ACS Biomaterials SCIENCE & ENGINEERING

pubs.acs.org/journal/abseba

Review

Dexamethasone: Insights into Pharmacological Aspects, Therapeutic Mechanisms, and Delivery Systems

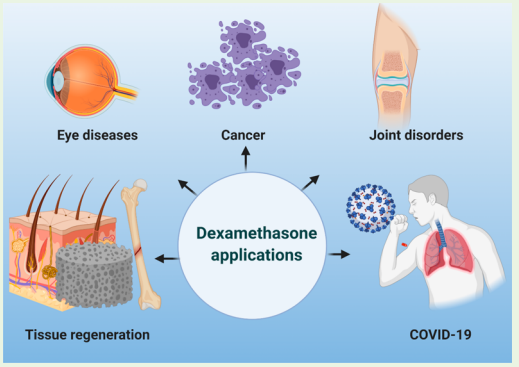
Vijay Sagar Madamsetty,[†] Reza Mohammadinejad,[*,†] Ilona Uzieliene, Noushin Nabavi, Ali Dehshahri, Jomarien García-Couce, Shima Tavakol, Saeid Moghassemi, Arezoo Dadashzadeh, Pooyan Makvandi, Abbas Pardakhty, Abbas Aghaei Afshar, and Ali Seyfoddin*

Cite This: https://doi.org/10.1021/acsbiomaterials.2c00026

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Dexamethasone (DEX) has been widely used to treat a variety of diseases, including autoimmune diseases, allergies, ocular disorders, cancer, and, more recently, COVID-19. However, DEX usage is often restricted in the clinic due to its poor water solubility. When administered through a systemic route, it can elicit severe side effects, such as hypertension, peptic ulcers, hyperglycemia, and hydro-electrolytic disorders. There is currently much interest in developing efficient DEX-loaded nanoformulations that ameliorate adverse disease effects inhibiting advancements in scientific research. Various nanoparticles have been developed to selectively deliver drugs without destroying healthy cells or organs in recent years. In the present review, we have summarized some of the most attractive applications of DEX-loaded delivery systems, including liposomes, polymers, hydrogels, nanofibers, silica, calcium phosphate, and hydroxyapatite. This review provides our readers with a broad spectrum of nanomedicine approaches to deliver DEX safely.



KEYWORDS: *dexamethasone, drug delivery, drug repurposing, nanomaterials, tissue engineering*

1. INTRODUCTION

The majority of human cells express glucocorticoid receptors (GRs) which can act as ligand-dependent transcription factors. These members of the nuclear receptor superfamily are present in the free form in the cytosol. The high-affinity state of the receptors for glucocorticoid (GC) binding occurs following the interaction of GRs with heat shock proteins (Figure 1).[1−3] Various naturally occurring cortisols and their synthetic counterparts including dexamethasone (DEX) interact with the cytosolic GRs resulting in the dissociation of heat shock proteins from the receptors.[4] This dissociation leads to conformational changes in the GRs leading to entry into the nucleus. In the cell nucleus, GCs bind to the GC response elements resulting in changes in transcription (Figure 1).[5,6] The molecular mechanism of GCs and their influences on the cells are not limited to the interaction and binding of the molecules with target sites in the genes but also include protein−protein interactions between the liganded GRs and other transcription factors in the cytosol. These interactions lead to changes in the capacity of other transcription factors that regulate transcription.[7] Other major targets for GCs are nongenomic in nature, including mitochondrial translocation, interactions with the plasma membrane, and signaling pathways.[8] The widespread cellular mechanisms involved in the action of GCs make these molecules suitable candidates for evaluation of their efficacy in various physiological processes, such as apoptosis and cell growth, as well as of their role in pathological conditions including inflammation.[8−10] The immunomodulatory effects of GCs such as DEX come from their impact on B cells and T cells via different molecular pathways. Their effect on B cells is through up-regulation of interleukin-10 (IL-10) as an anti-inflammatory cytokine and down-regulation of Toll-like receptor 7 signaling. GCs modulate T cells through regulating their cytokine expression and T cell receptor signaling. GCs are also able to inhibit the production of pro-inflammatory cytokines, including IL-1 and IL-6 as wells as prostaglandin E_2 and histamine.[11,12] Another major anti-inflammatory effect of these molecules occurs through the interaction of GRs and transcription factors such as NF-κB and AP-1 which act as critical modulators of several signaling pathways associated with B and T cell receptors.[11,13−15]

Received: January 9, 2022
Accepted: March 28, 2022

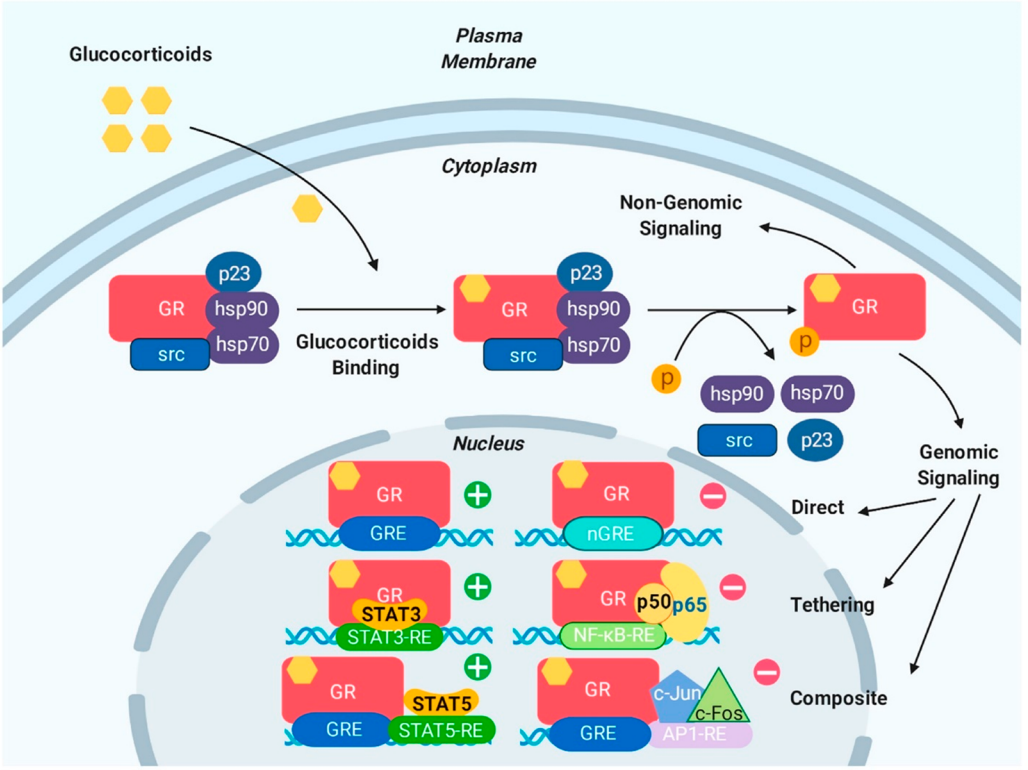


Figure 1. GCs binding the GR mediate genomic and nongenomic signaling. In the genomic pathways, the GR can affect gene expression via activation or repression. Reproduced with permission from ref 4. Copyright 2019 Multidisciplinary Digital Publishing Institute.

Drug repurposing makes the process of drug discovery faster and more affordable. Drug repurposing has been contemplated through various methods including computational and experimental approaches. The diverse molecular pathways and mechanisms associated with the effect of GCs on cells make these molecules appropriate candidates for drug repurposing.[16] The high costs of drug development along with the essential needs for therapeutic agents to manage global health issues such as the novel 2019 coronavirus (COVID-19) pandemic have led researchers to repurpose available medications with low cost for widespread global applications.[14,17] Among the repurposed therapeutic molecules suggested for COVID-19, DEX has attracted considerable attention due to its low cost, various available formulations, well-known mechanism of action, and different routes of administration.[18,19] This review summarizes some of the most attractive repurposed applications of DEX and its delivery systems, including liposomes, polymers, hydrogels, nanofibers, silica, calcium phosphate, and hydroxyapatite.

2. DEXAMETHASONE FOR EYE DISEASES' THERAPY

Anterior and posterior segments of the eye could be affected by various types of diseases. There are different pathological conditions associated with the anterior segment, including allergic conjunctivitis, pain, inflammatory reactions, glaucoma, Meibomian gland disease, and dry eye. On the other hand, common illnesses of the posterior segment comprise proliferative diabetic retinopathy, age-related macular degeneration (AMD), and macular edema.[20,21] The most convenient approach for drug delivery to the eye for diseases associated with the anterior segment is topical formulations such as eye drops which include approximately 90% of available eye formulations in the market. Several disadvantages limit the wide application of such ophthalmic formulations, including nasolacrimal drainage, tear dilution, and low bioavailability.[22] Therefore, substantial attention has been directed to the intraocular administration systems with the ability to transfer sufficient concentrations of therapeutic molecules to the target site for long periods of time. This goal could be achieved by the application of intravitreal injections and ocular implants.[23] The main disadvantages of intravitreal injection that limit this administration route include patient compliance, retinal damage, hemorrhages, and endophthalmitis. Therefore, substantial efforts have been made to develop intraocular implants to maintain the drug concentration within the therapeutic levels for long periods of time.[23,24]

Corticosteroids have been recognized as one of the most efficient anti-inflammatory therapeutics. Since various diseases affecting the eye are among the inflammatory diseases, corticosteroids can be employed to manage the inflammatory conditions following ocular injuries or surgeries as well as conjunctivitis, uveitis, scleritis, episcleritis, redness, itching, and pain.[25−27] In addition to their anti-inflammatory effect, these medications have demonstrated a remarkable effect to inhibit the formation of new blood vessels. This anti-neovascular property is important for the treatment of some eye diseases related to blood vascularization including diabetic retinopathy (DR) and AMD.[28,29] Moreover, corticosteroids have been proposed as suitable alternative therapeutic agents for anti-vascular endothelial growth factor (anti-VEGF) medications in diabetic macular edema (DME) following cataract surgery.[28] These applications make corticosteroids a key therapeutic agent in various eye diseases. Among corticosteroids used for the treatment of eye diseases, DEX has been considered as the

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

most powerful.[30] This corticosteroid agent could be applied as a topical formulation, intravitreal injection, or implant. For topical formulations of DEX, ophthalmic solutions or suspensions could be prepared for different purposes. Ophthalmic solutions could be made by DEX salts with higher hydrophilicity (e.g., sodium phosphate and hydrochloride) while the suspensions are prepared with acetate and alcohol derivatives. The effectiveness of these formulations in the reduction of eye inflammation has been proved.[31] However, the risk of increase in intraocular pressure along the infections, uveitis, and cataract formation may lead researchers to seek novel drug delivery systems that enable the maintenance of the DEX therapeutic levels in the site of action.[32] Intravitreal injection of DEX (0.4 mg/mL) is available for the treatment of severe vitreous inflammation.[33] However, its short half-life following the intravitreal injection has led researchers to seek controlled release delivery systems for DEX. These efforts led to the preparation of Ozurdex as an intravitreal implant containing DEX (0.7 mg). The implant was prepared using the Novadur solid drug delivery system. This solid polymer system comprises poly(lactic-*co*-glycolic acid) (PLGA) as a biodegradable drug delivery carrier.[34,35] Following the application of such a drug delivery system in the eye, PLGA degrades to lactic acid and glycolic acid, leading to the formation of carbon dioxide and water at the end. In other words, no residue will remain in the eye after the complete degradation of the drug delivery system. Ozurdex is a single-use, preservative-free, rod-shaped implant which is injected to the vitreous cavity through a 22-gauge applicator. This controlled delivery system leads to the maximum therapeutic effectiveness 2−3 months post implementation while the maintenance of therapeutic doses in the target site has been observed up to six months after the injection (Figure 2).[34−36] One of the major advantages of this implant is its application in vitrectomized eyes where the conventional intravitreal injections lead to a rapid clearance of the drug due to the short half-life.[37] In order to assess the efficacy and safety of Ozurdex in eyes with vision loss due to macular edema (ME) associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), a randomized, sham-controlled trial of the DEX implant was carried out called the GENEVA study. The global evaluation of implantable DEX in retinal vein occlusion with macular edema (GENEVA) study was designed with a total of 1267 patients receiving a single injection of 0.7 mg of DEX implant, 0.35 mg of DEX implant, or sham. The results of this study demonstrated that both DEX implant groups improved the best-corrected visual acuity (BCVA) in the patients compared with sham at 30−90 days post implementation.[38] There are some contraindications for Ozurdex, including hypersensitivity to the drug or the delivery system as well as glaucoma or ocular infections.[39] The side effects of implantation of Ozurdex consist of increased intraocular pressure, retinal detachment, endophthalmitis, and vitreous hemorrhages in 2−5% of the patients.[35,40] In summary, DEX could be used to manage various anterior and posterior ophthalmic diseases with effectively designed drug delivery systems.

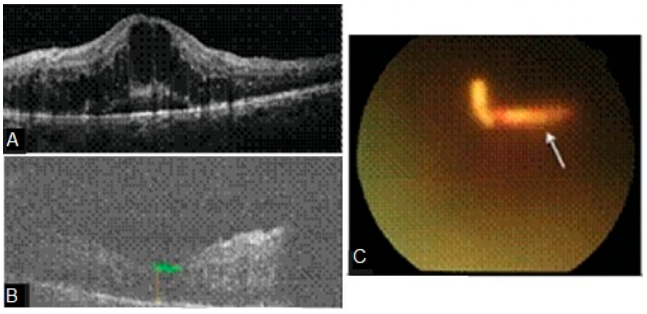


Figure 2. Optical coherence tomography (A) before Ozurdex injection and (B) two months after Ozurdex injection. (C) Vitreous hemorrhage after Ozurdex injection. The white arrow points out the implant. Reproduced with permission from ref 41. Copyright 2019 Medknow Publications.

3. DEXAMETHASONE FOR THE TREATMENT OF JOINT DISORDERS

The global prevalence of rheumatic and musculoskeletal diseases (RMDs) is rising, with osteoarthritis (OA) and rheumatoid arthritis (RA) the most frequent joint disorders worldwide.[42,43] OA is primarily associated with aging, obesity, joint traumas, and genetic disorders, whereas RA is an autoimmune disease, which may begin at any time in life.[44] Both diseases are typically painful, lead to disability with a significant impact on the quality of life,[45,46] and are most prevalent in women.[47,48] Currently, there is no effective treatment for OA,[49] and to reduce the burden of OA, patients are recommended to have regular exercise and use anti-inflammatory medications.[50,51] In the case of RA, GCs and disease-modifying anti-rheumatic drugs, mostly methotrexate, are used to reduce the symptoms.[52]

Corticosteroids, including DEX, have been considered potent anti-inflammatory agents for the treatment of RMDs and have been used for more than 50 years to treat OA and RA pain.[53] A number of preclinical and clinical studies have demonstrated that DEX inhibits inflammation and joint tissue damage.[17,18,20,21] For instance, a clinical study assessed patients' positive functional mobility and pain relief when DEX was administered by applying phonophoresis with ultrasound on knee OA.[54] Furthermore, low-dose sustained DEX delivery in combination with an agarose hydrogel carrier has demonstrated chondroprotection in the presence of IL-1 in canine chondrocytes *in vitro* and improved *in vivo* outcomes in a canine model.[55] Moreover, meta-analyses were performed to evaluate the effects of injected DEX on pain and recovery after total knee arthroplasty in patients. According to different studies, DEX decreased postoperative pain when compared to placebo groups.[56,57] In addition, DEX and growth factors play a pivotal role in stimulating mesenchymal stem cell (MSC) differentiation toward chondrogenic, osteogenic, and adipogenic lineages.[58,59] However, to drive MSC differentiation toward specific lineages, it has been shown that the amount of applied DEX is critical. For instance, higher amounts of DEX (more than 100 nM) might diminish human synovial MSCs' potential to differentiate into the chondrogenic lineage but instead promote adipogenesis; however, when used up to 10 nM, chondrogenesis is remarkably promoted by extracellular matrix protein synthesis.[60]

However, despite all of the advantageous DEX characteristics, its usage for RMDs has become controversial due to its potentially harmful side effects.[61,62] A comprehensive review of biological processes that can be negatively affected by DEX has been recently published, including clinical data and animal model studies.[61] Even though the precise mechanism of DEX action on cellular pathways is still not well understood, this

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

review highlights the importance of the dosage and duration of DEX administration as crucial factors that can lead to either beneficial or harmful effects. For example, it has been shown that repeated DEX injections at high clinical doses can lose their analgesic drug effects but cause a variety of side effects such as hypertension, psychological disturbance, adrenal gland depression, osteoporosis, and susceptibility to infections. Also, it has been reported that even low doses of DEX are cytotoxic, as they cause chondrocyte death and reduce cell proliferation. Moreover, it has been reported that repeated intra-articular corticosteroid injections (every 3 months for over a 2 year period) are associated with cartilage loss and degradation, according to radiographic OA progression.[63] A cohort of participants with an intra-articular injection of corticosteroids was compared with another cohort of mild to moderate knee OA (684 participants in total). Two parameters were reported for the evaluation of disease progression: (a) an increase in Kellgren and Lawrence grade, which is a radiographic OA scoring system, and (b) a decrease in joint space width. Both measures revealed worsening of OA symptoms after continued injections of corticosteroids, which is associated with an increased risk of OA progression.[63]

Taken together, the positive role of DEX on joint tissues remains conflicting and confounded in many studies and, therefore, worthy of further investigations.[64] Considering the history of DEX use in OA and RA, the beneficial effects of corticosteroids for intra-articular administration occur at low doses (around <2−3 mg/dose or 8−12 mg of cumulative total dose), whereas higher doses are associated with cartilage degradation.[65] Thus, the full understanding of the therapeutic potential of DEX requires many more controlled studies and optimizations for further clinical applications.[61]

4. APPLICATIONS OF DEXAMETHASONE FOR CANCER THERAPY

Drug repurposing is an emerging research field for the treatment of different types of cancers.[66,67] DEX as a synthetic GC is widely used for treating severe inflammation and autoimmune diseases. It exerts this effect by binding to the ubiquitous intracellular GC steroid receptor in the cytoplasm of most cells and can particularly affect lymphocytes and macrophages.[68] In the field of cancer therapy, DEX can decrease the secondary inflammatory response via interfering with the production of IL-1 and TNF-α.[69] Therefore, the anti-inflammatory nature of DEX can reduce cancer treatments' side effects, including chemo-, radio-, and immunotherapies. According to the recent literature, DEX has been used as a pretreatment coadministration agent to optimize the treatment of various cancer types, such as breast cancer,[70−72] multiple myeloma,[73−76] glioblastoma,[77,78] pancreatic cancer, leukemia,[79−81] and lung[82−84] and gastrointestinal cancer.[85,86]

One of the most common DEX applications is to improve the treatment of multiple myeloma (MM), a malignancy of B cells, to reduce the immunoglobulin levels.[87,88] Lenalidomide (an immunomodulatory derivative of thalidomide) has a relatively great potential due to its anti-MM activities when used in association with DEX, for both *in vitro* and in clinical studies. This approach has the Food and Drug Administration's (FDA) approval for MM relapsing therapy after prior treatment. Lenalidomide−DEX combination improves the success of MM treatments due to extending its progression time and survival rates.[89−91] Recently, Garderet et al. also studied the efficiency and safety of weekly administrated oral pomalidomide/cyclophosphamide (PCD)/DEX as a second-line treatment in a MM population cohort. In this study, all patients received 4 mg of pomalidomide, 300 mg of cyclophosphamide, and 40 mg of DEX within a spaced-out schedule. They concluded that this combination was highly effective and safe to be considered as having a great potential for MM therapy.[92]

DEX is often used as a pretreatment drug in breast cancer patients before chemotherapy to prevent allergic reactions and chemotherapeutic side effects.[93] To prevent stomatitis in breast cancer patients, DEX-based mouthwash has been assessed. In this study, 86 patients received 10 mg of everolimus plus 25 mg of exemestane with 10 mL of an alcohol-free oral solution of DEX at 0.1 mg/mL per day for 8 weeks. The results showed that prophylactic usage of a DEX oral solution causes a gradual reduction of stomatitis incidence and severity.[94] In another study, it was shown that pretreatment with DEX also improves the chemotherapeutic functions and increases the cancer therapy efficacy against breast tumors and metastases. Martin et al. studied murine breast cancer treatment by cisplatin-loaded polymeric micelles and reported that DEX could normalize vessels and increase nanocarriers' penetration by enhancing the interstitial hydraulic conductivity.[70]

In 2018, Ge et al. investigated coadministration of DEX and pemetrexed, which is used as an antineoplastic agent, in lung cancer treatment. In the *in vitro* study on nonsquamous non-small cell lung cancer (NSCLC), squamous human bronchial epithelial cells, and pleural mesothelioma cells, there was an induction in the insensitivity of the senescence associate secretory phenotype (SASP) to the DEX combination with pemetrexed. Senescent cells expressed SASPs which are involved in inflammatory cytokines and chemokine production. This expression profile ultimately altered the tumor microenvironment, suggesting that DEX can the optimize cellular therapeutic response by changing SASP expression and the IL-6, IL-8, MCP-1, and IL-1β cascade. This results in inhibition of pemetrexed-induced cellular senescence and insensitivity to pemetrexed.[83,95] In another study on lung cancer, it was found that DEX can suppress the growth of NSCLC xenograft tumors by inducing estrogen sulfotransferase and reducing the estradiol levels in tumor models. These results suggest that DEX can be used as an anti-estrogenic agent for lung cancer therapy.[84]

5. DEXAMETHASONE FOR TISSUE ENGINEERING APPLICATIONS

Using drugs in tissue engineering can lead to the development of bioactive scaffolds that regulate the rate of cellular proliferation and differentiation.[96] One of the drugs used in tissue engineering applications is DEX, which can affect cellular behaviors such as proliferation, mitosis, growth, gene expression, and osteogenic differentiation of MSCs *in vitro*.[97−99] DEX can bind to the GC inside the cytoplasmic matrix and act as an osteogenic factor. The controlled release of DEX can improve osteogenic differentiation and increase osteocalcin gene expression.[100,101] Indeed, DEX incorporated scaffolds have the ability to increase the concentration of proteins such as alkaline phosphate (ALP), an important osteogenic marker, osteocalcin expression, and biomineralization.[102−104] Qiu et al. created a composite polymeric scaffold incorporating DEX-loaded carriers as an engineered bone structure for assessing the osteogenic activity of the construct

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

both *in vitro* and *in vivo*. They found that DEX nanoparticles (NPs) were biocompatible and induced osteogenic differentiation in rat bone marrow-derived MSCs compared to NPs without DEX supplementation. DEX could also improve the regeneration of calvarial defects *in vivo*.[105] Besides, Panek et al. investigated the optimal concentration of DEX released under perfusion force for bone tissue engineering applications and suggested the concentration of 4 × 10−4 M with a perfusion rate of 0.1 mL/min was beneficial for bone tissue engineering and osteogenic differentiation *in vitro*.[106]

DEX can also be used in engineered cartilage constructs to prevent collagen degradation in response to IL-1α and shield them from the negative impacts of IL-1α. Other benefits include reduction in degradation of proteoglycan, preservation of biosynthesis of tumor necrosis factor-α (TNF-α) and mechanical damage-exposed cartilage constructs, action in pro-anabolic and anti-catabolic processes,[107] assistance of the functional maturation of MSCs, and protection and preservation of cellular properties during a long-term culture.[108] DEX, as an anti-inflammatory reagent, can suppress activated macrophages[109] and induce chondrogenic differentiation through modulating the synthesis of proteoglycan.[110] Westin et al. suggested incorporating DEX, diclofenac sodium, and gallic acid in polysaccharide-based thermosensitive hydrogels as a suitable injectable material for the restoration of damaged osteoarthritic joints.[110]

In addition to cartilage[60,107,111,112] and bone regeneration,[113−116] the application of DEX has been considered for adipose tissue engineering to preserve the stability of adipose tissue reconstruction. As such, the sustained release of DEX can improve both adipogenesis and angiogenesis in the constructs.[117] For instance, Jia et al. studied a magnetic hyaluronic acid (HA) nanosphere system which can control the release of DEX as an adipogenic factor by an external magnetic field for adipose tissue engineering.[118] The results demonstrated the potential of this system for adipose regeneration and viability of human adipose-derived stem cells. Moreover, DEX has been used as a myogenic differentiation agent in several investigations. It can improve the fusion of myogenic cells and increase the expression of dysferlin and other myogenic transcription factors[119] that regulate myogenesis.[120] It has also been shown to regulate the endogenous expression of insulin-like growth factor (IGF)-II during muscle differentiation.[121] Han et al. investigated the effects of DEX on myocyte differentiation in two different stages of development, the myoblast and myotube phases. The results indicate that at the myotube stage, DEX treatment can lead to a thinner myotube, induction of the atrogin-1 expression, and inhibition of the amount of myosin heavy chains. However, DEX has an opposite role at the myoblast stage by increasing the myotube's diameter, decreasing the expression of the atrogin-1, and raising the amount of myosin heavy chain.[122]

6. DEXAMETHASONE FOR COVID-19 TREATMENT

On December 8, 2019, the lethal outbreak of a coronavirus strain named COVID-19 started in the Chinese province of Hubei.[123,124] It spread rapidly worldwide and turned into a huge pandemic.[125,126] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) attaches to the two well-known cell surface receptors ACE2 and CD147 through spike glycoproteins.[127] However, it seems that ACE2 is its main receptor involved in cytokine storm and pathogenesis thereof[128] while CD147, a transmembrane glycoprotein and metalloproteinase inducer, is another potent receptor in host cells involved in SARS-CoV-2 virus invasion.[129] Besides, following cell target entry, the aryl hydrocarbon receptor is activated and promotes inflammation, fibrosis, and thromboembolism.[130] It is demonstrated that spike-CD147 blockage decreases the virus virulence's pathogenesis. However, CD147 is overexpressed in other pathological conditions such as tumors, diabetes, and inflammation.[131,132] Therefore, it explains further complicated reactions and comorbidities in COVID-19 patients who have underlying diseases. Notably, the moderate effectiveness of the anti-malaria drug chloroquine in COVID-19 patients is partly due to the involvement of CD147 in the pathogenesis of both COVID-19 and malaria. Interestingly, this receptor is responsible for the interaction of the malaria parasite on red blood cells. Moreover, coadministration of DEX and hydroxychloroquine decreases the rate of mortality compared to hydroxychloroquine alone.[133]

