs	ACLT	rats	reduced inflammation, cartilage protection (12 weeks)	[138]
	GDF-5	chitosan/HA/CS nano-microspheres	ACLT, MCLT, MMT	rabbits	cartilage protection (4 weeks)	[139]
	CRISPR/Cas9 sgMMP-13	CAP-Exo liposomes	DMM	rats	cartilage protection (4 weeks)	[140a]
	CRISPR/Cas9 sgFGF-18	CAP-Exo/HAMA hydrogel	ACLT	rats	reduced inflammation, cartilage protection (12 weeks)	[140b]
rAAV vectors	SOX9	PF127 hydrogel	PTOA	minipigs	cartilage protection (4 weeks)	[142]
	IGF-I	alginate hydrogel	PTOA	minipigs	reduced inflammation, cartilage protection (52 weeks)	[141]
mRNAs	RUNX1 mRNA	PEG-PAsp DET/TET nanomicelles	MCLT, MMx	mice	cartilage protection (4 weeks)	[143]
	ATF5 mRNA	PLGA-PEG-PLGA/Exos hydrogel	DMM	rats	cartilage protection (12 weeks)	[144]
ASOs	IL-1β ASO	Au NR/HA hydrogel	DMM	mice	reduced inflammation, cartilage protection (12 weeks)	[145]
siRNAs	Hif-2α siRNA	PEI (DWRVIIPPRPSA) NPs	ACLT, MCLT, DMM	mice	reduced inflammation, cartilage protection (7 weeks)	[146]
		MOF NPs	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[81d]
	NF-$_K$B siRNA	p5RHH peptide NPs	PTOA	mice	reduced inflammation (2 weeks)	[147]
	Ihh siRNA	Dlin-KC2-DMA/DPPC/CLS/PEG NPs	ACLT	rats	cartilage protection (5 weeks)	[148]
	Notch1 siRNA	NO-Hb/PLGA/PEG NPs	papain	mice	reduced inflammation, cartilage protection (2 weeks)	[149]
	p47phox siRNA	PLGA NPs	MIA	rats	cartilage protection (2 weeks)	[150]
	p66shc siRNA	PLGA NPs	MIA	rats	pain relief, reduced inflammation, cartilage protection (3 weeks)	[151]
	periostin siRNA	p5RHH peptide NPs	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[152]
	MMP-13 siRNA	DDPB/PLGA/PVA microplates	PTOA	mice	reduced inflammation, cartilage protection (4 weeks)	[153a]
		PEG/ECT/DB (mAbCII) NPs	PTOA	mice	cartilage protection (6 weeks)	[153b,c]
		$(EG_{18}L)_2$ (albumin hitchhiking) lipids	PTOA	mice	reduced inflammation (4 weeks)	[153d]
	p16INK4a siRNA	PLGA NPs	MMx	mice	pain relief, cartilage protection (5 weeks)	[154]
	JMJD3 siRNA	p5RHH peptide NPs	ACLT	mice	cartilage protection (8 weeks)	[155]
	Cd61 siRNA	PNIPMAM (RGD) nanogel	DMM	mice	cartilage protection (8 weeks)	[156]
	CA9 siRNA	NAHA-CaP NPs	MIA	mice	reduced inflammation, cartilage protection (8 weeks)	[157a]
			DMM	rats	reduced inflammation, cartilage protection (4 weeks)	[157a]
		AHK-CaP NPs	MIA	mice	cartilage protection (2 weeks)	[157b]
miRNAs	miR-9-5p	Liposomes	ACLT, MCLT	rats	cartilage protection (7 weeks)	[158]
	miR-29b-5p	SAP (SKPPGTSS) hydrogel	ACLT	rats	cartilage protection (10 weeks)	[159]
	miR-140	Lamp2b (DWRVIIPPRPSA) Exos	DMM	rats	cartilage protection (4 weeks)	[160a,b]
		lornoxicam cationic liposomes	DMM	rats	reduced inflammation, cartilage protection (4 weeks)	[160c]
		G5-AHP/GelMA NPs	DMM	mice	cartilage protection (12 weeks)	[160d]

(*Continued*)