Notably, the effective dose and half-life of DEX are higher than other corticosteroids such as prednisone, methylprednisolone, and hydrocortisone, respectively.[134] However, administration of DEX in hospitalized hypoxic COVID-19 patients showed less clinical status, longer hospital stay, and more need for a ventilator compared to methylprednisolone.[135] The superior effect of methylprednisolone points back to higher lung penetration of methylprednisolone than DEX.[136] The administration of DEX is not recommended at the primary stage of the disease. In other words, the body needs to combat the SARS-CoV-2 virus at the first stage, and therefore, the administration of DEX will suppress the immune system and decline the body's defense. However, when the disease progresses and a cytokine storm is started, corticosteroids would be promising. The World Health Organization recommends 6 mg/day of DEX for up to 10 days in COVID-19 patients.[137] However, its adverse reactions such as psychiatric effects, hyperglycemia, hypokalemia, secondary infections, mucormycosis, gastrointestinal hemorrhage, and prolongation of viral clearance should be monitored.[138] DEX, at the 6 mg/daily dose, did not change the incidence of cardiac arrhythmia compared to conventional therapeutics.[139] It postponed the viral RNA clearance in patients with mild symptoms compared to patients that did not receive DEX.[140]

In fact, there are controversial outcomes derived from clinical trial studies related to the efficacy of corticosteroids in COVID-19 patients. Although a meta-analysis study in China shows an increased risk of mortality and multiorgan dysfunction,[141,142] some other studies indicated a decline of mortality in patients.[143−145]

It is demonstrated that the mechanism of action of DEX in COVID-19 patients is partly related to the reversion of histone deacetylase activation. In fact, it acts through two genomic and nongenomic mechanisms. In other words, SARS-CoV-2 suppresses the transportation of HDAC2 to the nucleolus by CREB, AP-1, and NF-κB activation and disturbs cytokine responses and inflammation.[146] Moreover, Wang et al. reported that DEX decreases CD147 expression through suppression of the NF-κB signaling pathway. Notwithstanding, inflammation led to CD147 up-regulation and higher availability of receptors for the SARS-CoV-2 virus. DEX treatment also led to down-regulation of CD147 to decrease virus attachment, virulence, and the expression of TNF-α and IL-6 as regulated by NF-κB.[147] DEX decreases inflammation, TNF-α, and IL-6 and indirectly reduces the cytokine storm

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

Table 1. DEX-Loaded Nanostructures Used for Human Diseases' Treatment

nanoparticles	drugs	disease	major applications	ref
Nanostructured lipid carriers (NLCs)	DEX	*In vitro*	NLC-DEX thermosensitive hydrogels showed sustainable release of DEX over 3 days	166
Solid lipid nanoparticles (SLNs)	DEX + butyrate	Bowel disease	The oral treatment of DEX + butyrate coloaded SLNs demonstrated strong anti-inflammatory effects at lower doses.	167
Lipid/alginate NPs	DEX	Nasal mucosa	DEX-lipid-alginate NPs showed effectiveness with nasal delivery.	168
Lipid/calcium phosphate gel core NPs	DEX	Acute kidney injury (AKI)	These NPs showed effective results in ischemia-reperfusion (I/R)-induced AKI with reduced side effects.	169
Sialic acid liposomes (SALs)	DEX palmitate (DP)	Rheumatoid arthritis (RA)	DP-SAL showed higher accumulation in the joints and a more potent anti-inflammatory effect in RA suppression.	170
Targeted liposomes	DEX	Rheumatoid arthritis (RA)	ART-2-targeting ligand labeled-DEX-liposomes were significantly effective in inhibiting arthritis progression compared to control-DEX liposomes or free DEX.	171
Liposomes	DEX palmitate (DP)	Inflammation	DEX-palmitate liposomes (DPLs) showed a more potent anti-inflammatory effect and higher acute toxicity on mice.	172, 173
Multilamellar vesicles (MLVs)	DEX	*In vitro*	Lipid composition significantly affected the DEX incorporation efficiency and had a minor influence on the percentage of drugs released per time.	174
Targeted liposomes	DEX	Rheumatoid arthritis in rats	DEX-liposomes demonstrated improved hematological profiles, and no significant impact on the body weight alleviated the hyperglycemia of rheumatoid arthritis rats.	175
Collagen/gelatin/alginate hydrogels liposomes (CGA-Lipo)	Moxifloxacin (MFX) and DEX	Corneal infection and wound healing	CGA-Lipo-MFX/DEX significantly inhibited pathogen microorganism growth and improved corneal wound healing.	176
Sialic acid-modified liposomes	DEX and DOX	S180 tumor-bearing Kunming mice	DEX + DOX-loaded liposomes showed better antitumor activity with lower side effects.	177
Liposomes	DEX	multiple myeloma	DEX-LPs showed improved pharmacokinetic profile, limited adverse effects, and improved antitumor activity.	178
Targeted liposomes	DEX/Bortezomib/Nutlin	Waldenstrom macroglobulinemia	D1XB + D1XN treatment showed significant tumor growth inhibition in bortezomib-resistant Waldenstrom macroglobulinemia.	179
Liposomes	DEX	Prostate cancer bone metastatic tumor	DEX-LPs showed significant inhibition of tumor growth of established bone metastases.	180
Liposomes	Bupivacaine (Bup)/DEX/Dexmedetomidine (DMED)	Local anesthesia	Co-injection of Lipo-Bup with Lipo-DP and Lipo-DMED prolonged the duration of sciatic nerve block 2.9-fold compared to Lipo-Bup alone.	181
Liposomes	DEX	Inflammatory liver diseases	DEX-liposomes significantly reduced liver injury and liver fibrosis.	182
Liposomes	DEX/Minocycline	Anti-inflammatory and antibacterial	Liposomes reduced the expression of IL-6 and TNF-α in lipopolysaccharide-stimulated human gingival fibroblasts and human mesenchymal stem cells.	183
Liposomes	DEX	Age-related macular degeneration (AMD)	DEX-liposomes significantly suppressed neovascularization and replacement of the lost RPE cells.	184
Liposomal hyaluronic acid gel	DEX	Cochlear implantation	The harmful effect of manual insertion during cochlear implantation was significantly prevented with local DEX-liposomes' administration.	185
PHEA-*g*-C18-Arg8 (PCA) NPs	DEX/connexin 26 [Cx26] siRNA	Inner ear therapy	PCA/DEX/gene NPs demonstrated anti-inflammatory effects and enhanced gene expression.	186
Polymeric micelles	DEX	Skin care and dermatological treatments	DEX-polymeric micelles showed enhanced DEX deposition in targeted skin sites in normal and dermatological diseases such as psoriasis and acne.	187, 188
pH-sensitive polymeric NPs	DEX	Dermal applications	Various pH-sensitive NPs worked differently on the skin surface. The obtained NPs dissolved and released in the hair follicles.	189
Dendritic core-multishell (CMS) NPs	DEX	Topical application	Dendritic CMS DEX-NPs showed enhanced skin penetration properties.	190
Biopolymeric NPs	DEX	Fibroblast differentiation	DEX-NPs treated cells acquired the osteoblast phenotype faster than those treated with the free drug.	191
Zein/PLLA scaffolds	DEX/rhBMP-2	Osteogenesis	BMP-2/DEX-loaded nanofiber scaffolds induced osteogenic differentiation and enhanced the osteogenic differentiation of MSCs.	192
Cellulose acetate scaffolds	DEX	Bone implants	DEX-scaffolds provided the environment where cells grow and proliferate, making this nanoplatform cytocompatible.	193
Spherical polymeric nanoconstructs (SPNs)	DEX	Inflammatory bowel disease (IBD)	DEX-SPNs treatments showed improved weight loss, reduced macrophage infiltration, expression of inflammatory cytokines, rectal bleeding, and histological scoring and exerted a strong systemic anti-inflammatory effect and facilitated animal recovery compared to free DEX.	194

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

Table 1. continued

nanoparticles	drugs	disease	major applications	ref
Cross-linked hyaluronic acid (HA)-itaconic acid (IT) films	Dexamethasone sodium phosphate	Topical ocular therapy	Compared to commercial DEX eye drops, an ascetically decreased proliferation rate was induced in HCE cells by DEX-loaded films.	195
Gelatin scaffold	DEX	Bone tissue engineering (BTE)	Scaffold implant exhibited long-term DEX releasing behavior, had excellent viability of murine osteoblasts MC3T3-E1, and showed positive proliferation, osteogenic differentiation, and calcium deposition.	196
Reactive oxygen species (ROS)-responsive NPs	DEX	Rheumatoid arthritis (RA)	NPs effectively internalized activated macrophages and significantly downregulated the expression of iRhom2, TNF-α, and BAFF in activated Raw264.7. Significantly accumulated at inflamed joints in collagen-induced arthritis (CIA) mice alleviated joint swelling and cartilage destruction.	197
Poly(vinyl alcohol) (PVA) hydrogel	DEX	Inflammatory	*In vitro* release from PVA hydrogels was sustained for 33 days and appeared to fit the Higuchi and Korsmeyer−Peppas models.	198
Silk-polyethylene glycol hydrogel	DEX/Cisplatin	Cisplatin-induced ototoxicity	DEX-SILK displayed significant protective effects against cisplatin-induced cellular ototoxicity.	199
Chitosan-genipin-hydrogel	DEX/Cisplatin	cisplatin-induced ototoxicity	Dex-loaded NPs showed adequate functional and structural protection against CP-induced ototoxicity in a guinea pig model	200
Click-cross-linked hydrogel	DEX	*In vitro* kinetics	Dex-loaded hydrogel persisted *in vivo* for 28 days after injection into the subcutaneous tissue of Sprague−Dawley rats.	201
Hydrogel	DEX	Inflammatory	DEX-Hydrogel displayed sustained delivery and showed anti-inflammatory activity in protecting it by absorbing toxins, bacteria, and viruses.	202
Hydrogel	DEX/Avastin	Corneal neovascularization (CNV)	Dexp-Ava hydrogel significantly attenuated the alkali burn-induced corneal inflammation and remarkably suppressed the corneal neovascularization via the downregulation of VEGF, CD31, and α-SMA expression in the rat alkali burn model.	203
Hyaluronic acid hydrogels	DEX	Knee osteoarthritis (OA)	Dex hydrogel showed a better chondroprotective and anti-inflammatory effect in rat surgery-induced osteoarthritis.	204
Hydrogel	DEX	Hearing restoration	Cochlear implantation using DEX-eluting electrode alone and combined with DEX-Hydrogel protected auditory nerve fibers on day 120.	205
Hydrogel	DEX	Hearing preservation	DEX hydrogel application 1 day before surgery resulted in significantly reduced hearing threshold shifts at low, middle, and high frequencies measured at postoperative day 28.	206
Hyaluronic acid hydrogels	DEX	Tissue engineering	DEX-hydrogel showed completely noncytotoxic and preserved proliferation of entrapped human adipose-derived stem cells.	207
pH-responsive guar gum hydrogels	DEX	Intestinal delivery	These DEX-hydrogels exhibited sustained intestinal delivery of DEX over free DEX.	208
Polyethylene glycol hydrogels	DEX	*In vitro* kinetics	DEX-gels showed higher levels of activity for extended time periods than free DEX.	209
Chitosan NPs	DEX	Topical ocular delivery	DEX-CS-NPs demonstrated excellent pHA conditions, refractive index, surface tension, and viscosity of the suspensions for promising ocular use.	210, 211
Chitosan NPs	DEX	Ocular delivery	DEX-CS-NPs displayed an excellent release profile indicating that drug levels were within the therapeutic requirement for anti-inflammatory use.	212
Chitosan-coated poly(ε-caprolactone) NPs	DEX/ropivacaine (RPV)	Local anesthetic pain relief therapy	RPV/DEX-CS-PCL-NPs induced remarkably better anesthetic effects than non-DEX-loaded RPV CH-PCL NPs.	213
PLGA NPs	DEX	oral precancerous lesions	DEX-PLGA-NPs were stable for 6 months and demonstrated 80% release of DEX from NPs and were noncytotoxic against the HK-2 and NIH-3T3 cell lines.	214
PLGA NPs	DEX/RUNX2, SP7, and ATF4 pDNAs	Osteogenesis	pDNAs entered the nuclei of hMSCs, and RUNX2 and SP7 proteins were translated and triggered osteogenesis.	215
PLGA microspheres	DEX	Hard tissue engineering applications	Scaffolds showed required mechanical and physicochemical features to support defects' regeneration and maintain their stability during the neo-tissue formation.	216
PLGA microparticles	DEX	*In vitro*	NPs showed an initial burst release, a phase with a constant drug release rate, and rapid drug release properties.	217
PLGA implants	DEX/vancomycin	Postoperative endophthalmitis	Drugs controlled released from implants, and the eluted vancomycin showed bactericidal effects.	218
Biodegradable NPs	DEX sodium phosphate (DSP)/zinc ion	Corneal neovascularization (CNV)	Single subconjunctival SCT administration of DSP-Zn-NP prevented suture-induced CNV in rats.	219
PLGA NPs	DEX	Chronic joint diseases	NPs demonstrated relevant, flexible, and promising results in the local treatment of joint diseases.	220
PLGA implants	DEX	Intraocular delivery	PLGA-DEX formed *in situ* implants and showed control of drug release.	221
Intracochlear PLGA implants	DEX	Diseases of the inner ear/cochlea	*Ex vivo* implantation of the extrudates into a guinea pig cochlea indicates that PEG-containing extrudates have the desired balance between mechanical strength and flexibility for direct implantation into the cochlea.	222
PLGA-based microspheres	DEX	Chronic diseases	PLGA-microspheres showed promising pharmaceutical systems for intraocular administration and controlled DEX release.	223

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

Table 1. continued

nanoparticles	drugs	disease	major applications	ref
Polymeric nanoparticle dispersions	DEX	Inhalation therapy	These NPs showed excellent inhalation therapy properties with minimal toxicity.	224
PLGA microspheres	DEX	*In vitro* kinetics	The microspheres were characterized for particle size/size distribution, thermal properties, and morphology.	225
PLGA/chitosan/polyvinylpyrrolidone hydrogel scaffolds	DEX	Chronic rhinosinusitis	DEX-NPs showed suitable alternatives for the treatment of allergic rhinitis and chronic sinusitis.	226
Cyclodextrin NPs	DEX	Diabetic macular edema (DME)	Topical DexNP significantly improves visual acuity and decreases macular thickness in DME patients.	227
Cyclodextrin NPs	DEX	noninfectious Uveitic macular edema and vitritis	CD-NPs demonstrated a favorable effect on eyes with noninfectious uveitic macular edema and vitritis.	228
Cyclodextrin and hydrogel formulation	Dexamethasone acetate	Ocular delivery	*In vitro* drug release assays exhibited favorable release from the mixed gels.	229
PCL-PEG-PCL and γ-cyclodextrin NPs	DEX	Kinetics	NPs containing 10 wt % copolymer, 20 wt % γ-CD, and 0.5% or 0.1 wt % DEX released around 100% and 45% of the drug over up to 23 days.	230
Hyaluronic acid and beta cyclodextrins films	DEX/corneal epithelial cells	Corneal delivery	DEX-NPs showed excellent drug release studies that can extend the release of this drug for at least 5 days.	231
Chitosan-mesoporous silica NPs	DEX/BMP-2	Osteoblast differentiation and bone regeneration	BMP-2 and DEX NPs significantly stimulated osteoblast differentiation and bone regeneration *in vitro* and *in vivo*.	232
Silicone rods	DEX	Reduce the inflammatory reactions	DEX-silicone rods were implanted through a cochleostomy into the basal turn of the scala tympani of guinea pigs, which displayed excellent results.	233
Mesoporous silica particles	DEX	Airway inflammation	DEX-loaded MSPs displayed MEL-induced airway inflammation.	234
Mesoporous silica NPs	DEX	Osteogenesis	DEX-MSP treatment significantly promoted the osteogenic differentiation of murine primary bone marrow mesenchymal stem cells.	235

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

derived from the activation of two ACE2 and CD147 receptors through the anti-inflammatory cytokines of IL-10 and lipocortin-1.[148] It is noteworthy that a bioinformatics study on transcriptomic data showed that DEX is not involved in IL-6 signaling.[149]

There are studies reporting DEX's ability to down-regulate[150] and up-regulate ACE2 expression.[151,152] This has a double-edge effect on COVID-19 because the body needs ACE2 at a baseline level to protect lung and other tissues from damage, whereas the up-regulation of ACE2 makes it ideal for higher levels of virus attachment and entrance. It is noteworthy that the SARS-CoV-2 virus decreases the levels of ACE2 availability, and therefore, ACE2 reduction to baseline will enhance tissue damage protection derived from virus entrance. This also prevents the signaling pathways involved in a cytokine storm. Specifically, consideration should be given to decreasing the C-terminal cleavage site of ACE2 and not the whole ACE2 expression.[153]

Findings confirm the efficacy of DEX in decreasing the mortality and duration of hospitalization among COVID-19 patients receiving respiratory support and not in the mild form of COVID-19.[139] It is noteworthy that there was no significant difference between two doses of 12 and 6 mg/daily in the alive day number without life support.[154] High doses of DEX applied through nongenomic mechanisms combine to the integrin and activate focal adhesion kinas. It, at the high dose, rapidly decreases inflammation through the alteration in the movement of the ionic channel of Ca^{2+} and Na^{+}.[155] Moreover, the effect of DEX is dependent on the stage of the COVID-19. At the early stage of inflammation, it decreases exudation of inflammatory cells, vasodilation, and phagocytosis, and in the severe condition of inflammation, it inhibits fibrosis through the diminishing of fibroblast proliferation.[130] To sum up, it seems that DEX would be a promising medication to modulate COVID-19 in the middle and advanced stages of the COVID-19 infection and not in patients who have mild symptoms and are in the virus proliferation phase of COVID-19 with low inflammation. However, the particular lung cells in COVID-19 are glucocorticoids resistant.[156]

7. DEXAMETHASONE DELIVERY SYSTEMS

7.1. Lipid-Based Nanostructures. Several medicinally active small molecules are biologically less potent because most of them are water-insoluble, resulting in severe side effects.[157,158] Recently, lipid-based nanoparticles (LNPs) have become versatile platforms for drug carriers of biologically active small molecules.[159−161] LNPs have many advantages over other NPs, such as ease of preparation, high thermal stability, low production costs, high loading capacity, preparation from natural sources, and being amenable to large-scale industrial manufacturing.[162−165]

For example, recently, scientists have developed modified LNPs using a positively charged chitosan loaded with DEX. This nanosystem showed promising ocular bioavailability by enhancing the retention time and permeation into the cornea. This strategy improved the status quo strategies for the treatment of ocular disease.[236] DEX has been established as an effective treatment strategy for a variety of inflammatory diseases, including arthritis. However, its usage is limited due to poor water solubility, tissue distribution, and *in vivo* bioavailability. To overcome these limitations, researchers have developed DEX palmitate-loaded lipid-based mixed micelles containing sodium glycocholate/egg yolk lecithin for the treatment of RA with effectiveness.[237] In summary, LNPs such as SLNs, liposomes, and niosomes, comprised of DEX, provide excellent benefits in treating various diseases and may have the potential to develop future clinical treatment options.[238]

7.1.1. Liposomes. Liposomes are well-established lipid-based drug delivery systems.[239,240] Even though liposome discovery dates back to the 1980s, it has recently become more attractive following FDA approval of several liposomal-based therapeutics, and many are in clinical trials.[241,242] Among several types of nanoformulations, the liposomal-based drugs were approved by the FDA to treat various diseases, including cancer.[241,243,244] Liposomes have a wide diversity of applications in various disease treatments caused by viruses, bacteria, or protozoa.[245,246] Even though liposomes are the most widely used LNPs,[247] their therapeutic outcomes can be further improved with several surface modifications.[247] Both hydrophobic and hydrophilic drugs can successfully be loaded in liposomes, and DEX-loaded liposomes are well-established in preclinical studies (Table 1).[248] Recently, researchers developed DEX-loaded stealth liposomes for improving the anti-inflammatory effects of DEX in the treatment of RA. They report that DEX-loaded liposomes have a preferential accumulation at inflamed joint sites with extended blood circulation time with improved results in reducing the swelling of the inflamed joint tissues by suppressing the levels of the proinflammatory cytokines TNF-α and IL-1β, in joint tissues in RA (Figure 3).[249]

7.1.2. Solid Lipid Nanoparticles. Solid lipid nanoparticles (SLNs) are a rapidly developing field of nanotechnology with numerous applications in research and clinical medicine.[250,251] In SLNs, the solid lipid core comprises triglycerides, fatty acids lightened by the interfacial surfactant layer.[251] SLNs are low-toxic sphere-shaped colloidal NPs with average sizes ranging from 50 to 100 nm. These SLNs offer the development of new, efficient formulations due to their exceptional size-dependent properties. Further, SLNs hold remarkable potential for controlling and site-specific drug delivery and, hence, have widely fascinated scientists.[252] It is important that these SLNs are also used to develop several anti-inflammatory drugs, including DEX.[253,254] For example, scientists developed SLNs to deliver DEX and butyrate (DxCb-SLN) to improve anti-inflammatory activity with low doses to treat inflammatory bowel disease.[167] These SLN formulations showed significance in inducing *in vitro* inhibition of cell adhesion and significantly reducing pro-inflammatory cytokines (IL-1β and TNF-α) in both *in vitro* and *in vivo* settings.[167] Another study established novel DEX-loaded SLN formulations for the lung-targeting delivery of DEX acetate upon intravenous administration. They developed dexamethasone acetate (DXM)-SLNs with an average size of 552 ± 6.5 nm, 8.79 ± 0.04% of drug loading capacity, 92.1 ± 0.41% entrapment efficiency, and initial burst *in vitro* release. A 17.8-fold greater area under the curve of DXM-SLNs was accomplished in comparison with pristine DEX.[255]

7.1.3. Other Lipid-Based Nanoparticles. Similarly, several other lipid-based NPs, such as nanostructured lipid carriers (NLCs), lipid nanocapsules (LNCs), polymer lipid NPs, and lipid-based micelles, were developed to deliver various drugs.[256−260] For instance, Kiss et al. developed DEX-encapsulated nanostructured lipid carriers for ophthalmic use.[261] Toxicity assessments on human cornea cells showed favorable ophthalmic tolerability of NLCs.[261] Kumari et al.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

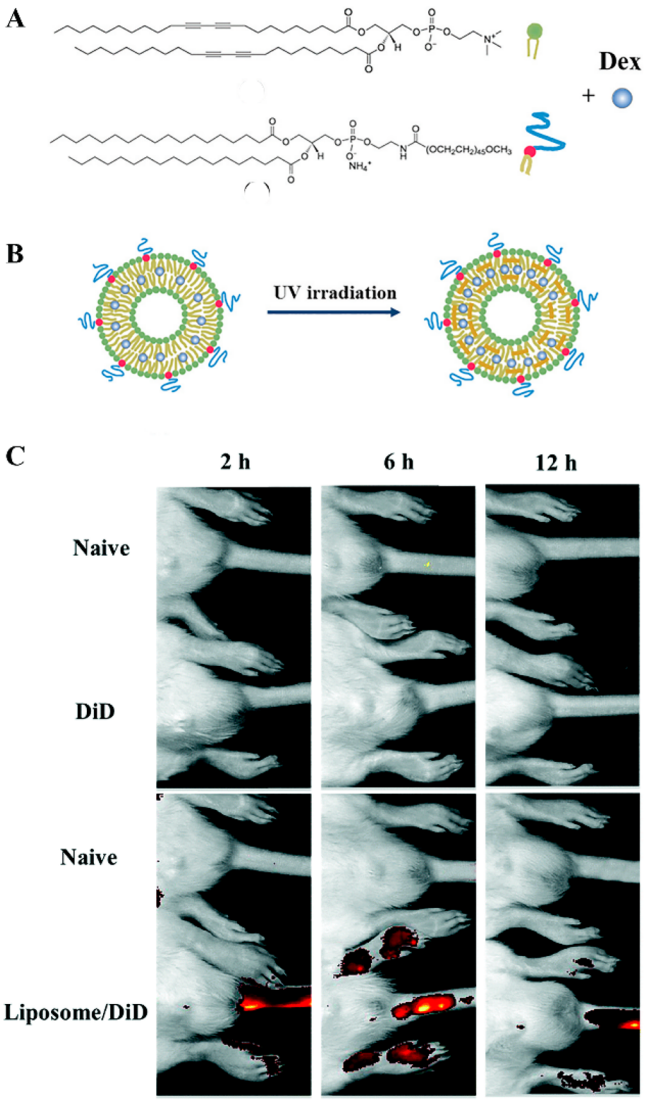


Figure 3. (A) Chemical structure of f 1,2-bis(10,12-tricosadiynoyl)-*sn*-glycero-3-phosphocholine (DC8,9PC) and 1,2-distearoyl-*sn*-glycero3-phospho-ethanolamine-poly(ethylene glycol) (DSPE-PEG2000). (B) Schematic of nonpolymerized and polymerized stealth liposomes with loaded DEX due to UV irradiation. (C) Biodistribution of free 1,1′-dioctadecyl-3,3,3′,3′-Tetramethylindodicarbocyanine (DiD) or polymerized stealth liposomes with loaded DiD in rats at different time points following intravenous injection. Reproduced with permission from ref 249. Copyright 2020 Royal Society of Chemistry.

performed a similar study, and they developed a DEX-loaded cholesterol-Labrafac lipophile nanostructured lipid carrier to treat dry eye disease.[262] This NLC formulation showed a 5-fold reduction of TNF-α production over free DEX.[262] Similarly, other lipid-chitosan,[263] lipid-hydrogel,[264] lipid-alginate,[265] and polymeric-based[266,267] lipid NPs were developed to deliver DEX.

7.2. Polymeric Platforms. Polymeric NPs represent additional drug delivery systems with a vast potential for targeted and localized delivery of drugs/genes.[268−276] Natural polymers such as chitosan, arginine, dextrin, poly(glycolic acid), polysaccharides, poly(lactic acid), and hyaluronic acid have been used for developing polymeric drug delivery systems.[277] Some synthetic polymers, including poly(2-hydroxyethyl methacrylate), poly(ethylenimine)s, poly(*N*-isopropylacrylamide)s, and dendritic polymers, have also been used for polymeric-based NPs' development.[278] Polymeric NPs are excellent micro-/nanocarriers for drugs/genes that are loaded through either encapsulation or covalent bonding for a controlled release of loaded therapeutic cargoes in *in vivo* settings in a highly selective manner.[279−285] Notably, polymers can deliver both hydrophilic and hydrophobic drugs and the convenience of administering to patients through diverse pathways, such as oral, ocular, nasal, and inhalation.[286−289] These maintain the therapeutic dose of drugs in plasma for more extended periods by controlling their release.[290,291]

GCs are extensively used for the treatment of several diseases, such as RA, systemic lupus erythematosus, asthma, lymphoid neoplasia, and eye and skin inflammations.[292] Additionally, DEX and α-tocopheryl succinate are being used to avoid chemotherapy-induced ototoxicity. However, they have low water solubility and present severe systemic side effects upon prolonged use. Researchers have developed incorporated polymeric NPs to lower cisplatin-induced toxicity in both *in vitro* and *in vivo* settings.[293] A similar study was performed to assess the possible protective effect of DEX-loaded PEG-coated polylactic acid NPs against cisplatin-induced hearing loss.[294] In another study, DEX-loaded polycaprolactone-PEG-polycaprolactone NPs were used to improve the anti-inflammatory effects of DEX.[295]

7.2.1. Chitosan Nanoparticles. Chitosan is a cationic natural polysaccharide consisting of D-glucosamine and *N*-acetyl D-glucosamine groups linked by β-(1−4) glycosidic bonds.[296] It is obtained by alkaline deacetylation of chitin, the second most abundant polysaccharide in nature.[297,298] Among its properties, biocompatibility, biodegradability, and non-toxicity are the most attractive, while antimicrobial activity and muco-adhesiveness add additional advantages.[299−302] DEX-loaded chitosan-coated BSA polydopamine-layered NPs provide the potential to modify adhesive and transferable free-standing films.[303] Additionally, chitosan has functional groups, such as amino and hydroxyl groups, that allow it to easily react and functionalize.[302,304] Due to all of the above, chitosan and its derivatives have been used in a wide variety of biomedical applications, such as tissue engineering, wound healing, and drug delivery systems.[300,305]

Chitosan-based systems have also been used for the controlled release of DEX in recent years.[306−308] The release of DEX using platforms, such as membranes, fibers, and micro,/nanoparticles of chitosan or its derivatives, has been one of the most studied applications in ocular disease. In almost all of the studies, the incorporation of DEX in a chitosan matrix enhances the effects and favors the permanence of drug in the ocular regions. Self-assembled NPs obtained from a series of DEX−chitosan glycol conjugates turn out to have very good biocompatibility in human colonic epithelial cells (HCEC), L-929, and RAW 264.7 cells after 24 h, and the controlled release of DEX continues up to 48 h without the drug losing its anti-inflammatory properties.[309] Similarly, other DEX-loaded self-assembled succinyl-cholesterol chitosan particles released 50% of DEX in 2 h and 95% after 24 h and were not cytotoxic. The released DEX elicited an anti-inflammatory activity comparable to that of pure DEX treatment.[310]

7.2.2. Polylactic Acid Nanoparticles. Polylactic acid (PLA) is categorized as an aliphatic polyester because of the ester

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

bonds that connect the monomer units.[311] PLA-based NPs have a key role in the biomedical field with a wide range of applications.[312−315] PLA has been recognized as a multipurpose material with high-biodegradability and -biocompatibility properties and approved for use by the FDA.[316] PLA has been used in suture threads, bone fixing screws, medical devices, and drug delivery vehicles.[317] The benefit of PLA is that it naturally degrades *in situ* through a hydrolysis mechanism (water molecules break the ester bonds that constitute the polymer backbone). This avoids the necessity for further surgeries to remove medical devices (e.g., sutures), lowering health system costs and benefiting patient recoveries.[318]

PLA-based NPs are used to deliver several drugs, including DEX. For example, a single dose of DEX-loaded PEG-fabricated PLA NPs diminishes cisplatin-induced hearing loss with its prolonged sustained release property. Importantly, coumarin 6-loaded NPs entered round window membrane (RWM) quickly and accumulated on the organ of Corti, ganglion cells, and stria vascularis in guinea pigs.[319] Researchers synthesized DEX bioconjugated poly(phenylacetylene) and poly(phenylacetylene-*co*-acrylic acid) NPs to induce apoptosis of human tumor cells.[320] DEX-loaded PLA NPs are also used in tissue engineering. Recently, scientists developed DEX-loaded PLA/PCL nanofibrous scaffolds with mesoporous silica NPs and used in bone tissue engineering applications.[105] Another group developed a similar approach for the treatment of tissue engineering applications. In their study, a DEX-loaded scaffold of PLA and mesoporous silica was fabricated with chitosan through electrospinning and used for bone tissue engineering application.[101]

7.2.3. Poly(lactic-co-glycolic acid) Nanoparticles. Poly(lactic-*co*-glycolic acid) (PLGA) is another biocompatible and biodegradable polymer used for making polymeric NPs.[321] The US FDA has approved PLGA NPs for use in the delivery of drugs, proteins, peptides, imaging agents, and small molecules owing to their sustained and controlled release properties with negligible toxicity to cells and tissues.[322] With the use of PLGA NPs, the limitations of poor tissue permeability and low aqueous solubility are resolved.[322] Notably, PLGA NPs have demonstrated no immunogenicity *in vivo*, which is precarious for the safety of drug delivery systems. PLGA NPs are tunable and malleable so that their surfaces can be easily altered with other polymers, including poly(β-amino esters), PLA, and chitosan, to improve the drug loading and delivery efficacy. Additionally, PLGA NPs can be fabricated with targeting ligands such as small peptides, proteins, small molecules, or antibodies.[323] PLGA NPs mediated delivery of anti-inflammatory drugs is now well-established in various diseases.[322,324]

Recently, scientists found a simple and efficient method for loading DEX into the PLGA NPs and evaluated the resulting characteristic properties. They evaluated the drug loading efficiency, encapsulation efficiency, and cumulative release and reported improvement compared to stand-alone drugs separately.[325] Gómez-Gaete et al. developed a similar optimized method for DEX loading of biodegradable PLGA NPs using a solvent evaporation technique. The size and zeta potentials of empty and DEX-loaded NPs were not altered, and a high drug encapsulation was attained using 100 mg of PLGA in a mixture of 1:1 (v:v) acetone−dichloromethane and 10 mg of DEX.[326] Recently, investigators developed novel biodegradable PLGA NPs containing both ovalbumin and DEX NP[OVA+DEX] to induce antigen-specific immune tolerance. Interestingly, in their findings, NP[OVA+DEX] treated immature dendritic cells did not mature to immunogenic dendritic cells. Instead, they were converted to tolerogenic dendritic cells with strongly suppressed OVA-specific cytotoxic T cells' generation. Moreover, the production of OVA-specific IgG was tested in mice vaccinated with NP[OVA+DEX]. The findings strongly support that NPs loaded with both antigens (OVA) and DEX are useful in inducing antigen-specific immune tolerance, key for the treatment of several autoimmune diseases.[327] DEX can also be used to treat age-related macular degeneration diseases which involve inflammation and choroidal neovascularization. Liu et al. developed DEX-loaded NPs using poly(D,L-lactide-*co*-glycolide) and polyethylenimine on the surface of human umbilical vein endothelial cells (HUVEC) cells in combination with bevacizumab for impending intravitreal applications. These NPs showed an excellent antiangiogenic outcome and a robust inhibitory effect on VEGF secretion in HUVEC cells. Moreover, the treatment significantly reduced the number of blood vessels, and the leakage area of CNV was lessened *in vivo*.[328] More recently, PLGA loaded with DEX was used in low doses with a sustained release via an acellular osteochondral implant. This treatment resulted in a dual anti-catabolic and pro-anabolic effect, supportive of the functional integrity of adjacent graft and host tissue. It also reduced the inflammation caused by the iatrogenic injury (Figure 4).[329] In summary, DEX-loaded PLGA NPs have potential in therapeutic applications.

7.2.4. Cyclodextrin Nanostructures. Cyclodextrins (CDs) are cyclic oligosaccharide-based NPs comprised of a lipophilic central cavity and hydrophilic outer surface.[330] CD molecules do not permeate lipophilic membranes because they contain quite a large number of hydrogen acceptors and donors.[331] CDs were first discovered nearly 100 years ago, and the first

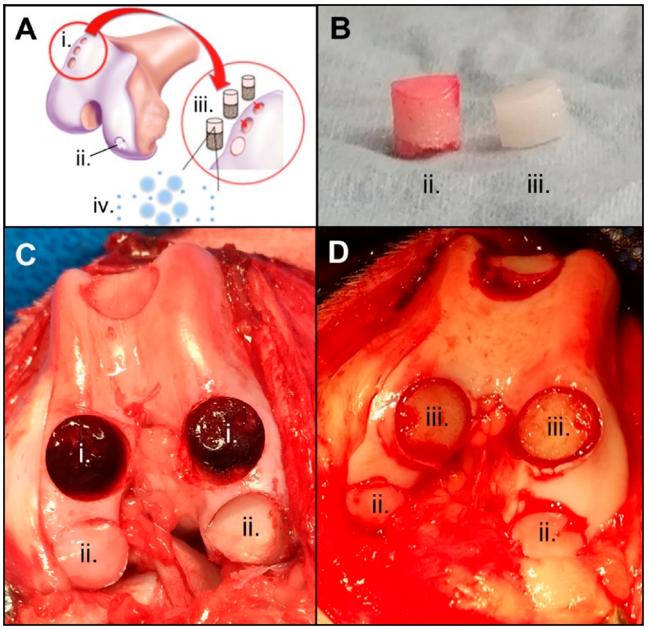


Figure 4. (A) Schematic study showing the autograft donor site (i), repair site (ii), DEX-loaded poly(lactic-co-glycolic) acid (PLGA) microspheres (DLMS) implant (iii), and DEX−PLGA microsphere release (iv). (B) Cartilage autograft (ii) and DLMS implant (iii). (C) Autograft donor (i) and repair (ii) sites. (D) DLMS implant (iii) and repair (ii) sites. Reproduced with permission from ref 329. Copyright 2020 Elsevier.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

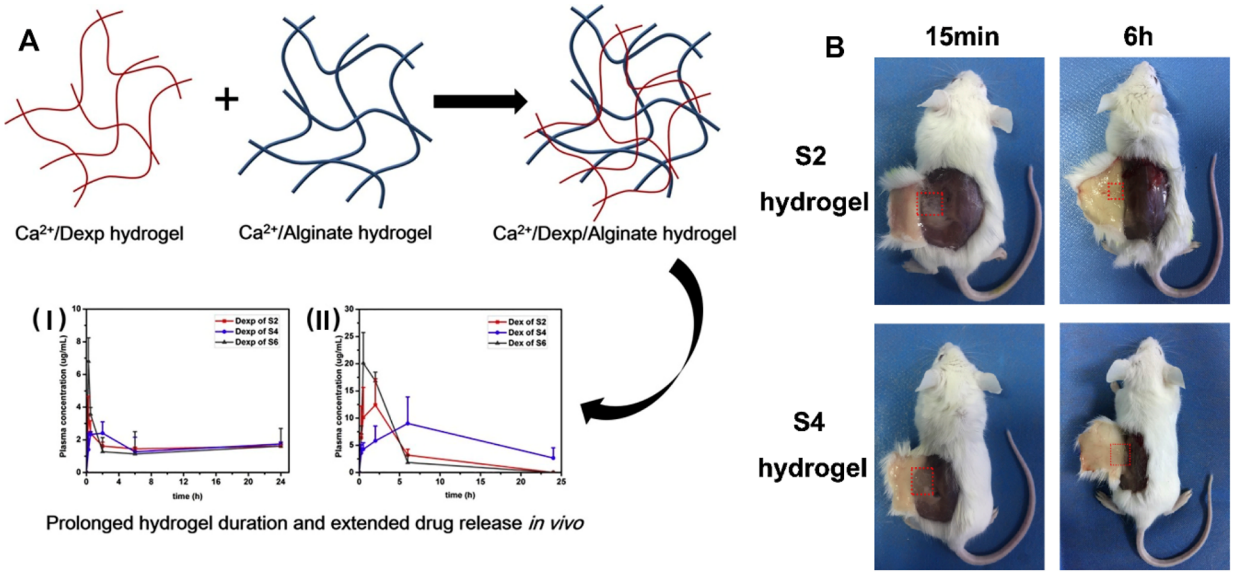


Figure 5. (A) *In vivo* pharmacokinetics data of (I) Dexp and (II) Dex after subcutaneous injection of 0.5 mL of Ca^{2+}/Dexp hydrogel (S2), Ca^{2+}/Dexp/alginate hydrogel (S4), and Dexp/alginate aqueous solution (S6). (B) *In vivo* clearance of the hydrogels after subcutaneous injection of 0.5 mL of Ca^{2+}/Dexp hydrogel (S2) and Ca^{2+}/Dexp/alginate hybrid hydrogel (S4). The red square indicates the remaining hydrogel. Reproduced with permission from ref 353. Copyright 2019 Elsevier.

patent on CD-based drug complexes was recorded in 1953.[332] They are increasingly used in the medical field mainly to increase the solubility of poorly soluble drugs and to increase their stability and biodegradability.

CDs have been found as one of the potential candidates in the drug delivery field due to their ability to be physically, chemically, and biologically modified with small molecules/drugs through the formation of insertion complexes.[333] CDs form noncovalent complexes between host molecules (hydrophobic drugs) and hydrophilic guest molecules and form intermolecular interactions such as weak van der Waals forces, electrostatic interactions, hydrogen bonds, and hydrophobic interactions. Water-soluble CD products have a low propensity to form aggregates and can naturally interact in water solutions. Recent developments have ensued in dramatic improvements in CD-based nanoformulations. For example, DEX-loaded CD NPs were used as eye drops for the treatment of noninfectious ophthalmic inflammatory diseases.[334] There are several similar DEX complexed CD nanoformulations that are established for the treatment of various inflammatory diseases.[335,336]

7.2.5. Hydrogels. Hydrogel-based drug delivery systems are commonly being used in medical treatments.[337,338] Hydrogels have the finest tunable physical properties that offer spatial and sequential control in the release of several therapeutic agents, such as small-molecule drugs and genes, protecting them from degradation.[339,340] They are 90% water and vastly porous, to house large amounts of drugs for delivery.[341] Present conventional treatment methods are plagued by concerns about systemic toxicity with using repeated dosing.[342] Hydrogels offer potential as the best drug delivery systems to minimize these disadvantages and improve the therapeutic benefits of drugs.[343] Hydrogels help as a platform for various physiochemical interfaces to encapsulate drugs/genes and ensure controlled drug release.[344] As cross-linked three-dimensional frameworks of water-soluble polymers, hydrogels can be prepared from any water-soluble polymer. This allows packing a varied range of chemical and physical configurations to form microparticles, slabs, NPs, films, and coatings.[345]

Hence, hydrogels are used in clinical practice or in experimental medicine for a vast range of applications, such as diagnostics, tissue engineering, wound healing, contact lenses, topical treatments, and regenerative medicine.[346] Other uses include the separation of biomolecules or cells, cellular immobilization, and barrier materials to regulate biological adhesions. There are several techniques available for the preparation of charges and hydrogel structures.[347] Hydrogels are commonly categorized as homopolymer, multipolymer, or copolymer, depending on the preparation methods. Based on the ionic charges, hydrogels can be classified into neutral, cationic, anionic, and ampholytic hydrogels.[343] Additionally, they can be classified into amorphous, hydrogen-bonded, and semicrystalline hydrogels based on their structure.[348] Hydrogels can release drugs because of diffusion, chemical and swelling control release systems, or environment responsive release systems. Despite numerous applications and advantages, hydrogels have some limitations.[349,350] Because of their low tensile strength, many hydrogels are limited in their use within load-bearing environments, which can lead to an untimely dissolution or leak before reaching the target sites. However, these limitations are circumvented with various drug delivery applications, such as subcutaneous injection.[351] Some other hydrogels are adequately injectable or are topical applications and may not demand surgical implantation.[352] A homogeneous drug loading and multipurpose applications of hydrogels may be limited.

Here we focus on recent developments in the use of hydrogels for various anti-inflammatory diseases. For example, DEX-loaded hydrogels are increasingly used as platforms for local drug delivery to bone tissues. Scientists developed a DEX-loaded $[COCH_3]$-RADARADARADARADA-$[CONH_2]$ peptide comprised of hydrogels and successfully used them in the application of regenerative orthopedics.[106] Recently, investigators developed a calcium ion cross-linking and DEX sodium phosphate-containing alginate hybrid hydrogel to

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

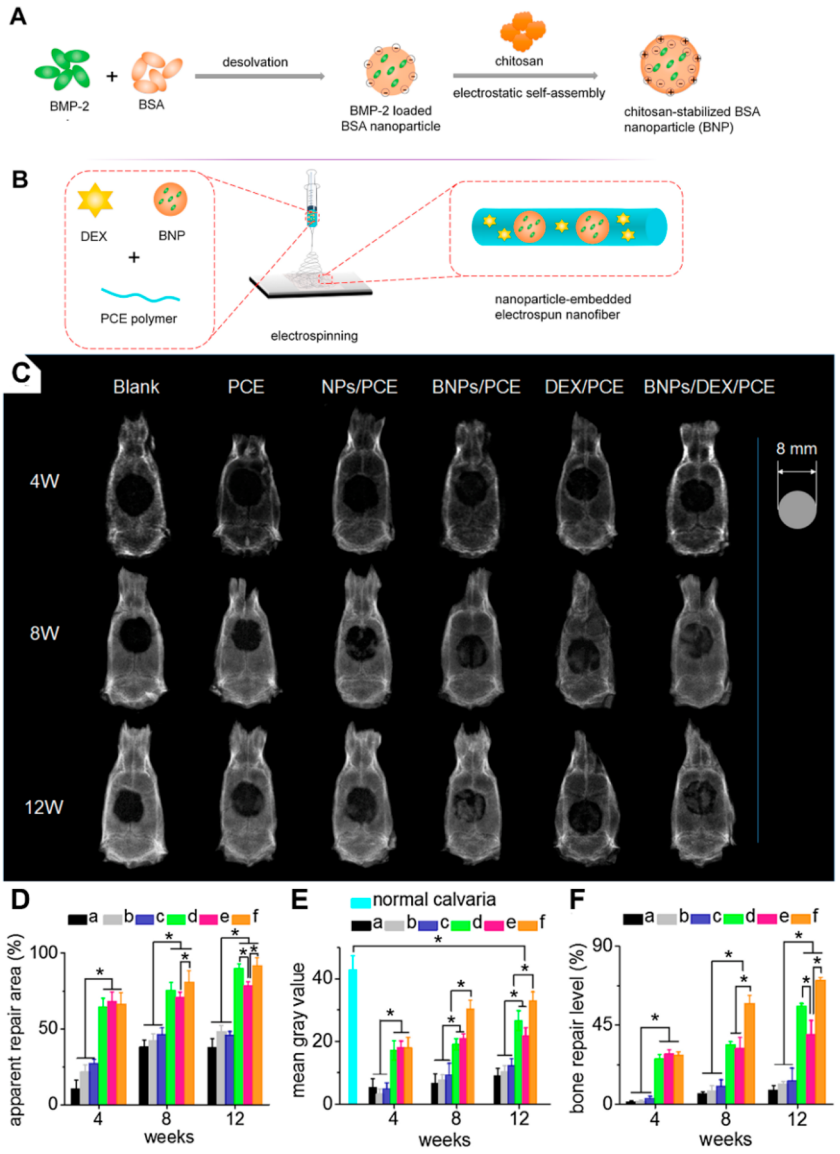


Figure 6. Schematic illustration of (A) the fabrication of BMP-2-loaded BSA NPs stabilized with chitosan and (B) electrospinning of NP-embedded PCE copolymer nanofibers. (C) Radiograms of the X-ray detection after implantation *in vivo* for 4, 8, and 12 weeks. The rightmost disk is a calvarial defect template with a diameter of 8 mm. The statistical evaluations of (D) apparent repair area, (E) mean gray value, (F) and bone repair level were calculated from the radiograms (n = 3) for (a) the control group without material, (b) PCE, (c) NPs/PCE, (d) BNPs/PCE, (e) DEX/PCE, and (f) BNPs/DEX/PCE. Reproduced with permission from ref 359. Copyright 2015 Elsevier.

extend drug release. These Ca^{2+}/DEX/alginate hybrid hydrogels demonstrated excellent improvements in the drug bioavailability (Figure 5).[353] A similar Ca^{2+}/DEX supramolecular hydrogel was used as a therapeutic alternative for the treatment of noninfectious uveitis.[354] Recently, a silk-based hydrogel was developed by researchers to deliver DEX to the inner ear using an injectable silk−PEG hydrogel.[355] In summary, DEX-loaded hydrogels have the potential to translate from preclinical settings to the clinical setting.

7.2.6. Electrospun Nanofibers. Drug delivery systems applying nanofiber-based materials have been considered as a potential therapeutic strategy in tissue engineering over the past decade.[356,357] Various technological approaches using electrospun nanofibers in combination with DEX have been proposed for treating various diseases, such as cancer, ocular, bone, and skin diseases.[358−361] Nanofibers, fabricated from different types of synthetic polymers, such as PCL, PLGA, PLA, and poly(ether sulfone),[282] and natural components (gelatin, chitosan, and collagen) are biocompatible in physiological conditions and possess potential characteristics for sustained drug release.[360,362] The advantage of electrospun nanofibers as a carrier for DEX, as compared to other materials, is, first of all, their high surface-to-volume ratio, which increases the solubility of DEX and improves its efficacy. Furthermore, they possess tunable porosity and, most importantly, similarity to a natural extracellular matrix structure.

7.2.6.1. Combination of DEX with Other Stimulating Factors. DEX was applied in different kinds of nanofiber scaffolds as a single active molecule or in a combination with other stimulating factors. For instance, a dual delivery of BMP-2 and DEX electrospun nanofiber (PCL + PEG) has been proposed for treating critical-sized calvarial defects. The sequential release of both compounds has offered an efficient

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

way of delivery and maintaining both compounds for at least 35 days, which results in strong osteogenesis responses in both *in vitro* and *in vivo* models (Figure 6).[359]

7.2.6.2. Controlled Release of DEX. An extended and sustained release of DEX from nanofiber scaffolds is one of the most desired options for tissue repair studies; however, sometimes, the embedded drugs may show undesired burst releases. To overcome these issues, the osteogenic properties of cells were analyzed on multilayer PLA pluronic P123 scaffolds loaded with DEX. DEX was included in the middle of a multilayered scaffold, which controlled its release and resulted in improved MSCs osteogenesis compared to single-layer scaffolds.[97] Other studies suggest the use of nanofiber matrices loaded with DEX to stimulate the odontogenic differentiation of human dental pulp cells (HDPCs). The HDPCs are cultured on designed electrospun nanofiber matrices with bioactive glass NPs loaded with DEX for 14 days. This promotes odontogenesis of cells, including bone morphogenetic protein (BMPs), integrins, mTOR, and alkaline phosphatase, by stimulating molecular signaling pathways.[363]

For an extended release of DEX, it has been shown that hybrid electrospun PCL nanofiber mats are made up of microbeads for the treatment of ocular diseases.[364] It has been reported that controlling electrospinning parameters modifies the duration of drug releases from nanofibers. Another option developed for ocular disease management is using self-assembled succinate DEX (DEX-SA) supramolecular hydrogel to extend precorneal retention.[365] This method introduces the gelling system with DEX-SA and lowers the cytotoxicity of DEX, maintains long-term stability, and shows excellent biocompatibility with intraocular tissues in rabbit eyes.

7.2.6.3. Inflammation Modulating Release of DEX. Inflammatory responses have also been modulated by DEX release from nanofibers. A study has developed a peptide amphiphile covalently conjugated to DEX through a labile hydrazone bond. Injection of this compound *in vivo* reduced the acute inflammatory response without systemic immune suppression. This technique is proposed to be used for treating different types of diseases, such as myocardial infarction.[366] Furthermore, silk fibroin nanofibers with embedded DEX, prepared by "green" electrospinning without any toxic agents, are considered one of the safest and most environment-friendly nanofibers. They have also been proposed as inflammatory modulating agents *in vitro*. The sustained release of DEX from these nanofibers has been shown to protect porcine endothelial cells from damage and apoptosis caused by lipopolysaccharide (LPS).[367]

Furthermore, DEX is known to bind to astrocyte GRs and inhibit astrocyte proliferation.[368] A controlled release of DEX sodium phosphate loaded on chitosan NPs with gelatin electrospun nanofibers (PCL) was introduced as a promising therapy for the treatment of the nervous system during spinal cord injuries.[369] The developed scaffolds were mechanically stable with a controlled release of DEX and are proposed to be used as a bridging material to allow axons to grow through them, avoiding glial scar formation.