Table 2. (Continued)

Family	Genes	Biomaterials	OA models	Species	Effects	References
	miR-141/200c	tgg2-PEG-PAMAM NPs	DMM	mice	cartilage protection (8 weeks)	[161]
	miR-223	(WYRGRL) EVs	MIA	rats	reduced inflammation, cartilage protection (4 weeks)	[162]
	miR-224-5p	urchin-like ceria NPs	DMM	mice	reduced inflammation, cartilage protection (8 weeks)	[163a]
		G5-AHP NPs	DMM	mice	reduced inflammation, cartilage protection (9 weeks)	[163b]
	miR365 antagomir	YCWP nanotubes	PTOA	mice	reduced inflammation, cartilage protection (7 weeks)	[164]

Abbreviations: DNA, deoxyribonucleic acid; rAAV, recombinant adeno-associated virus; mRNA, messenger RNA; ASOs, antisense oligonucleotides; siRNA, small interfering RNA; RNA, ribonucleic acid; miRNA, microRNA; IL-1Ra, interleukin 1 receptor antagonist; CrmA, cytokine response modifier A; GDF-5, growth and differentiation factor-5; CRISPR, clustered regularly interspaced short palindromic repeat; Cas9, CRISPR-associated protein 9; sgRNA, single guide RNA; MMP-13, matrix metalloproteinase 13; FGF-18, fibroblast growth factor 18; SOX9, sex-determining region Y-type high mobilitygroup box 9; IGF-I, insulin-like growth factor I; RUNX1, runt-related transcription factor 1; ATF5, activating transcription factor 5; IL-1β, interleukin 1 beta; Hif-2α, hypoxia-inducible factor 2 alpha; NF-$_{K}$B, nuclear factor kappa B; Ihh, indian hedgehog; Notch1, neurogenic locus notch homolog protein 1; p47phox, cytosolic subunit of the NADPH oxidase; NADPH, nicotinamide adenine dinucleotide phosphate; p66shc, isoform of the shcA adaptor protein family; shcA, Src homology and collagen A; Src, sarcoma tyrosine kinase; p16INK4a, cyclin-dependent kinase inhibitor 2A; JMJD3, Jumonji domain-containing protein D3; Cd61, integrin β3; CA9, carbonic anhydrase IX; miR, microRNA; NPs, nanoparticles; HA, hyaluronic acid; CS, chondroitin sulfate; CAP, chondrocyte-affinity peptide; HAMA, methacrylic anhydride-modified hyaluronic acid; PF127, pluronic 127; PEG-PAsp (DET), polyethylene glycol-polyamino acid (poly{N-[N′-(2-aminoethyl)-2-aminoethyl]aspartamide}) block copolymer; PEG, polyethylene glycol; PAsp DET/TET, polyamino acid (poly{N-[N′-(2-aminoethyl)-2-aminoethyl]aspartamide}) block copolymer (PAsp DET)/polyamino acid (poly(N-{N′-[N′′-(2-aminoethyl)-2-aminoethyl]-2-aminoethyl}aspartamide) block copolymer (TET); PLGA, poly(lactide-co-glycolic acid); Exos, exosomes; Au NR, gold nanorod; PEI, polyethylenimine; DWRVIIPPRPSA, cartilage-targeting peptide; MOF, metal-organic framework; p5RHH, VLTTGLPALISWIRRRHRRHC; Dlin-KC2-DMA, 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1, 3]-dioxolane; DPPC, dipalmitoyl phosphatidylcholine; CLS, cholesterol; NO, nitric oxide; Hb, hemoglobin; DDPB, poly(DMAEMA$_{67}$-b-(DMAEMA$_{29}$-co-PAA$_{40}$-co-BMA$_{75}$)); DMAEMA, 2-(dimethylamino)ethyl methacrylate; PAA, 2-propylacrylic acid; BMA, butyl methacrylate; PVA, polyvinyl alcohol; ECT, 4-cyano-4 (ethylsulfanylthiocarbonyl) sulfanylpentanoic acid; DB, poly(DMAEMA-co-BMA); mAbCII, collagen II-targeting monoclonal antibody; (EG$_{18}$L)$_2$, bivalent C18 lipids with three repeats of EG$_6$ and phosphoramidite spacers; EG, ethylene glycol; PNIPMAM, poly(N-isopropylmethacrylamide); RGD, Gly-Arg-Gly-Asp-Thr-Pro peptide; NAHA-CaP, NO, alendronate and o-phenylenediamine-CaP; AHK-CaP, alendonic acid-kartogenin-CaP; CaP, calcium phosphate; SAP, self-assembling peptide; SKPPGTSS, bone marrow-homing peptide; Lamp2b, lysosome-associated membrane glycoprotein 2b; G5-AHP, arginine, histidine, and phenylalanine-modified generation 5 polyamidoamine; GelMA, methacrylate gelatin; tgg2, chondrocyte-specific aptamer; PEG-PAMAM, PEGylated polyamidoamine; WYRGRL, collagen II-targeting peptide; EVs, extracellular vesicles; YCWP, yeast cell wall particle; OA, osteoarthritis; MCLT, medial collateral ligament transection; ACLT, anterior cruciate ligament transection; MMT, medial meniscal transection; DMM, destabilization of the medial meniscus; PTOA, post-traumatic OA; MMx, medial meniscectomy; MIA, monosodium iodoacetate.