Therefore, electrospun nanofibers incorporated with drugs are promising alternative drug delivery systems for biomedical and nanotechnological applications with therapeutic potential. This technology is cost-effective, versatile, easy to fabricate, and easy to use in any kind of research facility.

7.3. Calcium Phosphate and Hydroxyapatite Structures. Bone-related diseases and injuries caused by trauma or congenital disorders pose a significant burden on health systems at both social and economic levels. Self-healing of the bones depends mainly on the size of the injury, the stability of the fracture site, and bone quality.[370] Many common diseases, such as diabetes, can significantly affect the quality and self-healing potential of bones. Thus, there is an amassed need for the development of effective therapies for bone regeneration. Calcium phosphate-based bioceramics are the most prevalent bone substituents that closely resemble natural human bone.[371] However, these compositional similarities make it challenging to distinguish calcium phosphate fragments from native bone under imaging such as X-ray, magnetic resonance imaging, and computed tomography when screening the healing process.[372] Currently, radiologists use external contrast agents to improve the imaging contrast of calcium phosphate fragments, but these can affect their physicochemical properties and produce artifacts. Hence, improving calcium phosphate-based NPs and loading with anti-inflammatory drugs can enhance the quality of healing. Researchers have developed DEX-encapsulated calcium phosphate NPs along with collagen spongy complex frameworks for bone tissue engineering applications. These NPs presented virtuous biocompatibility and encouraged osteogenic differentiation of hMSCs when used for 3D culture of human bone marrow-derived MSCs. Further, *in vivo* implantation experiments demonstrate the synergistic effects of NPs for both osteogenic differentiation of hMSCs and bone regeneration.[114] A similar study was performed using bibasic-calcium phosphate NPs encapsulated with DEX for osteogenic differentiation of human MSCs.[373] DEX-encapsulated porous calcium phosphate/laponite cement significantly improved the proliferation of MG63 cells used for bone grafts.[374]

Additionally, hydroxyapatite microspheres are recognized as excellent drug packing delivery vehicles.[375,376] These NPs have biocompatibility for specific biomedical applications and can be prepared using an emulsion cross-link technique such as calcium ions as cross-linking agent.[377,378] These provide an excellent application for pH-responsive drug delivery in bone tissue. For instance, DEX-encapsulated hollow hydroxyapatites were used to treat the odontogenic differentiation of human dental pulp cells.[379] In another study, a surface-fabricated hydroxyapatite framework was used for delivery of DEX and stromal cell-derived factor-1 for osteogenesis. *In vitro* cell culture experiments show that initial release of SDF-1 stimulated the migration of MSCs to the deep interior of the scaffold. Additionally, *in vivo* experiments show that cell-guided systems efficiently enhance the early cell recruitment and vascularization for cell-free bone tissue engineering applications.[98]

7.4. Silica Nanoparticles. Silica NPs, especially mesoporous silica NPs, have modernized the field of drug delivery systems.[380,381] Due to their porous configuration, huge surface area, large pore volume, and selective surface functionality, silica NPs enable a high therapeutic drug loading especially with hydrophobic water-insoluble drugs.[380,382] The silica matrix framework protects loaded drugs from degradation by enzymes. Additionally, silica NPs help in prolonged sustained drug release by stopping burst releases using pore-gating approaches.[383,384] Furthermore, silica NPs can be modified with stimuli-responsive groups, polymers, protein, or targeting ligands that can further selectively direct them to diseased sites. Silica-based NPs can easily be administered intravenously to resolve the side effects associated with other routes of delivery. Mesoporous silica-based NPs were first manufactured by

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

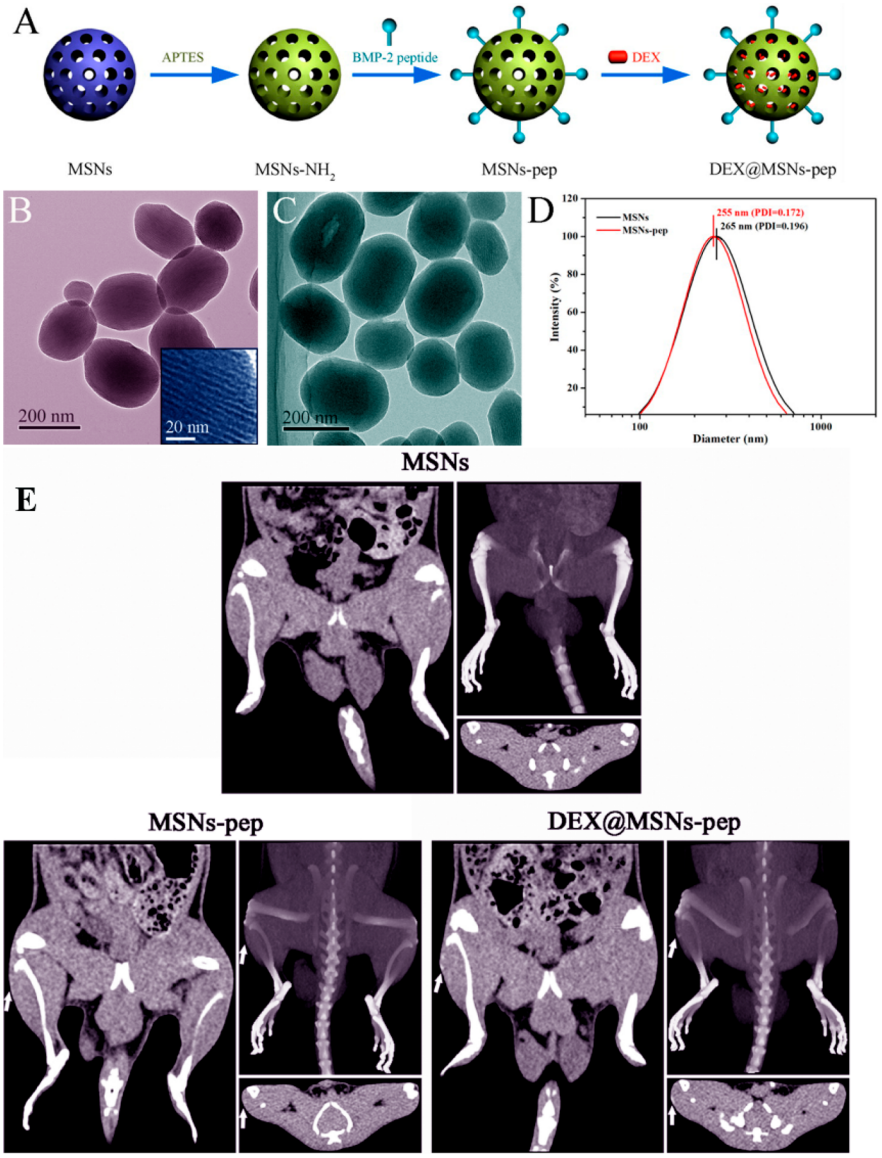


Figure 7. (A) Schematic illustration of the preparation of DEX@MSNs-pep. (B and C) TEM images of (B) Mesoporous silica nanoparticles (MSN) (inset is the enlarged image) and (C) MSNs-pep. (D) Size distribution of MSNs and MSNs-pep. (E) CT images of rats implanted with different implants for 3 weeks. Images of (left) plain CT scanning, (upper right) three-dimensional CT reconstruction, and (bottom right) transverse section for MSNs, MSNs-pep, and DEX@MSNs-pep. MSNs-pep also includes BMP-2 peptide functionalized mesoporous silica NPs. Reproduced with permission from ref 388. Copyright 2015 American Chemical Society.

Mobil corporation scientists in 1992[385] and are being used for a variety of anti-inflammatory diseases. For example, researchers developed covalently grafted DEX into the pore walls of fully oxidized mesoporous silicon particles (pSiO2-COO-Dex) and evaluated their pharmacological effects in ARPE19 cells. Further, *in vivo* efficacy was evaluated in both rabbit eyes and human VEGF-induced retinal models for vascular permeability.[386] In another study, DEX-loaded silica NPs significantly enhanced the *in vitro* proliferation and osteogenic differentiation of rat bone marrow-derived MSCs. Additionally, *in vivo* experiments report significant new bone formation abilities.[387] Furthermore, BMP-2 peptide decorated DEX-loaded mesoporous silica NPs improved osteogenic differentiation of bone MSCs (Figure 7).[388] In summary, silica-based DEX NPs show improved potential for the treatment of several inflammatory diseases.

8. CONCLUSION

Nanomedicine is revolutionizing advances in the diagnosis and treatment of several diseases. Numerous nanoparticle-based formulations have already been industrialized and play an imperative role in the management of diseases. Nano-formulations that combine therapeutic agents, molecular targeting, and imaging capabilities act as the next generation of disease treatment options. There are numerous advantages in using nanomaterials for drug delivery: (i) they increase the concentration of drug in the disease site; (ii) they allow a sustained and slow release of the drug, which improves its efficacy; (iii) they solve issues related to the poor solubility and bioavailability of drugs; and (iv) they are small, nontoxic, biodegradable, and biocompatible. DEX is a glucocorticoid family of steroids used as an anti-inflammatory, immunosuppressive, and anticancer drug in the clinic. One of the major complications with this drug is its low solubility in water,

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

resulting in poor bioavailability and numerous side effects after oral administration. A single optimal postoperative drug delivery system that minimizes systemic side effects remains to be developed. In the present review, we have summarized the main nanobased DEX formulations and their applications in several diseases. We report that several DEX nanoformulations significantly improve the survival of mice with minimal side effects compared to the free forms of drugs. Translation of this technology into the clinic may decrease treatment-related side effects for patients who have no other effective treatment options currently in the clinic.

AUTHOR INFORMATION

Corresponding Authors

Reza Mohammadinejad − *Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman 7618866749, Iran;* orcid.org/0000-0003-3511-9282; Email: r.mohammadinejad@kmu.ac.ir

Ali Seyfoddin − *Drug Delivery Research Group, Auckland University of Technology (AUT), School of Science, Auckland 1010, New Zealand;* orcid.org/0000-0003-4343-9905; Email: ali.seyfoddin@aut.ac.nz

Authors

Vijay Sagar Madamsetty − *Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine and Science, Jacksonville, Florida 32224, United States;* orcid.org/0000-0001-9883-190X

Ilona Uzieliene − *Department of Regenerative Medicine, State Research Institute Centre for Innovative Medicine, LT-08406 Vilnius, Lithuania*

Noushin Nabavi − *Department of Urologic Sciences, Vancouver Prostate Centre, Vancouver, British Columbia, Canada V6H 3Z6*

Ali Dehshahri − *Center for Nanotechnology in Drug Delivery, Shiraz University of Medical Sciences, Shiraz 7146864685, Iran*

Jomarien García-Couce − *Department of Radiology, Division of Translational Nanobiomaterials and Imaging, Leiden University Medical Center, Leiden 2333 ZA, The Netherlands; Department of Polymeric Biomaterials, Biomaterials Center (BIOMAT), University of Havana, Havana 10600, Cuba;* orcid.org/0000-0002-1105-3891

Shima Tavakol − *Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran 1417755469, Iran;* orcid.org/0000-0002-8531-7650

Saeid Moghassemi − *Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels 1200, Belgium;* orcid.org/0000-0002-5337-2903

Arezoo Dadashzadeh − *Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels 1200, Belgium*

Pooyan Makvandi − *Istituto Italiano di Tecnologia, Centre for Micro-BioRobotics, 56025 Pontedera, Pisa, Italy; Department of Medical Nanotechnology, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran 14496-14535, Iran*

Abbas Pardakhty − *Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman 7618866748, Iran*

Abbas Aghaei Afshar − *Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman 7618866749, Iran*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsbiomaterials.2c00026

Author Contributions

†V.S.M. and R.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Giguère, V.; Hollenberg, S. M.; Rosenfeld, M. G.; Evans, R. M. Functional domains of the human glucocorticoid receptor. *Cell* **1986**, *46* (5), 645−652.

(2) Thompson, E. B.; Lippman, M. E. Mechanism of action of glucocorticoids. *Metabolism* **1974**, *23* (2), 159−202.

(3) Ramamoorthy, S.; Cidlowski, J. A. Corticosteroids: mechanisms of action in health and disease. *Rheumatic Disease Clinics* **2016**, *42* (1), 15−31.

(4) Liu, B.; Zhang, T.-N.; Knight, J. K.; Goodwin, J. E. The glucocorticoid receptor in cardiovascular health and disease. *Cells* **2019**, *8* (10), 1227.

(5) Malaekeh-Nikouei, B.; Rezaee, M.; Gholami, L.; Behzad, M.; Mohajeri, M.; Oskuee, R. K. Dexamethasone conjugated polyallylamine: synthesis, characterization, and in vitro transfection and cytotoxicity. *Journal of Drug Delivery Science and Technology* **2017**, *40*, 172−179.

(6) Sadeghpour, H.; Khalvati, B.; Entezar-Almahdi, E.; Savadi, N.; Alhashemi, S. H.; Raoufi, M.; Dehshahri, A. Double domain polyethylenimine-based nanoparticles for integrin receptor mediated delivery of plasmid DNA. *Sci. Rep.* **2018**, *8* (1), 1−12.

(7) Gray, J. D.; Kogan, J. F.; Marrocco, J.; McEwen, B. S. Genomic and epigenomic mechanisms of glucocorticoids in the brain. *Nature Reviews Endocrinology* **2017**, *13* (11), 661−673.

(8) Payne, D.; Adcock, I. Molecular mechanisms of corticosteroid actions. *Paediatric respiratory reviews* **2001**, *2* (2), 145−150.

(9) Dehshahri, A.; Alhashemi, S. H.; Jamshidzadeh, A.; Sabahi, Z.; Samani, S. M.; Sadeghpour, H.; Mohazabieh, E.; Fadaei, M. Comparison of the effectiveness of polyethylenimine, polyamidoamine and chitosan in transferring plasmid encoding interleukin-12 gene into hepatocytes. *Macromol. Res.* **2013**, *21* (12), 1322−1330.

(10) Park, J. H.; Jiang, Y.; Zhou, J.; Gong, H.; Mohapatra, A.; Heo, J.; Gao, W.; Fang, R. H.; Zhang, L. Genetically engineered cell membrane−coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs. *Science Advances* **2021**, *7* (25), eabf7820.

(11) Franco, L. M.; Gadkari, M.; Howe, K. N.; Sun, J.; Kardava, L.; Kumar, P.; Kumari, S.; Hu, Z.; Fraser, I. D.; Moir, S. Immune regulation by glucocorticoids can be linked to cell type−dependent transcriptional responses. *Journal of Experimental Medicine* **2019**, *216* (2), 384−406.

(12) Nouri, F.; Sadeghpour, H.; Heidari, R.; Dehshahri, A. Preparation, characterization, and transfection efficiency of low molecular weight polyethylenimine-based nanoparticles for delivery of the plasmid encoding CD200 gene. *International journal of nanomedicine* **2017**, *12*, 5557.

(13) Cain, D. W.; Cidlowski, J. A. Immune regulation by glucocorticoids. *Nature Reviews Immunology* **2017**, *17* (4), 233−247.

(14) Cain, D. W.; Cidlowski, J. A. After 62 years of regulating immunity, dexamethasone meets COVID-19. *Nature Reviews Immunology* **2020**, *20*, 587−588.

(15) Sabahi, Z.; Samani, S. M.; Dehshahri, A. Conjugation of poly (amidoamine) dendrimers with various acrylates for improved delivery of plasmid encoding interleukin-12 gene. *Journal of biomaterials applications* **2015**, *29* (7), 941−953.

(16) Zhou, Y.; Hou, Y.; Shen, J.; Huang, Y.; Martin, W.; Cheng, F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery* **2020**, *6* (1), 1−18.
(17) OSKOUEI, R.; Dehshahri, A.; Shier, W. T.; Ramezani, M. Modified polyethylenimine: Self assemble nanoparticle forming polymer for pDNA delivery. *Iranian Journal of Basic Medical Sciences* **2008**, 33−40.
(18) The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine* **2021**, *384*, 693−704.
(19) Jermy, B. R.; Ravinayagam, V.; Almohazey, D.; Alamoudi, W.; Dafalla, H.; Akhtar, S.; Tanimu, G. PEGylated green halloysite/spinel ferrite nanocomposites for pH sensitive delivery of dexamethasone: A potential pulmonary drug delivery treatment option for COVID-19. *Appl. Clay Sci.* **2022**, *216*, 106333.
(20) Maia, J.; Ribeiro, M. P.; Ventura, C.; Carvalho, R. A.; Correia, I. J.; Gil, M. H. Ocular injectable formulation assessment for oxidized dextran-based hydrogels. *Acta biomaterialia* **2009**, *5* (6), 1948−1955.
(21) Dash, A.; Cudworth II, G. Therapeutic applications of implantable drug delivery systems. *Journal of pharmacological and toxicological methods* **1998**, *40* (1), 1−12.
(22) Gaudana, R.; Ananthula, H. K.; Parenky, A.; Mitra, A. K. Ocular drug delivery. *AAPS journal* **2010**, *12* (3), 348−360.
(23) Barcia, E.; Herradón, C.; Herrero-Vanrell, R. Biodegradable additives modulate ganciclovir release rate from PLGA microspheres destined to intraocular administration. *Letters in Drug Design & Discovery* **2005**, *2* (2), 148−149.
(24) Short, B. G. Safety evaluation of ocular drug delivery formulations: techniques and practical considerations. *Toxicologic pathology* **2008**, *36* (1), 49−62.
(25) Gaballa, S. A.; Kompella, U. B.; Elgarhy, O.; Alqahtani, A. M.; Pierscionek, B.; Alany, R. G.; Abdelkader, H. Corticosteroids in ophthalmology: Drug delivery innovations, pharmacology, clinical applications, and future perspectives. *Drug Delivery and Translational Research* **2021**, *11* (3), 866−893.
(26) The Loteprednol Etabonate US Uveitis Study Group.. Controlled evaluation of loteprednol etabonate and prednisolone acetate in the treatment of acute anterior uveitis. *American Journal of Ophthalmology* **1999**, *127* (5), 537−544.
(27) Luo, L.; Yang, J.; Oh, Y.; Hartsock, M. J.; Xia, S.; Kim, Y.-C.; Ding, Z.; Meng, T.; Eberhart, C. G.; Ensign, L. M. Controlled release of corticosteroid with biodegradable nanoparticles for treating experimental autoimmune uveitis. *Journal of Controlled Release* **2019**, *296*, 68−80.
(28) Schwartz, S. G.; Scott, I. U.; Stewart, M. W.; Flynn, H. W., Jr Update on corticosteroids for diabetic macular edema. *Clinical Ophthalmology (Auckland, NZ)* **2016**, *10*, 1723.
(29) Ayalasomayajula, S. P.; Ashton, P.; Kompella, U. B. Fluocinolone inhibits VEGF expression via glucocorticoid receptor in human retinal pigment epithelial (ARPE-19) cells and TNF-α−induced angiogenesis in chick chorioallantoic membrane (CAM). *Journal of ocular pharmacology and therapeutics* **2009**, *25* (2), 97−104.
(30) Wu, W.; Cao, W.; Chen, J.; Cai, Y.; Dong, B.; Chu, X. In Situ Liquid Crystal Gel as a Promising Strategy for Improving Ocular Administration of Dexamethasone: Preparation, Characterization, and Evaluation. *AAPS PharmSciTech* **2022**, *23* (1), 1−13.
(31) Kupferman, A.; Leibowitz, H. Anti-inflammatory effectiveness of topically administered corticosteroids in the cornea without epithelium. *Investigative Ophthalmology & Visual Science* **1975**, *14* (3), 252−255.
(32) Abadia, B.; Calvo, P.; Ferreras, A.; Bartol, F.; Verdes, G.; Pablo, L. Clinical applications of dexamethasone for aged eyes. *Drugs & aging* **2016**, *33* (9), 639−646.
(33) Albrecht, E.; Richards, J.; Pollock, T.; Cook, C.; Myers, L. Adjunctive use of intravitreal dexamethasone in presumed bacterial endophthalmitis: a randomised trial. *British Journal of Ophthalmology* **2011**, *95* (10), 1385−1388.
(34) Kwak, H. W.; D'Amico, D. J. Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. *Archives of Ophthalmology* **1992**, *110* (2), 259−266.
(35) Chang-Lin, J.-E.; Attar, M.; Acheampong, A. A.; Robinson, M. R.; Whitcup, S. M.; Kuppermann, B. D.; Welty, D. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Investigative ophthalmology & visual science* **2011**, *52* (1), 80−86.
(36) Massa, H.; Georgoudis, P.; Panos, G. D. Dexamethasone intravitreal implant (OZURDEX®) for macular edema secondary to noninfectious uveitis: a review of the literature. *Therapeutic delivery* **2019**, *10* (6), 343−351.
(37) Chen, H.; Sun, S.; Li, J.; Du, W.; Zhao, C.; Hou, J.; Xu, Y.; Cheng, L. Different intravitreal properties of three triamcinolone formulations and their possible impact on retina practice. *Investigative ophthalmology & visual science* **2013**, *54* (3), 2178−2185.
(38) Haller, J. A.; Bandello, F.; Belfort, R., Jr; Blumenkranz, M. S.; Gillies, M.; Heier, J.; Loewenstein, A.; Yoon, Y.-H.; Jacques, M.-L.; Jiao, J. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* **2010**, *117* (6), 1134−1146.e3.
(39) Nguyen, Q. D.; Brown, D. M.; Marcus, D. M.; Boyer, D. S.; Patel, S.; Feiner, L.; Gibson, A.; Sy, J.; Rundle, A. C.; Hopkins, J. J. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* **2012**, *119* (4), 789−801.
(40) Haller, J. A.; Kuppermann, B. D.; Blumenkranz, M. S.; Williams, G. A.; Weinberg, D. V.; Chou, C.; Whitcup, S. M. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Archives of Ophthalmology* **2010**, *128* (3), 289−296.
(41) Li, M.-S.; Sheu, S.-J. Persistent vitreous hemorrhage after intravitreal injection of dexamethasone intravitreal implant in patients with diabetic macular edema. *Taiwan journal of ophthalmology* **2019**, *9* (4), 280.
(42) Woetzel, D.; Huber, R.; Kupfer, P.; Pohlers, D.; Pfaff, M.; Driesch, D.; Häupl, T.; Koczan, D.; Stiehl, P.; Guthke, R. Identification of rheumatoid arthritis and osteoarthritis patients by transcriptome-based rule set generation. *Arthritis Research & Therapy* **2014**, *16* (2), R84.
(43) Van Der Heijde, D.; Daikh, D. I.; Betteridge, N.; Burmester, G. R.; Hassett, A. L.; Matteson, E. L.; Van Vollenhoven, R.; Lakhanpal, S. Common language description of the term rheumatic and musculoskeletal diseases (RMDs) for use in communication with the lay public, healthcare providers and other stakeholders endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). *Annals of the Rheumatic Diseases* **2018**, *77* (6), 829−832.
(44) Ross, C. A comparison of osteoarthritis and rheumatoid arthritis: diagnosis and treatment. *Nurse Practitioner* **1997**, *22* (9), 20−41.
(45) Reginster, J. Y. The prevalence and burden of arthritis. *Rheumatology* **2002**, *41* (suppl_1), 3−6.
(46) Guilak, F.; Nims, R. J.; Dicks, A.; Wu, C.-L.; Meulenbelt, I. Osteoarthritis as a disease of the cartilage pericellular matrix. *Matrix Biology* **2018**, *71*, 40−50.
(47) van Vollenhoven, R. F. Sex differences in rheumatoid arthritis: more than meets the eye. *BMC Medicine* **2009**, *7* (1), 12.
(48) Hame, S. L.; Alexander, R. A. Knee osteoarthritis in women. *Current reviews in musculoskeletal medicine* **2013**, *6* (2), 182−187.
(49) Grässel, S.; Muschter, D. Recent advances in the treatment of osteoarthritis. *F1000Research* **2020**, *9*, 325.
(50) Susko, A. M.; Fitzgerald, G. K. The pain-relieving qualities of exercise in knee osteoarthritis. *Open access rheumatology: research and reviews* **2013**, *5*, 81.
(51) Mobasheri, A.; van Spil, W. E.; Budd, E.; Uzieliene, I.; Bernotiene, E.; Bay-Jensen, A.-C.; Larkin, J.; Levesque, M. C.; Gualillo, O.; Henrotin, Y. Molecular taxonomy of osteoarthritis for patient stratification, disease management and drug development:

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

biochemical markers associated with emerging clinical phenotypes and molecular endotypes. *Current opinion in rheumatology* **2019**, *31* (1), 80−89.
(52) Köhler, B. M.; Günther, J.; Kaudewitz, D.; Lorenz, H.-M. Current therapeutic options in the treatment of rheumatoid arthritis. *Journal of clinical medicine* **2019**, *8* (7), 938.
(53) Perkins, C.; Whiting, B.; Lee, P. Y. Steroids and Osteoarthritis. *Journal of Arthritis* **2017**, DOI: 10.4172/2167-7921.1000e115.
(54) Ahmed, M. A. S.; Saweeres, E. S. B.; Abdelkader, N. A.; Abdelmajeed, S. F.; Fares, A. R. Improved pain and function in knee osteoarthritis with dexamethasone phonophoresis: A randomized controlled trial. *Indian Journal of Orthopaedics* **2019**, *53*, 700−707.
(55) Stefani, R. M.; Lee, A. J.; Tan, A. R.; Halder, S. S.; Hu, Y.; Guo, X. E.; Stoker, A. M.; Ateshian, G. A.; Marra, K. G.; Cook, J. L. Sustained low-dose dexamethasone delivery via a PLGA microsphere-embedded agarose implant for enhanced osteochondral repair. *Acta Biomaterialia* **2020**, *102*, 326−340.
(56) Fan, Z.; Ma, J.; Kuang, M.; Zhang, L.; Han, B.; Yang, B.; Wang, Y.; Ma, X. The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: a systematic review and meta-analysis. *International Journal of Surgery* **2018**, *52*, 149−155.
(57) Tammachote, N.; Kanitnate, S. Intravenous dexamethasone injection reduces pain from 12 to 21 h after total knee arthroplasty: a double-blind, randomized, placebo-controlled trial. *Journal of Arthroplasty* **2020**, *35* (2), 394−400.
(58) Derfoul, A.; Perkins, G. L.; Hall, D. J.; Tuan, R. S. Glucocorticoids promote chondrogenic differentiation of adult human mesenchymal stem cells by enhancing expression of cartilage extracellular matrix genes. *Stem cells* **2006**, *24* (6), 1487−1495.
(59) Johnstone, B.; Hering, T. M.; Caplan, A. I.; Goldberg, V. M.; Yoo, J. U. In vitrochondrogenesis of bone marrow-derived mesenchymal progenitor cells. *Experimental cell research* **1998**, *238* (1), 265−272.
(60) Chijimatsu, R.; Kobayashi, M.; Ebina, K.; Iwahashi, T.; Okuno, Y.; Hirao, M.; Fukuhara, A.; Nakamura, N.; Yoshikawa, H. Impact of dexamethasone concentration on cartilage tissue formation from human synovial derived stem cells in vitro. *Cytotechnology* **2018**, *70* (2), 819−829.
(61) Black, R.; Grodzinsky, A. J. Dexamethasone: chondroprotective corticosteroid or catabolic killer? *European cells & materials* **2019**, *38*, 246.
(62) Espinosa, M.; Vaisman, A.; Nazal, N.; Figueroa, D.; Gallegos, M.; Conget, P. Intraarticular administration of dexamethasone after mesenchymal stem cells implantation does not improve significantly the treatment of preestablished full-thickness chondral defect in a rabbit model. *Cartilage* **2013**, *4* (2), 144−152.
(63) Zeng, C.; Lane, N.; Hunter, D.; Wei, J.; Choi, H.; McAlindon, T.; Li, H.; Lu, N.; Lei, G.; Zhang, Y. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the osteoarthritis initiative. *Osteoarthritis and cartilage* **2019**, *27* (6), 855−862.
(64) Zhou, T.; Xiong, H.; Wang, S.; Zhang, H.; Zheng, W.; Gou, Z.; Fan, C.; Gao, C. An injectable hydrogel dotted with dexamethasone acetate-encapsulated reactive oxygen species-scavenging micelles for combinatorial therapy of osteoarthritis. *Materials Today Nano* **2022**, *17*, 100164.
(65) Wernecke, C.; Braun, H. J.; Dragoo, J. L. The effect of intra-articular corticosteroids on articular cartilage: a systematic review. *Orthopaedic Journal of Sports Medicine* **2015**, *3* (5), 2325967115581163.
(66) Ashrafizadeh, M.; Fekri, H. S.; Ahmadi, Z.; Farkhondeh, T.; Samarghandian, S. Therapeutic and biological activities of berberine: The involvement of Nrf2 signaling pathway. *Journal of Cellular Biochemistry* **2020**, *121* (2), 1575−1585.
(67) Liang, R.; Wong, K. H.; Yang, Y.; Duan, Y.; Chen, M. ROS-responsive dexamethasone micelles normalize the tumor microenvironment enhancing hypericin in cancer photodynamic therapy. *Biomaterials Science* **2022**, *10*, 1018.
(68) Graversen, J. H.; Svendsen, P.; Dagnæs-Hansen, F.; Dal, J.; Anton, G.; Etzerodt, A.; Petersen, M. D.; Christensen, P. A.; Møller, H. J.; Moestrup, S. K. Targeting the hemoglobin scavenger receptor CD163 in macrophages highly increases the anti-inflammatory potency of dexamethasone. *Molecular Therapy* **2012**, *20* (8), 1550−1558.
(69) Lutsar, I.; Friedland, I.; Jafri, H.; Wubbel, L.; Ahmed, A.; Trujillo, M.; McCoig, C.; McCracken, G., Jr Factors influencing the anti-inflammatory effect of dexamethasone therapy in experimental pneumococcal meningitis. *J. Antimicrob. Chemother.* **2003**, *52* (4), 651−655.
(70) Martin, J. D.; Panagi, M.; Wang, C.; Khan, T. T.; Martin, M. R.; Voutouri, C.; Toh, K.; Papageorgis, P.; Mpekris, F.; Polydorou, C. Dexamethasone increases cisplatin-loaded nanocarrier delivery and efficacy in metastatic breast cancer by normalizing the tumor microenvironment. *ACS Nano* **2019**, *13* (6), 6396−6408.
(71) Meng, G.; Tang, X.; Yang, Z.; Zhao, Y. Y.; Curtis, J. M.; McMullen, T. P.; Brindley, D. N. Dexamethasone decreases the autotaxin-lysophosphatidate-inflammatory axis in adipose tissue: implications for the metabolic syndrome and breast cancer. *FASEB J.* **2019**, *33* (2), 1899−1910.
(72) Kim, M. H.; Kim, D. W.; Park, S.; Kim, J. H.; Lee, K. Y.; Hwang, J.; Yoo, Y. C. Single dose of dexamethasone is not associated with postoperative recurrence and mortality in breast cancer patients: a propensity-matched cohort study. *BMC Cancer* **2019**, *19* (1), 251.
(73) Gasparetto, C.; Schiller, G. *Selinexor, daratumumab, and dexamethasone in patients with relapsed/refractory multiple myeloma (MM)*. American Society of Clinical Oncology, 2020.
(74) Gasparetto, C.; Lentzsch, S.; Schiller, G.; Callander, N.; Tuchman, S.; Chen, C.; White, D.; Kotb, R.; Sutherland, H.; Sebag, M. S1606 safety and efficacy of combination of selinexor, daratumumab, and dexamethasone (SDD) in patients with multiple myeloma (MM) previously exposed to proteasome inhibitors and immunomodulatory drugs. *HemaSphere* **2019**, *3* (S1), 740.
(75) Rifkin, R. M.; Melear, J. M.; Faber, E.; Bensinger, W. I.; Burke, J. M.; Narang, M.; Stevens, D.; Gunawardena, S.; Lutska, Y.; Qi, K. *Daratumumab (DARA) maintenance therapy improves depth of response and results in durable progression-free survival (PFS) following Dara plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): update of the Lyra study*; American Society of Hematology: Washington, DC, 2019.
(76) Chari, A.; Vogl, D. T.; Gavriatopoulou, M.; Nooka, A. K.; Yee, A. J.; Huff, C. A.; Moreau, P.; Dingli, D.; Cole, C.; Lonial, S. Oral selinexor−dexamethasone for triple-class refractory multiple myeloma. *New England Journal of Medicine* **2019**, *381* (8), 727−738.
(77) Dubinski, D.; Hattingen, E.; Senft, C.; Seifert, V.; Peters, K. G.; Reiss, Y.; Devraj, K.; Plate, K. H. Controversial roles for dexamethasone in glioblastoma−Opportunities for novel vascular targeting therapies. *Journal of Cerebral Blood Flow & Metabolism* **2019**, *39* (8), 1460−1468.
(78) Cenciarini, M.; Valentino, M.; Belia, S.; Sforna, L.; Rosa, P.; Ronchetti, S.; D'Adamo, M. C.; Pessia, M. Dexamethasone in glioblastoma multiforme therapy: mechanisms and controversies. *Frontiers in Molecular Neuroscience* **2019**, *12*, 65.
(79) August, K. J.; Guest, E. M.; Lewing, K.; Hays, J. A.; Gamis, A. S. Treatment of children with relapsed and refractory acute lymphoblastic leukemia with mitoxantrone, vincristine, pegaspargase, dexamethasone, and bortezomib. *Pediatric Blood & Cancer* **2020**, *67* (3), e28062.
(80) Tabchi, S.; Nair, R.; Kunacheewa, C.; Patel, K. K.; Lee, H. C.; Thomas, S. K.; Amini, B.; Ahmed, S.; Mehta, R. S.; Bashir, Q. Retrospective Review of the Use of High-Dose Cyclophosphamide, Bortezomib, Doxorubicin, and Dexamethasone for the Treatment of Multiple Myeloma and Plasma Cell Leukemia. *Clinical Lymphoma Myeloma and Leukemia* **2019**, *19* (9), 560−569.
(81) Phillips, N. S.; Cheung, Y. T.; Glass, J. O.; Scoggins, M. A.; Liu, W.; Ogg, R. J.; Mulrooney, D. A.; Pui, C. H.; Robison, L. L.; Reddick, W. E. Neuroanatomical abnormalities related to dexamethasone

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

exposure in survivors of childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer* **2020**, *67* (3), e27968.
(82) Zhang, D.; Zhang, Y.; Cai, Z.; Tu, Y.; Hu, Z. Dexamethasone and lenvatinib inhibit migration and invasion of non-small cell lung cancer by regulating EKR/AKT and VEGF signal pathways. *Experimental and Therapeutic Medicine* **2020**, *19* (1), 762−770.
(83) Ge, H.; Ke, J.; Xu, N.; Li, H.; Gong, J.; Li, X.; Song, Y.; Zhu, H.; Bai, C. Dexamethasone alleviates pemetrexed-induced senescence in non-small-cell lung cancer. *Food Chem. Toxicol.* **2018**, *119*, 86−97.
(84) Wang, L.-j.; Li, J.; Hao, F.-r.; Yuan, Y.; Li, J.-y.; Lu, W.; Zhou, T.-y. Dexamethasone suppresses the growth of human non-small cell lung cancer via inducing estrogen sulfotransferase and inactivating estrogen. *Acta pharmacologica sinica* **2016**, *37* (6), 845−856.
(85) Chen, Y.; Dong, C.; Lian, G.; Li, D.; Yin, Y.; Yu, W.; Du, C.; Liu, C.; Li, L.; Tian, F. Dexamethasone on postoperative gastrointestinal motility: A placebo-controlled, double-blinded, randomized controlled trial. *Journal of Gastroenterology and Hepatology* **2020**, *35*, 1549.
(86) McSorley, S. T.; Dolan, R. D.; Roxburgh, C. S.; Horgan, P. G.; MacKay, G. J.; McMillan, D. C. Possible dose dependent effect of perioperative dexamethasone and laparoscopic surgery on the postoperative systemic inflammatory response and complications following surgery for colon cancer. *European Journal of Surgical Oncology* **2019**, *45* (9), 1613−1618.
(87) Strömberg, T.; Dimberg, A.; Hammarberg, A.; Carlson, K.; Osterborg, A.; Nilsson, K.; Jernberg-Wiklund, H. Rapamycin sensitizes multiple myeloma cells to apoptosis induced by dexamethasone. *Blood* **2004**, *103* (8), 3138−3147.
(88) Moreaux, J.; Legouffe, E.; Jourdan, E.; Quittet, P.; Rème, T.; Lugagne, C.; Moine, P.; Rossi, J.-F.; Klein, B.; Tarte, K. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. *Blood* **2004**, *103* (8), 3148−3157.
(89) Hideshima, T.; Raje, N.; Richardson, P. G.; Anderson, K. C. A review of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma. *Therapeutics and Clinical Risk Management* **2008**, *4* (1), 129.
(90) Kleber, M.; Ihorst, G.; Udi, J.; Koch, B.; Engelhardt, M. *Use of lenalidomide may surmount the adverse prognosis induced by renal impairment in patients (pts) with relapsed/refractory multiple myeloma (MM)*; American Society of Hematology, 2010.
(91) Bartlett, J.; Tozer, A.; Stirling, D.; Zeldis, J. Recent clinical studies of the immunomodulatory drug (IMiD®) lenalidomide. *British journal of cancer* **2005**, *93* (6), 613−619.
(92) Garderet, L.; Kuhnowski, F.; Berge, B.; Roussel, M.; Escoffre-Barbe, M.; Lafon, I.; Facon, T.; Leleu, X.; Karlin, L.; Perrot, A. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. *Blood* **2018**, *132* (24), 2555−2563.
(93) Li, Z.; Dong, J.; Zou, T.; Du, C.; Li, S.; Chen, C.; Liu, R.; Wang, K. Dexamethasone induces docetaxel and cisplatin resistance partially through up-regulating Krüppel-like factor 5 in triple-negative breast cancer. *Oncotarget* **2017**, *8* (7), 11555.
(94) Rugo, H. S.; Seneviratne, L.; Beck, J. T.; Glaspy, J. A.; Peguero, J. A.; Pluard, T. J.; Dhillon, N.; Hwang, L. C.; Nangia, C.; Mayer, I. A. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncology* **2017**, *18* (5), 654−662.
(95) Canino, C.; Mori, F.; Cambria, A.; Diamantini, A.; Germoni, S.; Alessandrini, G.; Borsellino, G.; Galati, R.; Battistini, L.; Blandino, R. SASP mediates chemoresistance and tumor-initiating-activity of mesothelioma cells. *Oncogene* **2012**, *31* (26), 3148−3163.
(96) Mohammadinejad, R.; Kumar, A.; Ranjbar-Mohammadi, M.; Ashrafizadeh, M.; Han, S. S.; Khang, G.; Roveimiab, Z. Recent advances in natural gum-based Biomaterials for tissue engineering and regenerative medicine: A Review. *Polymers* **2020**, *12* (1), 176.
(97) Birhanu, G.; Tanha, S.; Akbari Javar, H.; Seyedjafari, E.; Zandi-Karimi, A.; Kiani Dehkordi, B. Dexamethasone loaded multi-layer poly-l-lactic acid/pluronic P123 composite electrospun nanofiber scaffolds for bone tissue engineering and drug delivery. *Pharm. Dev. Technol.* **2019**, *24* (3), 338−347.
(98) Zhang, B.; Li, H.; He, L.; Han, Z.; Zhou, T.; Zhi, W.; Lu, X.; Lu, X.; Weng, J. Surface-decorated hydroxyapatite scaffold with on-demand delivery of dexamethasone and stromal cell derived factor-1 for enhanced osteogenesis. *Materials Science and Engineering: C* **2018**, *89*, 355−370.
(99) Amjadian, S.; Seyedjafari, E.; Zeynali, B.; Shabani, I. The synergistic effect of nano-hydroxyapatite and dexamethasone in the fibrous delivery system of gelatin and poly (l-lactide) on the osteogenesis of mesenchymal stem cells. *International journal of pharmaceutics* **2016**, *507* (1−2), 1−11.
(100) Paun, I. A.; Zamfirescu, M.; Luculescu, C. R.; Acasandrei, A. M.; Mustaciosu, C. C.; Mihailescu, M.; Dinescu, M. Electrically responsive microreservoires for controllable delivery of dexamethasone in bone tissue engineering. *Appl. Surf. Sci.* **2017**, *392*, 321−331.
(101) Porgham Daryasari, M.; Dusti Telgerd, M.; Hossein Karami, M.; Zandi-Karimi, A.; Akbarijavar, H.; Khoobi, M.; Seyedjafari, E.; Birhanu, G.; Khosravian, P.; SadatMahdavi, F. Poly-l-lactic acid scaffold incorporated chitosan-coated mesoporous silica nanoparticles as pH-sensitive composite for enhanced osteogenic differentiation of human adipose tissue stem cells by dexamethasone delivery. *Artificial cells, nanomedicine, and biotechnology* **2019**, *47* (1), 4020−4029.
(102) Son, J. S.; Kim, S. G.; Oh, J. S.; Appleford, M.; Oh, S.; Ong, J. L.; Lee, K. B. Hydroxyapatite/polylactide biphasic combination scaffold loaded with dexamethasone for bone regeneration. *J. Biomed. Mater. Res., Part A* **2011**, *99* (4), 638−647.
(103) Ghorbani, F.; Zamanian, A. An efficient functionalization of dexamethasone-loaded polymeric scaffold with [3-(2, 3-epoxypropoxy)-propyl]-trimethoxysilane coupling agent for bone regeneration: Synthesis, characterization, and in vitro evaluation. *J. Bioact. Compat. Polym.* **2020**, *35* (2), 139−159.
(104) Eivazzadeh-Keihan, R.; Chenab, K. K.; Taheri-Ledari, R.; Mosafer, J.; Hashemi, S. M.; Mokhtarzadeh, A.; Maleki, A.; Hamblin, M. R. Recent advances in the application of mesoporous silica-based nanomaterials for bone tissue engineering. *Materials Science and Engineering: C* **2020**, *107*, 110267.
(105) Qiu, K.; Chen, B.; Nie, W.; Zhou, X.; Feng, W.; Wang, W.; Chen, L.; Mo, X.; Wei, Y.; He, C. Electrophoretic deposition of dexamethasone-loaded mesoporous silica nanoparticles onto poly (L-lactic acid)/poly (ϵ-caprolactone) composite scaffold for bone tissue engineering. *ACS Appl. Mater. Interfaces* **2016**, *8* (6), 4137−4148.
(106) Panek, M.; Antunović, M.; Pribolšan, L.; Ivković, A.; Gotić, M.; Vukasović, A.; Caput Mihalić, K.; Pušić, M.; Jurkin, T.; Marijanović, I. Bone tissue engineering in a perfusion bioreactor using dexamethasone-loaded peptide hydrogel. *Materials* **2019**, *12* (6), 919.
(107) Roach, B. L.; Kelmendi-Doko, A.; Balutis, E. C.; Marra, K. G.; Ateshian, G. A.; Hung, C. T. Dexamethasone release from within engineered cartilage as a chondroprotective strategy against interleukin-1α. *Tissue Engineering Part A* **2016**, *22* (7−8), 621−632.
(108) Kim, M.; Garrity, S. T.; Steinberg, D. R.; Dodge, G. R.; Mauck, R. L. Role of dexamethasone in the long-term functional maturation of MSC-laden hyaluronic acid hydrogels for cartilage tissue engineering. *Journal of Orthopaedic Research* **2018**, *36* (6), 1717−1727.
(109) Nejad, Z. M.; Torabinejad, B.; Davachi, S. M.; Zamanian, A.; Garakani, S. S.; Najafi, F.; Nezafati, N. Synthesis, physicochemical, rheological and in-vitro characterization of double-crosslinked hyaluronic acid hydrogels containing dexamethasone and PLGA/dexamethasone nanoparticles as hybrid systems for specific medical applications. *Int. J. Biol. Macromol.* **2019**, *126*, 193−208.
(110) Westin, C. B.; Nagahara, M. H.; Decarli, M. C.; Kelly, D. J.; Moraes, Â. M. Development and characterization of carbohydrate-based thermosensitive hydrogels for cartilage tissue engineering. *Eur. Polym. J.* **2020**, *129*, 109637.
(111) Tigh, R.; Gümüşderelioğlu, M. Dexamethasone releasing chitosan scaffold for cartilage development. *Eur. Cell Mater.* **2006**, *12*, 73.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

(112) Ghiaee, A.; Pournaqi, F.; Vakilian, S.; Mohammadi-Sangcheshmeh, A.; Ardeshirylajimi, A. Adapted dexamethasone delivery polyethylene oxide and poly (ε-caprolactone) construct promote mesenchymal stem cells chondrogenesis. *Artificial cells, nanomedicine, and biotechnology* **2017**, *45* (8), 1640−1648.
(113) Won, Y.-W.; Patel, A. N.; Bull, D. A. Cell surface engineering to enhance mesenchymal stem cell migration toward an SDF-1 gradient. *Biomaterials* **2014**, *35* (21), 5627−5635.
(114) Chen, Y.; Kawazoe, N.; Chen, G. Preparation of dexamethasone-loaded biphasic calcium phosphate nanoparticles/collagen porous composite scaffolds for bone tissue engineering. *Acta biomaterialia* **2018**, *67*, 341−353.
(115) He, J.; Zhang, Y.; Liu, X.; Li, H.; Xiong, C.; Zhang, L. Load-bearing PTMC-beta tri-calcium phosphate and dexamethasone biphasic composite microsphere scaffolds for bone tissue engineering. *Mater. Lett.* **2020**, *260*, 126939.
(116) Li, X.; Wang, Y.; Wang, Z.; Qi, Y.; Li, L.; Zhang, P.; Chen, X.; Huang, Y. Composite PLA/PEG/nHA/dexamethasone scaffold prepared by 3D printing for bone regeneration. *Macromol. Biosci.* **2018**, *18* (6), 1800068.
(117) Kelmendi-Doko, A.; Rubin, J. P.; Klett, K.; Mahoney, C.; Wang, S.; Marra, K. G. Controlled dexamethasone delivery via double-walled microspheres to enhance long-term adipose tissue retention. *Journal of Tissue Engineering* **2017**, *8*, 2041731417735402.
(118) Jia, Y.; Fan, M.; Chen, H.; Miao, Y.; Xing, L.; Jiang, B.; Cheng, Q.; Liu, D.; Bao, W.; Qian, B. Magnetic hyaluronic acid nanospheres via aqueous Diels−Alder chemistry to deliver dexamethasone for adipose tissue engineering. *J. Colloid Interface Sci.* **2015**, *458*, 293−299.
(119) Belanto, J. J.; Diaz-Perez, S. V.; Magyar, C. E.; Maxwell, M. M.; Yilmaz, Y.; Topp, K.; Boso, G.; Jamieson, C. H.; Cacalano, N. A.; Jamieson, C. A. Dexamethasone induces dysferlin in myoblasts and enhances their myogenic differentiation. *Neuromuscular Disorders* **2010**, *20* (2), 111−121.
(120) Perry, R.; Rudnick, M. Molecular mechanisms regulating myogenic determination and differentiation. *Front Biosci* **2000**, *5*, 750−767.
(121) Yoshiko, Y.; Hirao, K.; Maeda, N. Dexamethasone regulates the actions of endogenous insulin-like growth factor-II during myogenic differentiation. *Life sciences* **1998**, *63* (2), 77−85.
(122) Han, D.-S.; Yang, W.-S.; Kao, T.-W. Dexamethasone treatment at the myoblast stage enhanced C2C12 myocyte differentiation. *International journal of medical sciences* **2017**, *14* (5), 434.
(123) Sahin, A. R.; Erdogan, A.; Agaoglu, P. M.; Dineri, Y.; Cakirci, A. Y.; Senel, M. E.; Okyay, R. A.; Tasdogan, A. M. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. *EJMO* **2020**, *4* (1), 1−7.
(124) Hui, D. S.; I Azhar, E.; Madani, T. A.; Ntoumi, F.; Kock, R.; Dar, O.; Ippolito, G.; Mchugh, T. D.; Memish, Z. A.; Drosten, C. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. *International Journal of Infectious Diseases* **2020**, *91*, 264−266.
(125) Najafloo, R.; Majidi, J.; Asghari, A.; Aleemardani, M.; Kamrava, S. K.; Simorgh, S.; Seifalian, A.; Bagher, Z.; Seifalian, A. M. Mechanism of Anosmia Caused by Symptoms of COVID-19 and Emerging Treatments. *ACS Chem. Neurosci.* **2021**, *12* (20), 3795−3805.
(126) Tavakol, S.; Zahmatkeshan, M.; Mohammadinejad, M. R.; Mehrzadi, S.; Joghataei, M. T.; Alavijeh, M. S.; Seifalian, A. The role of Nanotechnology in current COVID-19 outbreak. *Heliyon* **2021**, *7*, e06841.
(127) Tavakol, S.; Alavijeh, M. S.; Seifalian, A. M. COVID-19 Vaccines in Clinical Trials and their Mode of Action for Immunity against the Virus. *Current pharmaceutical design* **2021**, *27* (13), 1553−1563.
(128) Mahmudpour, M.; Roozbeh, J.; Keshavarz, M.; Farrokhi, S.; Nabipour, I. COVID-19 cytokine storm: The anger of inflammation. *Cytokine* **2020**, *133*, 155151.
(129) Wang, K.; Chen, W.; Zhou, Y.-S.; Lian, J.-Q.; Zhang, Z.; Du, P.; Gong, L.; Zhang, Y.; Cui, H.-Y.; Geng, J.-J. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Sig. Transduct. Target. Ther.* **2020**, *5*, 283.
(130) Ahmed, M. H.; Hassan, A. Dexamethasone for the treatment of coronavirus disease (COVID-19): a review. *SN Comprehensive Clinical Medicine* **2020**, *2*, 1−10.
(131) Ulrich, H.; Pillat, M. M. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. *Stem Cell Reviews and Reports* **2020**, *16*, 1−7.
(132) Tavakol, S.; Seifalian, A. M. Vitamin E at a high dose as an anti-ferroptosis drug and not just a supplement for COVID-19 treatment. *Biotechnology and Applied Biochemistry* **2021**, DOI: 10.1002/bab.2176.
(133) Matthay, M. A.; Aldrich, J. M.; Gotts, J. E. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respiratory Medicine* **2020**, *8* (5), 433−434.
(134) NIH. *Corticosteroids (Including Dexamethasone)*; 2020.
(135) Ranjbar, K.; Moghadami, M.; Mirahmadizadeh, A.; Fallahi, M. J.; Khaloo, V.; Shahriarirad, R.; Erfani, A.; Khodamoradi, Z.; Saadi, M. H. G. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. *BMC Infectious Diseases* **2021**, *21* (1), 1−8.
(136) Braude, A.; Rebuck, A. Prednisone and methylprednisolone disposition in the lung. *Lancet* **1983**, *322* (8357), 995−997.
(137) WHO. Dexamethasone and COVID-19. https://www.who.int/news-room/q-a-detail/q-a-dexamethasone-and-covid-19.
(138) Azimi, S.; Sahebnasagh, A.; Sharifnia, H.; Najmeddin, F. Corticosteroids Administration Following COVID-19-induced Acute Respiratory Distress Syndrome. Is it harmful or Life-saving? *Advanced Journal of Emergency Medicine* **2020**, *4* (2s), e43−e43.
(139) Group, R. C. Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine* **2021**, *384* (8), 693−704.
(140) Ling, Y.; Xu, S.-B.; Lin, Y.-X.; Tian, D.; Zhu, Z.-Q.; Dai, F.-H.; Wu, F.; Song, Z.-G.; Huang, W.; Chen, J. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chinese Medical Journal* **2020**, *133* (9), 1039.
(141) Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *579*, 1−4.
(142) Lu, X.; Chen, T.; Wang, Y.; Wang, J.; Yan, F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Critical Care* **2020**, *24* (1), 1−4.
(143) Fadel, R.; Morrison, A.; Vahia, A.; Smith, Z. R.; Chaudhry, Z.; Bhargava, P.; Miller, J.; Kenney, R.; Alangaden, G.; Ramesh, M. S. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clinical Infectious Diseases* **2020**, *71*, 2114.
(144) Wu, C.; Chen, X.; Cai, Y.; Zhou, X.; Xu, S.; Huang, H.; Zhang, L.; Zhou, X.; Du, C.; Zhang, Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine* **2020**, *180*, 934−943.
(145) Corral, L.; Bahamonde, A.; delas Revillas, F. A.; Gomez-Barquero, J.; Abadia-Otero, J.; Garcia-Ibarbia, C.; Mora, V.; Hernandez, J. L.; Lopez-Muniz, G.; Hernandez-Blanco, F. GLUCO-COVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv* **2020**.
(146) Ferner, R. E.; DeVito, N.; Aronson, J. K. Dexamethasone. *CEBM* **2020**.
(147) Wang, Q.; Xu, B.; Fan, K.; Wu, J.; Wang, T. Inflammation suppression by dexamethasone via inhibition of CD147-mediated NF-κB pathway in collagen-induced arthritis rats. *Mol. Cell. Biochem.* **2020**, *2020*, 1−14.
(148) Zhong, J.; Tang, J.; Ye, C.; Dong, L. The immunology of COVID-19: is immune modulation an option for treatment? *Lancet Rheumatology* **2020**, *2* (7), e428−e436.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