D3 (JMJD3),[155] the integrin β3 (Cd61),[156] and the carbonic anhydrase IX (CA9)[157] using NPs,[81d,146–152,153b,c,154,155,157] microplates,[153a] nanogels,[156] and lipids.[153d]

For instance, in a papain OA model, a Notch1 siRNA reduced inflammation and afforded cartilage protection in mice for 2 weeks via NO-hemoglobin (Hb)/PLGA/PEG NPs.[149] In MIA-induced OA models, siRNAs against p47phox,[150] p66shc,[151] and CA9[157] promoted pain relief,[151] reduced inflammation,[151,157a] and afforded cartilage protection[150,151,157] in rats[150,151] and in mice[157] for 2–8 weeks using PLGA,[150,151] NO, alendronate and o-phenylenediamine-calcium phosphate (NAHA-CaP),[157a] or alendonic acid-kartogenin-calcium phosphate (AHK-CaP) NPs.[157b] In surgical ACLT models, an Ihh siRNA[148] and a JMJD3 siRNA[155] afforded cartilage protection in rats[148] and in mice[155] for 5–8 weeks via 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1, 3]-dioxolane/dipalmitoyl phosphatidylcholine/cholesterol/PEG (Dlin-KC2-DMA/DPPC/CLS/PEG)[148] or VLTTGLPALISWIRRRHRRHC (p5RHH) peptide NPs.[155] In surgical DMM models, siRNAs against Hif-2α,[81d] periostin,[152] Cd61,[156] and CA9[157a] reduced inflammation[81d,152,157a] and afforded cartilage protection[81d,152,156,157] in rats[157a] and mice[81d,152,156] for 4–8 weeks via MOF,[81d] p5RHH peptide,[152] and NAHA-CaP NPs[157a] or using a poly(N-isopropylmethacrylamide) (PNIPMAM) Gly-Arg-Gly-Asp-Thr-Pro (RGD) peptide nanogel.[156] In a surgical MMx model, a p16INK4a siRNA promoted pain relief and afforded cartilage protection in mice for 5 weeks via PLGA NPs.[154] In surgical PTOA models, siRNAs against NF-$_{K}$B[147] and MMP-13[153] reduced inflammation[147,153a,d] and afforded cartilage protection[153a,c] in mice for 2–6 weeks using p5RHH peptide[147] and PEG/4-cyano-4 (ethylsulfanylthiocarbonyl) sulfanylpentanoic acid (ECT)/poly(DMAEMA-co-BMA) (DB) (collagen II-targeting monoclonal antibody – mAbCII) NPs,[153b,c] poly((2-(dimethylamino)ethyl methacrylate – DMAEMA)$_{67}$-b-((2-(dimethylamino)ethyl methacrylate)$_{29}$-co-(2-propylacrylic acid)$_{40}$-co-(butyl methacrylate – BMA)$_{75}$)) (DDPB)/PLGA/PVA microplates,[153a] or bivalent C18 lipids with three repeats of (ethylene glycol)$_6$ (EG$_6$) and phosphoramidite spacers (albumin hitchhiking) lipids.[153d] In a surgical ACLT, MCLT, and DMM model, an Hif-2α siRNA reduced inflammation and afforded cartilage protection in mice for 7 weeks via polyethylenimine (PEI) (cartilage-targeting DWRVIIPPRPSA peptide) NPs.[146]