(149) Sharma, A. Inferring molecular mechanisms of dexamethasone therapy in severe COVID-19 from existing transcriptomic data. *Gene* **2021**, *788*, 145665.
(150) Ghadhanfar, E.; Alsalem, A.; Al-Kandari, S.; Naser, J.; Babiker, F.; Al-Bader, M. The role of ACE2, angiotensin-(1−7) and Mas1 receptor axis in glucocorticoid-induced intrauterine growth restriction. *Reproductive Biology and Endocrinology* **2017**, *15* (1), 1−9.
(151) Mendelsohn, F.; Lloyd, C.; Kachel, C.; Funder, J. Glucocorticoid induction of angiotensin converting enzyme production from bovine endothelial cells in culture and rat lung in vivo. *Clinical and Experimental Pharmacology & Physiology Supplement* **1982**, *7*, 57−62.
(152) Barreto-Chaves, M.; Heimann, A.; Krieger, J. Stimulatory effect of dexamethasone on angiotensin-converting enzyme in neonatal rat cardiac myocytes. *Braz. J. Med. Biol. Res.* **2000**, *33* (6), 661−664.
(153) Tavakol, S.; Tavakol, H.; Alavijeh, M. S.; Seifalian, A. The World Against Versatile SARS-Cov-2 Nanomachines: Mythological or Reality? *Current Stem Cell Research & Therapy* **2022**, *17*, 43.
(154) Munch, M. W.; Myatra, S. N.; Vijayaraghavan, B. K. T.; Saseedharan, S.; Benfield, T.; Wahlin, R. R.; Rasmussen, B. S.; Andreasen, A. S.; Poulsen, L. M.; Cioccari, L. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and Severe Hypoxemia: The COVID STEROID 2 randomized trial. *JAMA-Journal of the American Medical Association* **2021**, *326* (18), 1807−1817.
(155) Grzanka, A.; Misiołek, M.; Golusiński, W.; Jarząb, J. Molecular mechanisms of glucocorticoids action: implications for treatment of rhinosinusitis and nasal polyposis. *European Archives of Oto-Rhino-Laryngology* **2011**, *268* (2), 247−253.
(156) Greenwood, M. How does dexamethasone therapy work in severe COVID-19? *News Medical Life Science* **2021**.
(157) Ashrafizadeh, M.; Ahmadi, Z.; Kotla, N. G.; Afshar, E. G.; Samarghandian, S.; Mandegary, A.; Pardakhty, A.; Mohammadinejad, R.; Sethi, G. Nanoparticles targeting STATs in cancer therapy. *Cells* **2019**, *8* (10), 1158.
(158) Ashrafizadeh, M.; Ahmadi, Z.; Mohammadinejad, R.; Kaviyani, N.; Tavakol, S. Monoterpenes modulating autophagy: A review study. *Basic & Clinical Pharmacology & Toxicology* **2020**, *126* (1), 9−20.
(159) Kumar, R. Lipid-Based Nanoparticles for Drug-Delivery Systems. *Nanocarriers for Drug Delivery* **2019**, 249−284.
(160) Buse, J.; El-Aneed, A. Properties, engineering and applications of lipid-based nanoparticle drug-delivery systems: current research and advances. *Nanomedicine* **2010**, *5* (8), 1237−1260.
(161) Lorscheider, M.; Tsapis, N.; Gaudin, F.; Stolfa, I.; Abreu, S.; Mura, S.; Chaminade, P.; Espeli, M.; Fattal, E. Dexamethasone palmitate nanoparticles: An efficient treatment for rheumatoid arthritis. *J. Controlled Release* **2019**, *296*, 179−189.
(162) García-Pinel, B.; Porras-Alcalá, C.; Ortega-Rodríguez, A.; Sarabia, F.; Prados, J.; Melguizo, C.; López-Romero, J. M. Lipid-Based Nanoparticles: Application and Recent Advances in Cancer Treatment. *Nanomaterials* **2019**, *9* (4), 638.
(163) Puri, A.; Loomis, K.; Smith, B.; Lee, J.-H.; Yavlovich, A.; Heldman, E.; Blumenthal, R. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. *Crit Rev. Ther Drug Carrier Syst* **2009**, *26* (6), 523−580.
(164) Layek, B.; Gidwani, B.; Tiwari, S.; Joshi, V.; Jain, V.; Vyas, A. Recent advances in lipid-based nanodrug delivery systems in cancer therapy. *Curr. Pharm. Des.* **2020**, *26*, 3218.
(165) Fekri, H. S.; Ranjbar, M.; Pardakhty, A. A Systematic Study of Cu Nanospheres Embedded in Non-ionic Surfactant-Based Vesicle: Photocatalytic Efficiency and In Vivo Imaging Study. *Journal of Cluster Science* **2019**, *30* (3), 561−570.
(166) Tan, G.; Yu, S.; Li, J.; Pan, W. Development and characterization of nanostructured lipid carriers based chitosan thermosensitive hydrogel for delivery of dexamethasone. *Int. J. Biol. Macromol.* **2017**, *103*, 941−947.
(167) Dianzani, C.; Foglietta, F.; Ferrara, B.; Rosa, A. C.; Muntoni, E.; Gasco, P.; Della Pepa, C.; Canaparo, R.; Serpe, L. Solid lipid nanoparticles delivering anti-inflammatory drugs to treat inflammatory bowel disease: Effects in an in vivo model. *World J. Gastroenterol* **2017**, *23* (23), 4200−4210.
(168) Dukovski, B. J.; Plantić, I.; Čunčić, I.; Krtalić, I.; Juretić, M.; Pepić, I.; Lovrić, J.; Hafner, A. Lipid/alginate nanoparticle-loaded in situ gelling system tailored for dexamethasone nasal delivery. *Int. J. Pharm.* **2017**, *533* (2), 480−487.
(169) Liu, H.; Zhang, H.; Yin, N.; Zhang, Y.; Gou, J.; Yin, T.; He, H.; Ding, H.; Zhang, Y.; Tang, X. Sialic acid-modified dexamethasone lipid calcium phosphate gel core nanoparticles for target treatment of kidney injury. *Biomater Sci.* **2020**, *8* (14), 3871−3884.
(170) Hu, L.; Luo, X.; Zhou, S.; Zhu, J.; Xiao, M.; Li, C.; Zheng, H.; Qiu, Q.; Lai, C.; Liu, X.; Deng, Y.; Song, Y. Neutrophil-Mediated Delivery of Dexamethasone Palmitate-Loaded Liposomes Decorated with a Sialic Acid Conjugate for Rheumatoid Arthritis Treatment. *Pharm. Res.* **2019**, *36* (7), 97.
(171) Meka, R. R.; Venkatesha, S. H.; Acharya, B.; Moudgil, K. D. Peptide-targeted liposomal delivery of dexamethasone for arthritis therapy. *Nanomedicine (Lond)* **2019**, *14* (11), 1455−1469.
(172) Li, J.; Yang, J.; Wang, W.; Yu, J.; Fu, J.; Wang, X. A Novel Liposomal Dexamethasone Palmitate Formulation and Anti-inflammatory Effects on Mice. *Chin. J. Chem.* **2009**, *27* (7), 1411−1414.
(173) Benameur, H.; De Gand, G.; Brasseur, R.; Van Vooren, J.; Legros, F. Liposome-incorporated dexamethasone palmitate: Chemical and physical properties. *International journal of pharmaceutics* **1993**, *89* (3), 157−167.
(174) Tsotas, V.-A.; Mourtas, S.; Antimisiaris, S. G. Dexamethasone Incorporating Liposomes: Effect of Lipid Composition on Drug Trapping Efficiency and Vesicle Stability. *Drug Delivery* **2007**, *14* (7), 441−445.
(175) Jia, M.; Deng, C.; Luo, J.; Zhang, P.; Sun, X.; Zhang, Z.; Gong, T. A novel dexamethasone-loaded liposome alleviates rheumatoid arthritis in rats. *Int. J. Pharm.* **2018**, *540* (1−2), 57−64.
(176) Chang, M. C.; Kuo, Y. J.; Hung, K. H.; Peng, C. L.; Chen, K. Y.; Yeh, L. K. Liposomal dexamethasone-moxifloxacin nanoparticle combinations with collagen/gelatin/alginate hydrogel for corneal infection treatment and wound healing. *Biomed Mater.* **2020**, *15* (5), 055022.
(177) Sun, J.; Song, Y.; Lu, M.; Lin, X.; Liu, Y.; Zhou, S.; Su, Y.; Deng, Y. Evaluation of the antitumor effect of dexamethasone palmitate and doxorubicin co-loaded liposomes modified with a sialic acid-octadecylamine conjugate. *Eur. J. Pharm. Sci.* **2016**, *93*, 177−83.
(178) Deshantri, A. K.; Fens, M. H.; Ruiter, R. W. J.; Metselaar, J. M.; Storm, G.; van Bloois, L.; Varela-Moreira, A.; Mandhane, S. N.; Mutis, T.; Martens, A. C. M.; Groen, R. W. J.; Schiffelers, R. M. Liposomal dexamethasone inhibits tumor growth in an advanced human-mouse hybrid model of multiple myeloma. *J. Controlled Release* **2019**, *296*, 232−240.
(179) Madamsetty, V. S.; Paulus, A.; Akhtar, S.; Manna, A.; Rachamalla, H. R.; Banerjee, R.; Mukhopadhyay, D.; Chanan-Khan, A. Novel tumor-targeted liposomes comprised of an MDM2 antagonist plus proteasome inhibitor display anti-tumor activity in a xenograft model of bortezomib-resistant Waldenstrom macroglobulinemia. *Leuk Lymphoma* **2020**, *61* (10), 2399−2408.
(180) Kroon, J.; Buijs, J. T.; van der Horst, G.; Cheung, H.; van der Mark, M.; van Bloois, L.; Rizzo, L. Y.; Lammers, T.; Pelger, R. C.; Storm, G.; van der Pluijm, G.; Metselaar, J. M. Liposomal delivery of dexamethasone attenuates prostate cancer bone metastatic tumor growth In Vivo. *Prostate* **2015**, *75* (8), 815−824.
(181) Rwei, A. Y.; Sherburne, R. T.; Zurakowski, D.; Wang, B.; Kohane, D. S. Prolonged Duration Local Anesthesia Using Liposomal Bupivacaine Combined With Liposomal Dexamethasone and Dexmedetomidine. *Anesth Analg* **2018**, *126* (4), 1170−1175.
(182) Bartneck, M.; Scheyda, K. M.; Warzecha, K. T.; Rizzo, L. Y.; Hittatiya, K.; Luedde, T.; Storm, G.; Trautwein, C.; Lammers, T.; Tacke, F. Fluorescent cell-traceable dexamethasone-loaded liposomes

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

for the treatment of inflammatory liver diseases. *Biomaterials* **2015**, *37*, 367−82.
(183) Xu, X.; Wang, L.; Luo, Z.; Ni, Y.; Sun, H.; Gao, X.; Li, Y.; Zhang, S.; Li, Y.; Wei, S. Facile and Versatile Strategy for Construction of Anti-Inflammatory and Antibacterial Surfaces with Polydopamine-Mediated Liposomes Releasing Dexamethasone and Minocycline for Potential Implant Applications. *ACS Appl. Mater. Interfaces* **2017**, *9* (49), 43300−43314.
(184) Lin, T.-W.; Chien, Y.; Lin, Y.-Y.; Wang, M.-L.; Yarmishyn, A. A.; Yang, Y.-P.; Hwang, D.-K.; Peng, C.-H.; Hsu, C.-C.; Chen, S.-J.; Chien, K.-H. Establishing Liposome-Immobilized Dexamethasone-Releasing PDMS Membrane for the Cultivation of Retinal Pigment Epithelial Cells and Suppression of Neovascularization. *Int. J. Mol. Sci.* **2019**, *20* (2), 241.
(185) Mamelle, E.; Kechai, N. E.; Granger, B.; Sterkers, O.; Bochot, A.; Agnely, F.; Ferrary, E.; Nguyen, Y. Effect of a liposomal hyaluronic acid gel loaded with dexamethasone in a guinea pig model after manual or motorized cochlear implantation. *Eur. Arch Otorhinolaryngol* **2017**, *274* (2), 729−736.
(186) Yoon, J. Y.; Yang, K.-J.; Park, S.-N.; Kim, D.-K.; Kim, J.-D. The effect of dexamethasone/cell-penetrating peptide nanoparticles on gene delivery for inner ear therapy. *International journal of nanomedicine* **2016**, *11*, 6123.
(187) Gupta, S.; Bansal, R.; Gupta, S.; Jindal, N.; Jindal, A. Nanocarriers and nanoparticles for skin care and dermatological treatments. *Indian dermatology online journal* **2013**, *4* (4), 267.
(188) Makhmalzade, B. S.; Chavoshy, F. Polymeric micelles as cutaneous drug delivery system in normal skin and dermatological disorders. *J. Adv. Pharm. Technol. Res.* **2018**, *9* (1), 2−8.
(189) Sahle, F. F.; Gerecke, C.; Kleuser, B.; Bodmeier, R. Formulation and comparative in vitro evaluation of various dexamethasone-loaded pH-sensitive polymeric nanoparticles intended for dermal applications. *Int. J. Pharm.* **2017**, *516* (1−2), 21−31.
(190) Saeidpour, S.; Lohan, S. B.; Anske, M.; Unbehauen, M.; Fleige, E.; Haag, R.; Meinke, M. C.; Bittl, R.; Teutloff, C. Localization of dexamethasone within dendritic core-multishell (CMS) nanoparticles and skin penetration properties studied by multi-frequency electron paramagnetic resonance (EPR) spectroscopy. *Eur. J. Pharm. Biopharm* **2017**, *116*, 94−101.
(191) Chronopoulou, L.; Amalfitano, A.; Palocci, C.; Nocca, G.; Callà, C.; Arcovito, A. Dexamethasone-loaded biopolymeric nanoparticles promote gingival fibroblasts differentiation. *Biotechnol. Prog.* **2015**, *31* (5), 1381−7.
(192) Li, R.; Ma, Y.; Zhang, Y.; Zhang, M.; Sun, D. Potential of rhBMP-2 and dexamethasone-loaded Zein/PLLA scaffolds for enhanced in vitro osteogenesis of mesenchymal stem cells. *Colloids Surf. B Biointerfaces* **2018**, *169*, 384−394.
(193) Tsiapla, A.-R.; Karagkiozaki, V.; Bakola, V.; Pappa, F.; Gkertsiou, P.; Pavlidou, E.; Logothetidis, S. Biomimetic and biodegradable cellulose acetate scaffolds loaded with dexamethasone for bone implants. *Beilstein Journal of Nanotechnology* **2018**, *9*, 1986−1994.
(194) Lee, A.; De Mei, C.; Fereira, M.; Marotta, R.; Yoon, H. Y.; Kim, K.; Kwon, I. C.; Decuzzi, P. Dexamethasone-loaded Polymeric Nanoconstructs for Monitoring and Treating Inflammatory Bowel Disease. *Theranostics* **2017**, *7* (15), 3653−3666.
(195) Calles, J. A.; López-García, A.; Vallés, E. M.; Palma, S. D.; Diebold, Y. Preliminary characterization of dexamethasone-loaded cross-linked hyaluronic acid films for topical ocular therapy. *Int. J. Pharm.* **2016**, *509* (1−2), 237−243.
(196) Ran, J.; Zeng, H.; Pathak, J. L.; Jiang, P.; Bai, Y.; Yan, P.; Sun, G.; Shen, X.; Tong, H.; Shi, B. Constructing an Anisotropic Triple-Pass Tubular Framework within a Lyophilized Porous Gelatin Scaffold Using Dexamethasone-Loaded Functionalized Whatman Paper To Reinforce Its Mechanical Strength and Promote Osteogenesis. *Biomacromolecules* **2017**, *18* (11), 3788−3801.
(197) Ni, R.; Song, G.; Fu, X.; Song, R.; Li, L.; Pu, W.; Gao, J.; Hu, J.; Liu, Q.; He, F.; Zhang, D.; Huang, G. Reactive oxygen species-responsive dexamethasone-loaded nanoparticles for targeted treatment of rheumatoid arthritis via suppressing the iRhom2/TNF-α/BAFF signaling pathway. *Biomaterials* **2020**, *232*, 119730.
(198) Long, J.; Nand, A. V.; Bunt, C.; Seyfoddin, A. Controlled release of dexamethasone from poly(vinyl alcohol) hydrogel. *Pharm. Dev Technol.* **2019**, *24* (7), 839−848.
(199) Chen, Y.; Gu, J.; Liu, J.; Tong, L.; Shi, F.; Wang, X.; Wang, X.; Yu, D.; Wu, H. Dexamethasone-loaded injectable silk-polyethylene glycol hydrogel alleviates cisplatin-induced ototoxicity. *Int. J. Nanomedicine* **2019**, *14*, 4211−4227.
(200) Yüksel Aslıer, N. G.; Tağaç, A. A.; Durankaya, S. M.; Çalışır, M.; Ersoy, N.; Kırkım, G.; Yurdakoç, K.; Bağrıyanık, H. A.; Yılmaz, O.; Sütay, S.; Güneri, E. A. Dexamethasone-loaded chitosan-based genipin-cross-linked hydrogel for prevention of cisplatin induced ototoxicity in Guinea pig model. *Int. J. Pediatr Otorhinolaryngol* **2019**, *122*, 60−69.
(201) Heo, J. Y.; Noh, J. H.; Park, S. H.; Ji, Y. B.; Ju, H. J.; Kim, D. Y.; Lee, B.; Kim, M. S. An Injectable Click-Crosslinked Hydrogel that Prolongs Dexamethasone Release from Dexamethasone-Loaded Microspheres. *Pharmaceutics* **2019**, *11* (9), 438.
(202) Pramanik, A.; Sahoo, R. N.; Nanda, A.; Mohapatra, R.; Singh, R.; Mallick, S. Ocular Permeation and Sustained Anti-inflammatory Activity of Dexamethasone from Kaolin Nanodispersion Hydrogel System. *Curr. Eye Res.* **2018**, *43* (6), 828−838.
(203) Huang, J.; Wang, W.; Yu, J.; Yu, X.; Zheng, Q.; Peng, F.; He, Z.; Zhao, W.; Zhang, Z.; Li, X.; Wang, Q. Combination of dexamethasone and Avastin(®) by supramolecular hydrogel attenuates the inflammatory corneal neovascularization in rat alkali burn model. *Colloids Surf. B Biointerfaces* **2017**, *159*, 241−250.
(204) Zhang, Z.; Wei, X.; Gao, J.; Zhao, Y.; Zhao, Y.; Guo, L.; Chen, C.; Duan, Z.; Li, P.; Wei, L. Intra-Articular Injection of Cross-Linked Hyaluronic Acid-Dexamethasone Hydrogel Attenuates Osteoarthritis: An Experimental Study in a Rat Model of Osteoarthritis. *Int. J. Mol. Sci.* **2016**, *17* (4), 411.
(205) Ahmadi, N.; Gausterer, J. C.; Honeder, C.; Mötz, M.; Schöpper, H.; Zhu, C.; Saidov, N.; Gabor, F.; Arnoldner, C. Long-term effects and potential limits of intratympanic dexamethasone-loaded hydrogels combined with dexamethasone-eluting cochlear electrodes in a low-insertion trauma Guinea pig model. *Hear Res.* **2019**, *384*, 107825.
(206) Honeder, C.; Zhu, C.; Schöpper, H.; Gausterer, J. C.; Walter, M.; Landegger, L. D.; Saidov, N.; Riss, D.; Plasenzotti, R.; Gabor, F.; Arnoldner, C. Effects of sustained release dexamethasone hydrogels in hearing preservation cochlear implantation. *Hear Res.* **2016**, *341*, 43−49.
(207) Fan, M.; Ma, Y.; Zhang, Z.; Mao, J.; Tan, H.; Hu, X. Biodegradable hyaluronic acid hydrogels to control release of dexamethasone through aqueous Diels-Alder chemistry for adipose tissue engineering. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2015**, *56*, 311−7.
(208) Das, S.; Subuddhi, U. pH-Responsive guar gum hydrogels for controlled delivery of dexamethasone to the intestine. *Int. J. Biol. Macromol.* **2015**, *79*, 856−63.
(209) Bezuidenhout, D.; Oosthuysen, A.; Davies, N.; Ahrenstedt, L.; Dobner, S.; Roberts, P.; Zilla, P. Covalent incorporation and controlled release of active dexamethasone from injectable polyethylene glycol hydrogels. *J. Biomed Mater. Res. A* **2013**, *101* (5), 1311−8.
(210) Kalam, M. A. Development of chitosan nanoparticles coated with hyaluronic acid for topical ocular delivery of dexamethasone. *Int. J. Biol. Macromol.* **2016**, *89*, 127−36.
(211) Kalam, M. A. The potential application of hyaluronic acid coated chitosan nanoparticles in ocular delivery of dexamethasone. *Int. J. Biol. Macromol.* **2016**, *89*, 559−68.
(212) Behl, G.; Iqbal, J.; O'Reilly, N. J.; McLoughlin, P.; Fitzhenry, L. Synthesis and Characterization of Poly(2-hydroxyethylmethacrylate) Contact Lenses Containing Chitosan Nanoparticles as an Ocular Delivery System for Dexamethasone Sodium Phosphate. *Pharm. Res.* **2016**, *33* (7), 1638−48.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