miRNAs: Several miRNAs have been applied in OA models using controlled release systems, including miR-9-5p targeting syndecan-1 (SDC-1),[158] miR-29b-5p,[159] miR-140,[160] miR-141/200c targeting SIRT1,[161] miR-223 targeting the leucine-rich-containing family (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome,[162] miR-224-5p targeting pentraxin 3 (PTX3),[163] and miR365 antagomir[164] using liposomes,[158,160c] Exos and EVs from articular chondrocytes and from MSCs,[160a,b,162] NPs,[160d,161,163] nanotubes,[164] and hydrogels.[159]

In a MIA-induced OA model, miR-223 reduced inflammation and afforded cartilage protection in rats for 4 weeks using (collagen II-targeting WYRGRL peptide) EVs from MSCs.[162] In a surgical ACLT model, miR-29b-5p afforded cartilage protection in rats for 10 weeks via a self-assembling peptide (SAP) (bone marrow-homing SKPPGTSS peptide) hydrogel.[159] In surgical DMM models, miR-140,[160] miR-141/200c,[161] and miR-224-5p[163] reduced inflammation[160c,163] and afforded cartilage protection[160,161,163] in rats[160a–c] and in mice[160d,161,163] for 4–12 weeks using lysosome-associated membrane glycoprotein 2b (Lamp2b) (cartilage-targeting DWRVIIPPRPSA peptide) Exos from articular chondrocytes,[160a,b] lornoxicam cationic liposomes,[160c] arginine, histidine, and phenylalanine-modified generation 5 polyamidoamine (G5-AHP)/GelMA,[160d] G5-AHP,[163b] chondrocyte-specific aptamer (tgg2)-PEG-PAMAM,[161] and urchin-like ceria NPs.[163a] In a surgical PTOA model, a miR365 antagomir reduced inflammation and afforded cartilage protection in mice for 7 weeks via yeast cell wall particle (YCWP) nanotubes.[164] In a surgical ACLT and MCLT model, miR-9-5p afforded cartilage protection in rats for 7 weeks using liposomes.[158]

2.2.3. Comparison of Therapeutic Controlled Release with Alternative Emerging Technologies for OA In vivo

While therapeutic controlled release therefore proved to be a feasible and effective strategy to tackle OA in various models of the disease in vivo, it remains to be seen whether such a tool may be more potent than other emerging alternatives, in particular than direct (biomaterial-free), less complex gene therapy approaches. Interestingly, there is still very few evidence in the literature reporting a strict, systematic comparison of these two strategies for OA in vivo, with mostly a recent study demonstrating the superiority of controlling the release of an rAAV SOX9-gene vector from a thermosensitive hydrogel based on poly(ethylene oxide) (PEO)-poly(propylene oxide) (PPO)-PEO poloxamers to improve cartilage repair in a surgical PTOA model in minipigs for 4 weeks relative to the administration of the vector in a free form when applying the same vector dose,[142] showing the need for more parallel, similar evaluations in vivo.

3. Conclusions and Perspectives

Osteoarthritis (OA) is a global, progressive, and irreversible chronic, multifactorial whole debilitating disease of the joints with a high level of complexity and variability between phenotypes and patients.[13,14p,ab,16i,21y] Despite the availability of numerous treatments (non-pharmacological management, pharmacological drugs, orthobiologics, surgical interventions),[14v,w,aa,ab,29b,30] there is no definitive cure for OA to date[14ab,29b,30bh–bl,bn,31] due to limited or adverse effects of the therapies proposed.[30y,33a–i]