(213) Zhang, Y.; Yue, Y.; Chang, M. Local anaesthetic pain relief therapy: In vitro and in vivo evaluation of a nanotechnological formulation co-loaded with ropivacaine and dexamethasone. *Biomed Pharmacother* **2017**, *96*, 443−449.
(214) Rençber, S.; Aydın Köse, F.; Karavana, S. Y. Dexamethasone loaded PLGA nanoparticles for potential local treatment of oral precancerous lesions. *Pharm. Dev Technol.* **2020**, *25* (2), 149−158.
(215) Kim, H. J.; Park, J. S.; Yi, S. W.; Oh, H. J.; Kim, J.-H.; Park, K.-H. Sequential transfection of RUNX2/SP7 and ATF4 coated onto dexamethasone-loaded nanospheres enhances osteogenesis. *Sci. Rep.* **2018**, *8* (1), 1447.
(216) Ghorbani, F.; Nojehdehian, H.; Zamanian, A. Physicochemical and mechanical properties of freeze cast hydroxyapatite-gelatin scaffolds with dexamethasone loaded PLGA microspheres for hard tissue engineering applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2016**, *69*, 208−20.
(217) Gasmi, H.; Siepmann, F.; Hamoudi, M. C.; Danede, F.; Verin, J.; Willart, J. F.; Siepmann, J. Towards a better understanding of the different release phases from PLGA microparticles: Dexamethasone-loaded systems. *Int. J. Pharm.* **2016**, *514* (1), 189−199.
(218) Resende, A. F. C.; Pereira, A. F.; Moreira, T. P.; Patrício, P. S. O.; Fialho, S. L.; Cunha, G. M. F.; Silva-Cunha, A.; Magalhães, J. T.; Silva, G. R. PLGA Implants containing vancomycin and dexamethasone: development, characterization and bactericidal effects. *Pharmazie* **2016**, *71* (8), 439−446.
(219) Wang, B.; Tang, Y.; Oh, Y.; Lamb, N. W.; Xia, S.; Ding, Z.; Chen, B.; Suarez, M. J.; Meng, T.; Kulkarni, V.; Eberhart, C. G.; Ensign, L. M.; Stark, W. J.; Hanes, J.; Xu, Q. Controlled release of dexamethasone sodium phosphate with biodegradable nanoparticles for preventing experimental corneal neovascularization. *Nanomedicine* **2019**, *17*, 119−123.
(220) Chiesa, E.; Pisani, S.; Colzani, B.; Dorati, R.; Conti, B.; Modena, T.; Braekmans, K.; Genta, I. Intra-Articular Formulation of GE11-PLGA Conjugate-Based NPs for Dexamethasone Selective Targeting-In Vitro Evaluation. *Int. J. Mol. Sci.* **2018**, *19* (8), 2304.
(221) Bode, C.; Kranz, H.; Siepmann, F.; Siepmann, J. In-situ forming PLGA implants for intraocular dexamethasone delivery. *Int. J. Pharm.* **2018**, *548* (1), 337−348.
(222) Lehner, E.; Gündel, D.; Liebau, A.; Plontke, S.; Mäder, K. Intracochlear PLGA based implants for dexamethasone release: Challenges and solutions. *International Journal of Pharmaceutics: X* **2019**, *1*, 100015.
(223) Rodríguez Villanueva, J.; Bravo-Osuna, I.; Herrero-Vanrell, R.; Molina Martínez, I. T.; Guzmán Navarro, M. Optimising the controlled release of dexamethasone from a new generation of PLGA-based microspheres intended for intravitreal administration. *Eur. J. Pharm. Sci.* **2016**, *92*, 287−97.
(224) Fornaguera, C.; Llinàs, M.; Solans, C.; Calderó, G. Design and in vitro evaluation of biocompatible dexamethasone-loaded nanoparticle dispersions, obtained from nano-emulsions, for inhalatory therapy. *Colloids Surf. B Biointerfaces* **2015**, *125*, 58−64.
(225) Gu, B.; Burgess, D. J. Prediction of dexamethasone release from PLGA microspheres prepared with polymer blends using a design of experiment approach. *International journal of pharmaceutics* **2015**, *495* (1), 393−403.
(226) Saeedi Garakani, S.; Davachi, S. M.; Bagher, Z.; Heraji Esfahani, A.; Jenabi, N.; Atoufi, Z.; Khanmohammadi, M.; Abbaspourrad, A.; Rashedi, H.; Jalessi, M. Fabrication of chitosan/polyvinylpyrrolidone hydrogel scaffolds containing PLGA microparticles loaded with dexamethasone for biomedical applications. *Int. J. Biol. Macromol.* **2020**, *164*, 356−370.
(227) Ohira, A.; Hara, K.; Jóhannesson, G.; Tanito, M.; Ásgrímsdóttir, G. M.; Lund, S. H.; Loftsson, T.; Stefánsson, E. Topical dexamethasone γ-cyclodextrin nanoparticle eye drops increase visual acuity and decrease macular thickness in diabetic macular oedema. *Acta Ophthalmol* **2015**, *93* (7), 610−5.
(228) Shulman, S.; Jóhannesson, G.; Stefánsson, E.; Loewenstein, A.; Rosenblatt, A.; Habot-Wilner, Z. Topical dexamethasone-cyclodextrin nanoparticle eye drops for non-infectious Uveitic macular oedema and vitritis - a pilot study. *Acta Ophthalmol* **2015**, *93* (5), 411−5.
(229) Mazet, R.; Choisnard, L.; Levilly, D.; Wouessidjewe, D.; Gèze, A. Investigation of Combined Cyclodextrin and Hydrogel Formulation for Ocular Delivery of Dexamethasone Acetate by Means of Experimental Designs. *Pharmaceutics* **2018**, *10* (4), 249.
(230) Khodaverdi, E.; Gharechahi, M.; Alibolandi, M.; Tekie, F. S. M.; Khashyarmanesh, B. Z.; Hadizadeh, F. Self-assembled supramolecular hydrogel based on PCL-PEG-PCL triblock copolymer and γ-cyclodextrin inclusion complex for sustained delivery of dexamethasone. *Int. J. Pharm. Investig* **2016**, *6* (2), 78−85.
(231) Fiorica, C.; Palumbo, F. S.; Pitarresi, G.; Bongiovì, F.; Giammona, G. Hyaluronic acid and beta cyclodextrins films for the release of corneal epithelial cells and dexamethasone. *Carbohydr. Polym.* **2017**, *166*, 281−290.
(232) Gan, Q.; Zhu, J.; Yuan, Y.; Liu, H.; Qian, J.; Li, Y.; Liu, C. A dual-delivery system of pH-responsive chitosan-functionalized mesoporous silica nanoparticles bearing BMP-2 and dexamethasone for enhanced bone regeneration. *J. Mater. Chem. B* **2015**, *3* (10), 2056−2066.
(233) Liebau, A.; Schilp, S.; Mugridge, K.; Schön, I.; Kather, M.; Kammerer, B.; Tillein, J.; Braun, S.; Plontke, S. K. Long-Term in vivo Release Profile of Dexamethasone-Loaded Silicone Rods Implanted Into the Cochlea of Guinea Pigs. *Frontiers in Neurology* **2020**, *10* (1377), DOI: 10.3389/fneur.2019.01377.
(234) Gulin-Sarfraz, T.; Jonasson, S.; Wigenstam, E.; von Haartman, E.; Bucht, A.; Rosenholm, J. M. Feasibility Study of Mesoporous Silica Particles for Pulmonary Drug Delivery: Therapeutic Treatment with Dexamethasone in a Mouse Model of Airway Inflammation. *Pharmaceutics* **2019**, *11* (4), 149.
(235) Luo, J.; Ding, X.; Song, W.; Bai, J.-Y.; Liu, J.; Li, Z.; Meng, F.-H.; Chen, F.-H.; Zhang, Y.-M. Inducing Macrophages M2 Polarization by Dexamethasone Laden Mesoporous Silica Nanoparticles from Titanium Implant Surface for Enhanced Osteogenesis. *Acta Metallurgica Sinica (English Letters)* **2019**, *32* (10), 1253−1260.
(236) Ban, J.; Zhang, Y.; Huang, X.; Deng, G.; Hou, D.; Chen, Y.; Lu, Z. Corneal permeation properties of a charged lipid nanoparticle carrier containing dexamethasone. *Int. J. Nanomed.* **2017**, *12*, 1329−1339.
(237) Wang, X.; Feng, Y.; Fu, J.; Wu, C.; He, B.; Zhang, H.; Wang, X.; Dai, W.; Sun, Y.; Zhang, Q. A Lipid Micellar System Loaded with Dexamethasone Palmitate Alleviates Rheumatoid Arthritis. *AAPS PharmSciTech* **2019**, *20* (8), DOI: 10.1208/s12249-019-1449-1.
(238) Mavaddati, M. A.; Moztarzadeh, F.; Baghbani, F. Effect of formulation and processing variables on dexamethasone entrapment and release of niosomes. *Journal of Cluster Science* **2015**, *26* (6), 2065−2078.
(239) Monteiro, N.; Martins, A.; Ribeiro, D.; Faria, S.; Fonseca, N. A.; Moreira, J. N.; Reis, R. L.; Neves, N. M. On the use of dexamethasone-loaded liposomes to induce the osteogenic differentiation of human mesenchymal stem cells. *Journal of Tissue Engineering and Regenerative Medicine* **2015**, *9* (9), 1056−1066.
(240) Chang, M.-C.; Kuo, Y.-J.; Hung, K.-H.; Peng, C.-L.; Chen, K.-Y.; Yeh, L.-K. Liposomal dexamethasone−moxifloxacin nanoparticles combinations with collagen/gelatin/alginate hydrogel for corneal infection treatment and wound healing. *Biomedical Materials* **2020**, *15*, 055022.
(241) Rahman, M.; Souto, E. B.; Alam, K.; Beg, S. Liposomal nanotherapeutics in cancer treatment. *Nanoformulation Strategies for Cancer Treatment*; Elsevier, 2021; pp 121−129.
(242) Bulbake, U.; Doppalapudi, S.; Kommineni, N.; Khan, W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics* **2017**, *9* (2), 12.
(243) Bobo, D.; Robinson, K. J.; Islam, J.; Thurecht, K. J.; Corrie, S. R. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. *Pharm. Res.* **2016**, *33* (10), 2373−2387.
(244) Kim, E.-M.; Jeong, H.-J. Liposomes: Biomedical Applications. *Chonnam medical journal* **2021**, *57* (1), 27.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

(245) Sercombe, L.; Veerati, T.; Moheimani, F.; Wu, S. Y.; Sood, A. K.; Hua, S. Advances and Challenges of Liposome Assisted Drug Delivery. *Frontiers in Pharmacology* **2015**, *6*, DOI: 10.3389/fphar.2015.00286.
(246) Varzandeh, M.; Mohammadinejad, R.; Esmaeilzadeh-Salestani, K.; Dehshahri, A.; Zarrabi, A.; Aghaei-Afshar, A. Photodynamic therapy for leishmaniasis: recent advances and future trends. *Photodiagnosis and Photodynamic Therapy* **2021**, *36*, 102609.
(247) Amoabediny, G.; Haghiralsadat, F.; Naderinezhad, S.; Helder, M. N.; Akhoundi Kharanaghi, E.; Mohammadnejad Arough, J.; Zandieh-Doulabi, B. Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: A comprehensive review. *International Journal of Polymeric Materials and Polymeric Biomaterials* **2018**, *67* (6), 383−400.
(248) Al-Amin, M. D.; Bellato, F.; Mastrotto, F.; Garofalo, M.; Malfanti, A.; Salmaso, S.; Caliceti, P. Dexamethasone Loaded Liposomes by Thin-Film Hydration and Microfluidic Procedures: Formulation Challenges. *Int. J. Mol. Sci.* **2020**, *21* (5), 1611.
(249) Wang, Q.; He, L.; Fan, D.; Liang, W.; Fang, J. Improving the anti-inflammatory efficacy of dexamethasone in the treatment of rheumatoid arthritis with polymerized stealth liposomes as a delivery vehicle. *J. Mater. Chem. B* **2020**, *8* (9), 1841−1851.
(250) Mukherjee, S.; Ray, S.; Thakur, R. S. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. *Indian J. Pharm. Sci.* **2009**, *71* (4), 349−358.
(251) Rostami, E.; Kashanian, S.; Azandaryani, A. H.; Faramarzi, H.; Dolatabadi, J. E. N.; Omidfar, K. Drug targeting using solid lipid nanoparticles. *Chemistry and physics of lipids* **2014**, *181*, 56−61.
(252) Pardeshi, C.; Rajput, P.; Belgamwar, V.; Tekade, A.; Patil, G.; Chaudhary, K.; Sonje, A. Solid lipid based nanocarriers: an overview. *Acta Pharmaceutica* **2012**, *62* (4), 433−472.
(253) Shah, R. M.; Eldridge, D. S.; Palombo, E. A.; Harding, I. H. Microwave-assisted formulation of solid lipid nanoparticles loaded with non-steroidal anti-inflammatory drugs. *International journal of pharmaceutics* **2016**, *515* (1−2), 543−554.
(254) Kumar, R.; Singh, A.; Garg, N.; Siril, P. F. Solid lipid nanoparticles for the controlled delivery of poorly water soluble non-steroidal anti-inflammatory drugs. *Ultrasonics sonochemistry* **2018**, *40*, 686−696.
(255) Xiang, Q.-y.; Wang, M.-t.; Chen, F.; Gong, T.; Jian, Y.-l.; Zhang, Z.-r.; Huang, Y. Lung-targeting delivery of dexamethasone acetate loaded solid lipid nanoparticles. *Archives of pharmacal research* **2007**, *30* (4), 519−525.
(256) Bukhari, S. I.; Imam, S. S.; Ahmad, M. Z.; Vuddanda, P. R.; Alshehri, S.; Mahdi, W. A.; Ahmad, J. Recent Progress in Lipid Nanoparticles for Cancer Theranostics: Opportunity and Challenges. *Pharmaceutics* **2021**, *13* (6), 840.
(257) Tan, J. Y. B.; Yoon, B. K.; Cho, N.-J.; Lovrić, J.; Jug, M.; Jackman, J. A. Lipid Nanoparticle Technology for Delivering Biologically Active Fatty Acids and Monoglycerides. *Int. J. Mol. Sci.* **2021**, *22* (18), 9664.
(258) Rocha, E. D.; Ferreira, M. R. S.; dos Santos Neto, E.; Barbosa, E. J.; Löbenberg, R.; Lourenço, F. R.; Bou-Chacra, N. Enhanced In Vitro Antimicrobial Activity of Polymyxin B−Coated Nanostructured Lipid Carrier Containing Dexamethasone Acetate. *Journal of Pharmaceutical Innovation* **2021**, *16* (1), 125−135.
(259) Huynh, N. T.; Passirani, C.; Saulnier, P.; Benoît, J.-P. Lipid nanocapsules: a new platform for nanomedicine. *International journal of pharmaceutics* **2009**, *379* (2), 201−209.
(260) Madamsetty, V. S.; Mukherjee, A.; Mukherjee, S. Recent Trends of the Bio-Inspired Nanoparticles in Cancer Theranostics. *Frontiers in Pharmacology* **2019**, *10* (1264), DOI: 10.3389/fphar.2019.01264.
(261) Kiss, E.; Berkó, S.; Gácsi, A.; Kovács, A.; Katona, G.; Soós, J.; Csányi, E.; Gróf, I.; Harazin, A.; Deli, M. A.; Budai-Szűcs, M. Design and Optimization of Nanostructured Lipid Carrier Containing Dexamethasone for Ophthalmic Use. *Pharmaceutics* **2019**, *11* (12), 679.
(262) Kumari, S.; Dandamudi, M.; Rani, S.; Behaeghel, E.; Behl, G.; Kent, D.; O'Reilly, N. J.; O'Donovan, O.; McLoughlin, P.; Fitzhenry, L. Dexamethasone-Loaded Nanostructured Lipid Carriers for the Treatment of Dry Eye Disease. *Pharmaceutics* **2021**, *13* (6), 905.
(263) Santos-Neto, E.; Spuri-Ferreira, M.; Ruiz-Alves, M.; Bou-Chacra, N. Chitosan Coated Nanostructured Lipid Carriers Containing Dexamethasone Acetate. *Investigative Ophthalmology & Visual Science* **2014**, *55* (13), 1445−1445.
(264) Marchiori, M. L.; Lubini, G.; Dalla Nora, G.; Friedrich, R. B.; Fontana, M. C.; Ourique, A. F.; Bastos, M. O.; Rigo, L. A.; Silva, C. B.; Tedesco, S. B.; Beck, R. C. R. Hydrogel containing dexamethasone-loaded nanocapsules for cutaneous administration: preparation, characterization, and in vitro drug release study. *Drug Dev. Ind. Pharm.* **2010**, *36* (8), 962−971.
(265) Dukovski, B. J.; Plantić, I.; Čunčić, I.; Krtalić, I.; Juretić, M.; Pepić, I.; Lovrić, J.; Hafner, A. Lipid/alginate nanoparticle-loaded in situ gelling system tailored for dexamethasone nasal delivery. *Int. J. Pharm.* **2017**, *533* (2), 480−487.
(266) Beber, T. C.; de Andrade, D. F.; Santos Chaves, P. d.; Pohlmann, A. R.; Guterres, S. S.; Ruver Beck, R. C. Cationic polymeric nanocapsules as a strategy to target dexamethasone to viable epidermis: skin penetration and permeation studies. *J. Nanosci. Nanotechnol.* **2016**, *16* (2), 1331−1338.
(267) Pena-Rodríguez, E.; Lajarin-Reinares, M.; Mata-Ventosa, A.; Pérez-Torras, S.; Fernández-Campos, F. Dexamethasone-Loaded Lipomers: Development, Characterization, and Skin Biodistribution Studies. *Pharmaceutics* **2021**, *13* (4), 533.
(268) El-Say, K. M.; El-Sawy, H. S. Polymeric nanoparticles: Promising platform for drug delivery. *Int. J. Pharm.* **2017**, *528* (1), 675−691.
(269) Calzoni, E.; Cesaretti, A.; Polchi, A.; Di Michele, A.; Tancini, B.; Emiliani, C. Biocompatible Polymer Nanoparticles for Drug Delivery Applications in Cancer and Neurodegenerative Disorder Therapies. *Journal of Functional Biomaterials* **2019**, *10* (1), 4.
(270) Espinosa-Cano, E.; Aguilar, M. R.; Portilla, Y.; Barber, D. F.; San Román, J. Polymeric Nanoparticles that Combine Dexamethasone and Naproxen for the Synergistic Inhibition of Il12b Transcription in Macrophages. *Macromol. Biosci.* **2020**, *20*, 2000002.
(271) Fekri, H. S.; Ranjbar, M.; Noudeh, G. D.; Ziasistani, N. Green synthesis of strontium nanoparticles self-assembled in the presence of carboxymethyl cellulose: an in vivo imaging study. *Luminescence* **2019**, *34* (8), 870−876.
(272) Alemzadeh, E.; Dehshahri, A.; Izadpanah, K.; Ahmadi, F. Plant virus nanoparticles: novel and robust nanocarriers for drug delivery and imaging. *Colloids Surf., B* **2018**, *167*, 20−27.
(273) Dehshahri, A.; Oskuee, R. K.; Ramezani, M. Plasmid DNA delivery into hepatocytes using a multifunctional nanocarrier based on sugar-conjugated polyethylenimine. *Gene Ther Mol. Biol.* **2012**, *14*, 62−71.
(274) Khalvati, B.; Sheikhsaran, F.; Sharifzadeh, S.; Kalantari, T.; Behzad Behbahani, A.; Jamshidzadeh, A.; Dehshahri, A. Delivery of plasmid encoding interleukin-12 gene into hepatocytes by conjugated polyethylenimine-based nanoparticles. *Artificial cells, nanomedicine, and biotechnology* **2017**, *45* (5), 1036−1044.
(275) Sheikhsaran, F.; Sadeghpour, H.; Khalvati, B.; Entezar-Almahdi, E.; Dehshahri, A. Tetraiodothyroacetic acid-conjugated polyethylenimine for integrin receptor mediated delivery of the plasmid encoding IL-12 gene. *Colloids Surf., B* **2017**, *150*, 426−436.
(276) Dehshahri, A.; Sadeghpour, H.; Mohazzabieh, E.; Saatchi Avval, S.; Mohammadinejad, R. Targeted double domain nanoplex based on galactosylated polyethylenimine enhanced the delivery of IL-12 plasmid. *Biotechnology Progress* **2020**, *36* (5), e3002.
(277) Sung, Y. K.; Kim, S. W. Recent advances in polymeric drug delivery systems. *Biomaterials Research* **2020**, *24* (1), 12.
(278) Liechty, W. B.; Kryscio, D. R.; Slaughter, B. V.; Peppas, N. A. Polymers for drug delivery systems. *Annu. Rev. Chem. Biomol Eng.* **2010**, *1*, 149−173.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

(279) Chan, J. M.; Valencia, P. M.; Zhang, L.; Langer, R.; Farokhzad, O. C. Polymeric Nanoparticles for Drug Delivery. *Cancer Nanotechnology* **2010**, *624*, 163−175.
(280) Saini, R. K.; Bagri, L. P.; Bajpai, A. K.; Mishra, A. Responsive polymer nanoparticles for drug delivery applications. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications* **2018**, *1*, 289−320.
(281) Peine, K. J.; Guerau-de-Arellano, M.; Lee, P.; Kanthamneni, N.; Severin, M.; Probst, G. D.; Peng, H.; Yang, Y.; Vangundy, Z.; Papenfuss, T. L. Treatment of experimental autoimmune encephalomyelitis by codelivery of disease associated Peptide and dexamethasone in acetalated dextran microparticles. *Mol. Pharmaceutics* **2014**, *11* (3), 828−835.
(282) Shakeri, S.; Ashrafizadeh, M.; Zarrabi, A.; Roghanian, R.; Afshar, E. G.; Pardakhty, A.; Mohammadinejad, R.; Kumar, A.; Thakur, V. K. Multifunctional polymeric nanoplatforms for brain diseases diagnosis, therapy and theranostics. *Biomedicines* **2020**, *8* (1), 13.
(283) Dehshahri, A.; Sadeghpour, H.; Oskuee, R. K.; Fadaei, M.; Sabahi, Z.; Alhashemi, S. H.; Mohazabieh, E. Interleukin-12 plasmid DNA delivery using l-thyroxine-conjugated polyethylenimine nanocarriers. *J. Nanopart. Res.* **2014**, *16* (5), 2423.
(284) Ede, B. C.; Diamanti, P.; Williams, D. S.; Blair, A. Non-toxic polymer nanovectors for improved delivery of dexamethasone. *Sci. Rep.* **2021**, *11* (1), 1−7.
(285) Li, M.; Jiang, S.; Haller, A.; Wirsching, S.; Fichter, M.; Simon, J.; Wagner, M.; Mailänder, V.; Gehring, S.; Crespy, D. Encapsulation of polyprodrugs enables an efficient and controlled release of dexamethasone. *Nanoscale Horizons* **2021**, *6* (10), 791−800.
(286) Nižić Nodilo, L.; Ugrina, I.; Špoljarić, D.; Amidžić Klarić, D.; Jakobušić Brala, C.; Perkušić, M.; Pepić, I.; Lovrić, J.; Saršon, V.; Safundžić Kučuk, M. A Dry Powder Platform for Nose-to-Brain Delivery of Dexamethasone: Formulation Development and Nasal Deposition Studies. *Pharmaceutics* **2021**, *13* (6), 795.
(287) Etxabide, A.; Long, J.; Guerrero, P.; de la Caba, K.; Seyfoddin, A. 3D printed lactose-crosslinked gelatin scaffolds as a drug delivery system for dexamethasone. *Eur. Polym. J.* **2019**, *114*, 90−97.
(288) Abdelkader, H.; Fathalla, Z.; Seyfoddin, A.; Farahani, M.; Thrimawithana, T.; Allahham, A.; Alani, A. W.; Al-Kinani, A. A.; Alany, R. G. Polymeric long-acting drug delivery systems (LADDS) for treatment of chronic diseases: Inserts, patches, wafers, and implants. *Adv. Drug Delivery Rev.* **2021**, *177*, 113957.
(289) Zidan, G.; Greene, C. A.; Etxabide, A.; Rupenthal, I. D.; Seyfoddin, A. Gelatine-based drug-eluting bandage contact lenses: Effect of PEGDA concentration and manufacturing technique. *Int. J. Pharm.* **2021**, *599*, 120452.
(290) Kumadoh, D.; Adi-Dako, O.; Osei, Y. A.; Archer, M. A. Recent Trends in Applications of Nano-Drug Delivery Systems. *Handbook of Lung Targeted Drug Delivery Systems: Recent Trends and Clinical Evidences* **2021**, *8*, 225.
(291) Sur, S.; Rathore, A.; Dave, V.; Reddy, K. R.; Chouhan, R. S.; Sadhu, V. Recent developments in functionalized polymer nanoparticles for efficient drug delivery system. *Nano-Structures & Nano-Objects* **2019**, *20*, 100397.
(292) Brusini, R.; Varna, M.; Couvreur, P. Advanced nanomedicines for the treatment of inflammatory diseases. *Adv. Drug Delivery Rev.* **2020**, *157*, 161.
(293) Martín-Saldaña, S.; Palao-Suay, R.; Aguilar, M. R.; Ramírez-Camacho, R.; San Román, J. Polymeric nanoparticles loaded with dexamethasone or α-tocopheryl succinate to prevent cisplatin-induced ototoxicity. *Acta Biomaterialia* **2017**, *53*, 199−210.
(294) Sun, C.; Wang, X.; Chen, D.; Lin, X.; Yu, D.; Wu, H. Dexamethasone loaded nanoparticles exert protective effects against Cisplatin-induced hearing loss by systemic administration. *Neurosci. Lett.* **2016**, *619*, 142−148.
(295) Alami-Milani, M.; Zakeri-Milani, P.; Valizadeh, H.; Sattari, S.; Salatin, S.; Jelvehgari, M. Evaluation of anti-inflammatory impact of dexamethasone-loaded PCL-PEG-PCL micelles on endotoxin-induced uveitis in rabbits. *Pharm. Dev. Technol.* **2019**, *24* (6), 680−688.
(296) Peers, S.; Montembault, A.; Ladavière, C. Chitosan hydrogels incorporating colloids for sustained drug delivery. *Carbohydr. Polym.* **2022**, *275*, 118689.
(297) Ashrafizadeh, M.; Ahmadi, Z.; Mohamadi, N.; Zarrabi, A.; Abasi, S.; Dehghannoudeh, G.; Tamaddondoust, R. N.; Khanbabaei, H.; Mohammadinejad, R.; Thakur, V. K. Chitosan-based advanced materials for docetaxel and paclitaxel delivery: Recent advances and future directions in cancer theranostics. *Int. J. Biol. Macromol.* **2020**, *145*, 282−300.
(298) Madamsetty, V. S.; Tavakol, S.; Moghassemi, S.; Dadashzadeh, A.; Schneible, J. D.; Fatemi, I.; Shirvani, A.; Zarrabi, A.; Azedi, F.; Dehshahri, A. Chitosan: A versatile bio-platform for breast cancer theranostics. *J. Controlled Release* **2022**, *341*, 733−752.
(299) Kalam, M. A. Development of chitosan nanoparticles coated with hyaluronic acid for topical ocular delivery of dexamethasone. *Int. J. Biol. Macromol.* **2016**, *89*, 127−136.
(300) Rodrigues, L. B.; Leite, H. F.; Yoshida, M. I.; Saliba, J. B.; Junior, A. S. C.; Faraco, A. A. G. In vitro release and characterization of chitosan films as dexamethasone carrier. *Int. J. Pharm.* **2009**, *368* (1), 1−6.
(301) Tan, G.; Yu, S.; Li, J.; Pan, W. Development and characterization of nanostructured lipid carriers based chitosan thermosensitive hydrogel for delivery of dexamethasone. *Int. J. Biol. Macromol.* **2017**, *103*, 941−947.
(302) Xu, F.; Yin, M.; Wu, Y.; Ding, H.; Song, F.; Wang, J. Effects of drying methods on the preparation of dexamethasone-loaded chitosan microspheres. *Biomed. Mater.* **2014**, *9*, 055003.
(303) Han, L.; Wang, Z.-m.; Lu, X.; Dong, L.; Xie, C.-m.; Wang, K.-f.; Chen, X.-l.; Ding, Y.-h.; Weng, L.-t. Mussel-inspired adhesive and transferable free-standing films by self-assembling dexamethasone encapsulated BSA nanoparticles and vancomycin immobilized oxidized alginate. *Colloids Surf., B* **2015**, *126*, 452−458.
(304) Karava, A.; Lazaridou, M.; Nanaki, S.; Michailidou, G.; Christodoulou, E.; Kostoglou, M.; Iatrou, H.; Bikiaris, D. N. Chitosan Derivatives with Mucoadhesive and Antimicrobial Properties for Simultaneous Nanoencapsulation and Extended Ocular Release Formulations of Dexamethasone and Chloramphenicol Drugs. *Pharmaceutics* **2020**, *12*, 594.
(305) Akrami-Hasan-Kohal, M.; Eskandari, M.; Solouk, A. Silk fibroin hydrogel/dexamethasone sodium phosphate loaded chitosan nanoparticles as a potential drug delivery system. *Colloids Surf., B* **2021**, *205*, 111892.
(306) Xu, X.; Sun, L.; Zhou, L.; Cheng, Y.; Cao, F. Functional chitosan oligosaccharide nanomicelles for topical ocular drug delivery of dexamethasone. *Carbohydr. Polym.* **2020**, *227*, 115356.
(307) Oshi, M. A.; Naeem, M.; Bae, J.; Kim, J.; Lee, J.; Hasan, N.; Kim, W.; Im, E.; Jung, Y.; Yoo, J.-W. Colon-targeted dexamethasone microcrystals with pH-sensitive chitosan/alginate/Eudragit S multilayers for the treatment of inflammatory bowel disease. *Carbohydr. Polym.* **2018**, *198*, 434−442.
(308) Shrestha, S.; Diogenes, A.; Kishen, A. Temporal-controlled dexamethasone releasing chitosan nanoparticle system enhances odontogenic differentiation of stem cells from apical papilla. *Journal of endodontics* **2015**, *41* (8), 1253−1258.
(309) Yu, A.; Shi, H.; Liu, H.; Bao, Z.; Dai, M.; Lin, D.; Lin, D.; Xu, X.; Li, X.; Wang, Y. Mucoadhesive dexamethasone-glycol chitosan nanoparticles for ophthalmic drug delivery. *Int. J. Pharm.* **2020**, *575*, 118943.
(310) Dubashynskaya, N. V.; Golovkin, A. S.; Kudryavtsev, I. V.; Prikhodko, S. S.; Trulioff, A. S.; Bokatyi, A. N.; Poshina, D. N.; Raik, S. V.; Skorik, Y. A. Mucoadhesive cholesterol-chitosan self-assembled particles for topical ocular delivery of dexamethasone. *Int. J. Biol. Macromol.* **2020**, *158*, 811−818.
(311) Raquez, J.-M.; Habibi, Y.; Murariu, M.; Dubois, P. Polylactide (PLA)-based nanocomposites. *Prog. Polym. Sci.* **2013**, *38* (10), 1504−1542.
(312) Casalini, T.; Rossi, F.; Castrovinci, A.; Perale, G. A Perspective on Polylactic Acid-Based Polymers Use for Nanoparticles Synthesis