The use of therapeutic controlled release systems based on the manipulation of biomaterials capable of delivering one or multiple bioactive compounds might overcome the limitations of traditional OA treatments (potential clearance, dissemination, and/or deleterious effects).[30y,ay,33c,44b,45] Such emerging systems may provide effective and adapted tools promoting the durable and safe treatment of OA in a patient-independent manner, supporting the spatiotemporal availability and activity of the compound(s) being intra-articularly delivered in the affected joint(s).[18l,29b,30y,ar,33c,e,f,h,k,34c,g,j,35a,49a,h,w,y] Bioactive compounds to treat OA may include therapeutic recombinant molecules (NSAIDs, corticosteroids, glucocorticoids, viscosupplementation, SADOAs, drugs targeting inflammation, oxidation, autophagy, senolysis, catabolism, regeneration, orthobiologics, pleiotropic gas, bioactive ions) and gene sequences (plasmid DNAs, rAAV vectors, mRNAs, ASOs, siRNAs, and miRNAs) via gene vectors as reported here in a variety of models of the disease in vivo.

Yet, for an effective clinical translation in OA patients, this therapeutic approach will further have to take into account the complexity of the disease, including the different tissues affected,[14p,20k,l] the specific OA stage,[14w,15a,b,e,19,29a] its various phenotypes,[16] and age-, sex-, and gender-associated differences[14t,16b,21aa,ac,ae] for an adapted (personalized) treatment.[16b] In addition, the formulation, size, and charge of the control release system itself,[165] the amounts of therapeutic factor, and the frequency of administration will need to be carefully evaluated and optimized to successfully and definitely manage the progression of the disease that occurs in an environment comprising several physiological barriers (active/inflamed synovium and synovial fluid, pH, oxygen, inflammatory/biochemical/mechanical environment, enzymes, dense ECM) by enhancing joint entry and retention and allowing for specific tissue targeting while preventing joint clearance, dissemination to undesirable locations, and detrimental (inflammatory, immune, cytotoxic) effects.[30y,ay,33c,44b,45]

Even though a variety of release systems have been employed to control the delivery of such agents in experimental OA models in vivo as demonstrated here using natural and synthetic, classical and "smart" MPs, microspheres, microcapsules, NPs, nanospheres, nanosheets, nanocages, nanotubes, (nano-)micelles, nanoplexes, nanocarriers, fibers, liposomes, gels/hydrogels, Exos, and EVs as described here, limited information is available comparing the possible benefits of therapeutic controlled release over other emerging alternatives like direct gene therapy. In addition, few clinical trials using therapeutic controlled release strategies have been reported in OA patients, mostly using TCA in a hyaluronan hydrogel or in PLGA microspheres[62,63] and dex in TLC599 liposomes[67h] relative to the broad literature in preclinical animal models, while none have been established using a gene sequence as therapeutic cargo, showing the challenge to translate the strategy into safe and effective therapies for clinical use in humans. This might be due to regulatory issues, the high costs required to develop a safe, effective product and initiate a clinical trial for human OA, to strong placebo effects reported in some trials, the crucial need to identify biomarkers, and the balance of risks versus benefits to treat OA for which other options are available and drug repurposing is envisaged.[14z,30y,bh,166] Still, while gene therapy was long perceived as an unsafe procedure for a non-lethal disorder like OA,[166d] the high number of trials involving therapeutic gene transfer in thousands of human patients worldwide[167] and the application of gene therapy procedures in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (RNA) vaccines[168] now provide significant optimism about its pertinence for human OA.

Overall, even though some important questions remain to be addressed, remarkable progress has been made using biocompatible materials as controlled release systems, providing a promising avenue of research to treat OA in patients in the near future.

Acknowledgements

This research was funded by the China Scholarship Council (grant #202208080231 to DW, grant #201908150154 to WL), and the Deutsche Arthrose-Hilfe e.V. (MC, HM).

Open access funding enabled and organized by Projekt DEAL.

[Correction added on 29 November 2024 after first online publication: Figure 3 has been replaced.]

Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomaterials, controlled release, drugs, gene sequences, in vivo, osteoarthritis, recombinant molecules

Received: July 24, 2024
Revised: October 15, 2024
Published online: November 6, 2024

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