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

and Applications. *Frontiers in Bioengineering and Biotechnology* **2019**, *7*, DOI: 10.3389/fbioe.2019.00259.
(313) Park, J. H.; Kwon, D. Y.; Heo, J. Y.; Park, S. H.; Park, J. Y.; Lee, B.; Kim, J. H.; Kim, M. S. Effect of drug carrier melting points on drug release of dexamethasone-loaded microspheres. *Tissue Engineering and Regenerative Medicine* **2017**, *14* (6), 743−753.
(314) Assali, M.; Shawahna, R.; Shareef, M.; Alhimony, I.-A. Dexamethasone-diclofenac loaded polylactide nanoparticles: Preparation, release and anti-inflammatory activity. *European Journal of Pharmaceutical Sciences* **2018**, *122*, 179−184.
(315) Samarehfekri, H.; Ranjbar, M.; Pardakhty, A.; Amanatfard, A. Systematic Study of NaF Nanoparticles in Micelles loaded on Polylactic Acid Nanoscaffolds: In Vitro Efficient Delivery. *Journal of Cluster Science* **2020**, *31* (2), 453−461.
(316) Da Silva, J.; Jesus, S.; Bernardi, N.; Colaço, M.; Borges, O. Poly(D,L-Lactic Acid) Nanoparticle Size Reduction Increases Its Immunotoxicity. *Frontiers in Bioengineering and Biotechnology* **2019**, *7*, DOI: 10.3389/fbioe.2019.00137.
(317) Dehshahri, A.; Ashrafizadeh, M.; Afshar, E. G.; Pardakhty, A.; Mandegary, A.; Mohammadinejad, R.; Sethi, G. Topoisomerase inhibitors: Pharmacology and emerging nanoscale delivery systems. *Pharmacological Research* **2020**, *151*, 104551.
(318) Woodard, L. N.; Grunlan, M. A. Hydrolytic Degradation and Erosion of Polyester Biomaterials. *ACS Macro Lett.* **2018**, *7* (8), 976−982.
(319) Yu, D.; Wu, H.; Sun, C.; Shi, F.; Wang, X.; Zheng, Z.; Chen, D.; Wang, X. A single dose of dexamethasone encapsulated in polyethylene glycol-coated polylactic acid nanoparticles attenuates cisplatin-induced hearing loss following round window membrane administration. *Int. J. Nanomed.* **2015**, 3567.
(320) Fratoddi, I.; Venditti, I.; Cametti, C.; Palocci, C.; Chronopoulou, L.; Marino, M.; Acconcia, F.; Russo, M. V. Functional polymeric nanoparticles for dexamethasone loading and release. *Colloids Surf., B* **2012**, *93*, 59−66.
(321) Bala, I.; Hariharan, S.; Kumar, M. N. V. R. PLGA Nanoparticles in Drug Delivery: The State of the Art. *Crit Rev. Ther Drug Carrier Syst* **2004**, *21* (5), 387−422.
(322) Rezvantalab, S.; Drude, N. I.; Moraveji, M. K.; Güvener, N.; Koons, E. K.; Shi, Y.; Lammers, T.; Kiessling, F. PLGA-Based Nanoparticles in Cancer Treatment. *Frontiers in Pharmacology* **2018**, *9*, DOI: 10.3389/fphar.2018.01260,
(323) Pawley, D. C.; Goncalves, S.; Bas, E.; Dikici, E.; Deo, S. K.; Daunert, S.; Telischi, F. Dexamethasone (DXM)-Coated Poly (lactic-co-glycolic acid)(PLGA) Microneedles as an Improved Drug Delivery System for Intracochlear Biodegradable Devices. *Advanced Therapeutics* **2021**, *4* (11), 2100155.
(324) Kim, S. H.; Kim, J. E.; Kim, S. H.; Jung, Y. Substance P/dexamethasone-encapsulated PLGA scaffold fabricated using supercritical fluid process for calvarial bone regeneration. *Journal of tissue engineering and regenerative medicine* **2017**, *11* (12), 3469−3480.
(325) Mahmoodi, Z.; Mohammadnejad, J.; Razavi Bazaz, S.; Abouei Mehrizi, A.; Ghiass, M. A.; Saidijam, M.; Dinarvand, R.; Ebrahimi Warkiani, M.; Soleimani, M. A simple coating method of PDMS microchip with PTFE for synthesis of dexamethasone-encapsulated PLGA nanoparticles. *Drug Delivery and Translational Research* **2019**, *9* (3), 707−720.
(326) Gómez-Gaete, C.; Tsapis, N.; Besnard, M.; Bochot, A.; Fattal, E. Encapsulation of dexamethasone into biodegradable polymeric nanoparticles. *Int. J. Pharm.* **2007**, *331* (2), 153−159.
(327) Kim, S.-H.; Moon, J.-H.; Jeong, S.-U.; Jung, H.-H.; Park, C.-S.; Hwang, B. Y.; Lee, C.-K. Induction of antigen-specific immune tolerance using biodegradable nanoparticles containing antigen and dexamethasone. *Int. J. Nanomed.* **2019**, *14*, 5229−5242.
(328) Liu, J.; Zhang, X.; Li, G.; Xu, F.; Li, S.; Teng, L.; Li, Y.; Sun, F. Anti-Angiogenic Activity Of Bevacizumab-Bearing Dexamethasone-Loaded PLGA Nanoparticles For Potential Intravitreal Applications. *Int. J. Nanomed.* **2019**, *14*, 8819−8834.
(329) Stefani, R. M.; Lee, A. J.; Tan, A. R.; Halder, S. S.; Hu, Y.; Guo, X. E.; Stoker, A. M.; Ateshian, G. A.; Marra, K. G.; Cook, J. L.; Hung, C. T. Sustained low-dose dexamethasone delivery via a PLGA microsphere-embedded agarose implant for enhanced osteochondral repair. *Acta Biomaterialia* **2020**, *102*, 326−340.
(330) Tiwari, G.; Tiwari, R.; Rai, A. Cyclodextrins in delivery systems: Applications. *Journal of Pharmacy and Bioallied Sciences* **2010**, *2* (2), 72.
(331) Loftsson, T.; Jarho, P.; Másson, M.; Järvinen, T. Cyclodextrins in drug delivery. *Expert Opinion on Drug Delivery* **2005**, *2* (2), 335−351.
(332) Agu, R. U.; Vu Dang, H.; Jorissen, M.; Willems, T.; Kinget, R.; Verbeke, N. Nasal absorption enhancement strategies for therapeutic peptides: an in vitro study using cultured human nasal epithelium. *Int. J. Pharm.* **2002**, *237* (1−2), 179−191.
(333) Ashrafizadeh, M.; Hushmandi, K.; Rahmani Moghadam, E.; Zarrin, V.; Hosseinzadeh Kashani, S.; Bokaie, S.; Najafi, M.; Tavakol, S.; Mohammadinejad, R.; Nabavi, N. Progress in delivery of siRNA-based therapeutics employing nano-vehicles for treatment of prostate cancer. *Bioengineering* **2020**, *7* (3), 91.
(334) Imamachi, K.; Stefánsson, E.; Ohira, A.; Tanito, M. Treatment of non-infectious ophthalmic inflammatory diseases with 1.5% dexamethasone γ-cyclodextrin nanoparticle eye drops. *Acta Ophthalmologica* **2019**, *97* (8), 824−827.
(335) Piras, A. M.; Zambito, Y.; Burgalassi, S.; Monti, D.; Tampucci, S.; Terreni, E.; Fabiano, A.; Balzano, F.; Uccello-Barretta, G.; Chetoni, P. A water-soluble, mucoadhesive quaternary ammonium chitosan-methyl-β-cyclodextrin conjugate forming inclusion complexes with dexamethasone. *J. Mater. Sci.: Mater. Med.* **2018**, *29* (4), 42.
(336) Lee, S. J.; Choi, J. S.; Eom, M. R.; Jo, H. H.; Kwon, I. K.; Kwon, S. K.; Park, S. A. Dexamethasone loaded bilayered 3D tubular scaffold reduces restenosis at the anastomotic site of tracheal replacement: in vitro and in vivo assessments. *Nanoscale* **2020**, *12* (8), 4846−4858.
(337) Mohammadinejad, R.; Maleki, H.; Larrañeta, E.; Fajardo, A. R.; Nik, A. B.; Shavandi, A.; Sheikhi, A.; Ghorbanpour, M.; Farokhi, M.; Govindh, P. Status and future scope of plant-based green hydrogels in biomedical engineering. *Applied Materials Today* **2019**, *16*, 213−246.
(338) Alhadlaq, A.; Tang, M.; Mao, J. J. Engineered adipose tissue from human mesenchymal stem cells maintains predefined shape and dimension: implications in soft tissue augmentation and reconstruction. *Tissue engineering* **2005**, *11* (3−4), 556−566.
(339) Li, J.; Mooney, D. J. Designing hydrogels for controlled drug delivery. *Nature Reviews Materials* **2016**, *1* (12), 16071.
(340) Ashrafizadeh, M.; Zarrabi, A.; Hushmandi, K.; Hashemi, F.; Rahmani Moghadam, E.; Raei, M.; Kalantari, M.; Tavakol, S.; Mohammadinejad, R.; Najafi, M. Progress in natural compounds/siRNA co-delivery employing nanovehicles for cancer therapy. *ACS Combinatorial Science* **2020**, *22* (12), 669−700.
(341) Narayanaswamy, R.; Torchilin, V. P. Hydrogels and Their Applications in Targeted Drug Delivery. *Molecules* **2019**, *24* (3), 603.
(342) Hoare, T. R.; Kohane, D. S. Hydrogels in drug delivery: Progress and challenges. *Polymer* **2008**, *49* (8), 1993−2007.
(343) Dehshahri, A.; Kumar, A.; Madamsetty, V. S.; Uzieliene, I.; Tavakol, S.; Azedi, F.; Fekri, H. S.; Zarrabi, A.; Mohammadinejad, R.; Thakur, V. K. New Horizons in Hydrogels for Methotrexate Delivery. *Gels* **2021**, *7* (1), 2.
(344) Bao, Z.; Yu, A.; Shi, H.; Hu, Y.; Jin, B.; Lin, D.; Dai, M.; Lei, L.; Li, X.; Wang, Y. Glycol chitosan/oxidized hyaluronic acid hydrogel film for topical ocular delivery of dexamethasone and levofloxacin. *Int. J. Biol. Macromol.* **2021**, *167*, 659−666.
(345) Peppas, N. A.; Hoffman, A. S. Hydrogels. *Biomaterials science*; Elsevier, 2020; pp 153−166.
(346) Jeong, D. U.; Bae, S.; Macks, C.; Whitaker, J.; Lynn, M.; Webb, K.; Lee, J. S. Hydrogel-mediated local delivery of dexamethasone reduces neuroinflammation after traumatic brain injury. *Biomedical Materials* **2021**, *16* (3), 035002.
(347) Nautiyal, U.; Sahu, N.; Gupta, D. Hydrogel: Preparation, Characterization and Applications. *Asian Pacific Journal of Nursing and Health Sciences* **2020**, *3* (1), 1.

(348) Thakur, S.; Sharma, B.; Verma, A.; Chaudhary, J.; Tamulevicius, S.; Thakur, V. K. Recent progress in sodium alginate based sustainable hydrogels for environmental applications. *Journal of cleaner production* **2018**, *198*, 143−159.
(349) Varaprasad, K.; Raghavendra, G. M.; Jayaramudu, T.; Yallapu, M. M.; Sadiku, R. A mini review on hydrogels classification and recent developments in miscellaneous applications. *Materials Science and Engineering: C* **2017**, *79*, 958−971.
(350) Ahmed, E. M. Hydrogel: Preparation, characterization, and applications: A review. *Journal of advanced research* **2015**, *6* (2), 105−121.
(351) Zhang, Y. S.; Khademhosseini, A. Advances in Engineering Hydrogels. *Science* **2017**, *356* (6337), DOI: 10.1126/science.aaf3627.
(352) Chauhan, N.; Gupta, P.; Arora, L.; Pal, D.; Singh, Y. Dexamethasone-loaded, injectable pullulan-poly (ethylene glycol) hydrogels for bone tissue regeneration in chronic inflammatory conditions. *Materials Science and Engineering: C* **2021**, *130*, 112463.
(353) Zhang, R.; Lei, L.; Song, Q.; Li, X. Calcium ion cross-linking alginate/dexamethasone sodium phosphate hybrid hydrogel for extended drug release. *Colloids Surf., B* **2019**, *175*, 569−575.
(354) Wu, W.; Zhang, Z.; Xiong, T.; Zhao, W.; Jiang, R.; Chen, H.; Li, X. Calcium ion coordinated dexamethasone supramolecular hydrogel as therapeutic alternative for control of non-infectious uveitis. *Acta Biomaterialia* **2017**, *61*, 157−168.
(355) Yu, D.; Sun, C.; Zheng, Z.; Wang, X.; Chen, D.; Wu, H.; Wang, X.; Shi, F. Inner ear delivery of dexamethasone using injectable silk-polyethylene glycol (PEG) hydrogel. *Int. J. Pharm.* **2016**, *503* (1−2), 229−237.
(356) Mohammadinejad, R.; Ashrafizadeh, M.; Pardakhty, A.; Uzieliene, I.; Denkovskij, J.; Bernotiene, E.; Janssen, L.; Lorite, G. S.; Saarakkala, S.; Mobasheri, A. Nanotechnological strategies for osteoarthritis diagnosis, monitoring, clinical management, and regenerative medicine: recent advances and future opportunities. *Current Rheumatology Reports* **2020**, *22* (4), 1−17.
(357) Mohammadinejad, R.; Madamsetty, V. S.; Kumar, A.; Varzandeh, M.; Dehshahri, A.; Zarrabi, A.; Sharififar, F.; Mohammadi, M.; Fahimipour, A.; Ramakrishna, S. Electrospun nanocarriers for delivering natural products for cancer therapy. *Trends in Food Science & Technology* **2021**, *118*, 887−904.
(358) Kumar, S.; Singh, A. P.; Senapati, S.; Maiti, P. Controlling drug delivery using nanosheet-embedded electrospun fibers for efficient tumor treatment. *ACS Applied Bio Materials* **2019**, *2* (2), 884−894.
(359) Li, L.; Zhou, G.; Wang, Y.; Yang, G.; Ding, S.; Zhou, S. Controlled dual delivery of BMP-2 and dexamethasone by nanoparticle-embedded electrospun nanofibers for the efficient repair of critical-sized rat calvarial defect. *Biomaterials* **2015**, *37*, 218−229.
(360) Lee, J. W.; Lee, H. Y.; Park, S. H.; Park, J. H.; Kim, J. H.; Min, B. H.; Kim, M. S. Preparation and evaluation of dexamethasone-loaded electrospun nanofiber sheets as a sustained drug delivery system. *Materials* **2016**, *9* (3), 175.
(361) Da Silva, G. R.; Lima, T. H.; Fernandes-Cunha, G. M.; Oréfice, R. L.; Da Silva-Cunha, A.; Zhao, M.; Behar-Cohen, F. Ocular biocompatibility of dexamethasone acetate loaded poly (ε-caprolactone) nanofibers. *Eur. J. Pharm. Biopharm.* **2019**, *142*, 20−30.
(362) Nadim, A.; Khorasani, S. N.; Kharaziha, M.; Davoodi, S. M. Design and characterization of dexamethasone-loaded poly (glycerol sebacate)-poly caprolactone/gelatin scaffold by coaxial electro spinning for soft tissue engineering. *Materials Science and Engineering: C* **2017**, *78*, 47−58.
(363) Lim, H.-C.; Nam, O. H.; Kim, M.-j.; El-Fiqi, A.; Yun, H.-M.; Lee, Y.-M.; Jin, G.-Z.; Lee, H.-H.; Kim, H.-W.; Kim, E.-C. Delivery of dexamethasone from bioactive nanofiber matrices stimulates odontogenesis of human dental pulp cells through integrin/BMP/mTOR signaling pathways. *International journal of nanomedicine* **2016**, *11*, 2557.
(364) Hsu, K.-H.; Fang, S.-P.; Lin, C.-L.; Liao, Y.-S.; Yoon, Y.-K.; Chauhan, A. Hybrid electrospun polycaprolactone mats consisting of nanofibers and microbeads for extended release of dexamethasone. *Pharm. Res.* **2016**, *33* (6), 1509−1516.
(365) Zhang, Z.; Yu, J.; Zhou, Y.; Zhang, R.; Song, Q.; Lei, L.; Li, X. Supramolecular nanofibers of dexamethasone derivatives to form hydrogel for topical ocular drug delivery. *Colloids Surf., B* **2018**, *164*, 436−443.
(366) Webber, M. J.; Matson, J. B.; Tamboli, V. K.; Stupp, S. I. Controlled release of dexamethasone from peptide nanofiber gels to modulate inflammatory response. *Biomaterials* **2012**, *33* (28), 6823−6832.
(367) Chen, W.; Li, D.; Ahmed, E.-S.; El-Newehy, M.; EI-Hamshary, H. A.; Al-Deyab, S. S.; He, C.; Mo, X. Dexamethasone loaded core−shell SF/PEO nanofibers via green electrospinning reduced endothelial cells inflammatory damage. *Colloids Surf., B* **2015**, *126*, 561−568.
(368) Yu, S.; Yang, S.; Holsboer, F.; Sousa, N.; Almeida, O. F. Glucocorticoid regulation of astrocytic fate and function. *PLoS one* **2011**, *6* (7), e22419.
(369) Boroojen, F. R.; Mashayekhan, S.; Abbaszadeh, H.-A. The controlled release of dexamethasone sodium phosphate from bioactive electrospun PCL/gelatin nanofiber scaffold. *Iranian Journal of Pharmaceutical Research* **2019**, *18* (1), 111.
(370) Levingstone, T. J.; Herbaj, S.; Dunne, N. J. Calcium Phosphate Nanoparticles for Therapeutic Applications in Bone Regeneration. *Nanomaterials* **2019**, *9* (11), 1570.
(371) Chen, Y.; Chen, S.; Kawazoe, N.; Chen, G. Promoted angiogenesis and osteogenesis by dexamethasone-loaded calcium phosphate nanoparticles/collagen composite scaffolds with microgroove networks. *Sci. Rep.* **2018**, *8* (1), 14143.
(372) Kalidoss, M.; Yunus Basha, R.; Doble, M.; Sampath Kumar, T. S. Theranostic Calcium Phosphate Nanoparticles With Potential for Multimodal Imaging and Drug Delivery. *Frontiers in Bioengineering and Biotechnology* **2019**, *7*, DOI: 10.3389/fbioe.2019.00126.
(373) Chen, Y.; Li, J.; Kawazoe, N.; Chen, G. Preparation of dexamethasone-loaded calcium phosphate nanoparticles for the osteogenic differentiation of human mesenchymal stem cells. *J. Mater. Chem. B* **2017**, *5* (33), 6801−6810.
(374) Roozbahani, M.; Kharaziha, M. Dexamethasone loaded Laponite®/porous calcium phosphate cement for treatment of bone defects. *Biomedical Materials* **2019**, *14* (5), 055008.
(375) Son, J. S.; Appleford, M.; Ong, J. L.; Wenke, J. C.; Kim, J. M.; Choi, S. H.; Oh, D. S. Porous hydroxyapatite scaffold with three-dimensional localized drug delivery system using biodegradable microspheres. *J. Controlled Release* **2011**, *153* (2), 133−140.
(376) Dantas, M. J. L.; dos Santos, B. F. F.; Tavares, A. A.; Maciel, M. A.; de Medeiros Lucena, B.; Fook, M. V. L.; de L. Silva, S. M. The impact of the ionic cross-linking mode on the physical and in vitro dexamethasone release properties of chitosan/hydroxyapatite beads. *Molecules* **2019**, *24* (24), 4510.
(377) Bi, Y.-g.; Lin, Z.-t.; Deng, S.-t. Fabrication and characterization of hydroxyapatite/sodium alginate/chitosan composite microspheres for drug delivery and bone tissue engineering. *Materials Science and Engineering: C* **2019**, *100*, 576−583.
(378) Sambudi, N. S.; Cho, S.; Cho, K. Porous hollow hydroxyapatite microspheres synthesized by spray pyrolysis using a microalga template: preparation, drug delivery, and bioactivity. *RSC Adv.* **2016**, *6* (49), 43041−43048.
(379) Zhang, M.; Ni, S.; Zhang, X.; Lu, J.; Gao, S.; Yang, Y.; Wang, Z.; Sun, H.; Li, Y. Dexamethasone-loaded hollow hydroxyapatite microsphere promotes odontogenic differentiation of human dental pulp cells in vitro. *Odontology* **2020**, *108* (2), 222−230.
(380) Zhou, Y.; Quan, G.; Wu, Q.; Zhang, X.; Niu, B.; Wu, B.; Huang, Y.; Pan, X.; Wu, C. Mesoporous silica nanoparticles for drug and gene delivery. *Acta Pharmaceutica Sinica B* **2018**, *8* (2), 165−177.
(381) Argyo, C.; Weiss, V.; Bräuchle, C.; Bein, T. Multifunctional Mesoporous Silica Nanoparticles as a Universal Platform for Drug Delivery. *Chem. Mater.* **2014**, *26* (1), 435−451.
(382) Maleki, A.; Kettiger, H.; Schoubben, A.; Rosenholm, J. M.; Ambrogi, V.; Hamidi, M. Mesoporous silica materials: From physico-

chemical properties to enhanced dissolution of poorly water-soluble drugs. *J. Controlled Release* **2017**, *262*, 329−347.
(383) Li, Z.; Zhang, Y.; Feng, N. Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery. *Expert Opinion on Drug Delivery* **2019**, *16* (3), 219−237.
(384) Karimi, M.; Mirshekari, H.; Aliakbari, M.; Sahandi-Zangabad, P.; Hamblin, M. R. Smart mesoporous silica nanoparticles for controlled-release drug delivery. *Nanotechnol. Rev.* **2016**, *5* (2), DOI: 10.1515/ntrev-2015-0057.
(385) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature* **1992**, *359* (6397), 710−712.
(386) Hou, H.; Wang, C.; Nan, K.; Freeman, W. R.; Sailor, M. J.; Cheng, L. Controlled Release of Dexamethasone From an Intravitreal Delivery System Using Porous Silicon Dioxide. *Investigative Opthalmology & Visual Science* **2016**, *57* (2), 557.
(387) Zhou, X.; Liu, P.; Nie, W.; Peng, C.; Li, T.; Qiang, L.; He, C.; Wang, J. Incorporation of dexamethasone-loaded mesoporous silica nanoparticles into mineralized porous biocomposite scaffolds for improving osteogenic activity. *Int. J. Biol. Macromol.* **2020**, *149*, 116−126.
(388) Zhou, X.; Feng, W.; Qiu, K.; Chen, L.; Wang, W.; Nie, W.; Mo, X.; He, C. BMP-2 Derived Peptide and Dexamethasone Incorporated Mesoporous Silica Nanoparticles for Enhanced Osteogenic Differentiation of Bone Mesenchymal Stem Cells. *ACS Appl. Mater. Interfaces* **2015**, *7* (29), 15777−15789.

https://doi.org/10.1021/acsbiomaterials.2c00026
ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX