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"Old Drugs, New Tricks" – Local controlled drug release systems for treatment of degenerative joint disease

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ABSTRACT

Osteoarthritis (OA) and chronic low back pain (CLBP) caused by intervertebral disc (IVD) degeneration are joint diseases that have become major causes for loss of quality of life worldwide. Despite the unmet need, effective treatments other than invasive, and often ineffective, surgery are lacking. Systemic administration of drugs entails suboptimal local drug exposure in the articular joint and IVD. This review provides an overview of the potency of biomaterial-based drug delivery systems as novel treatment modality, with a focus on the biological effects of drug release systems that have reached translation at the level of *in vivo* models and relevant *ex vivo* models. These studies have shown encouraging results of biomaterial-based local delivery of several types of drugs, mostly inhibitors of inflammatory cytokines or other degenerative factors. Prevention of inflammation and degeneration and pain relief was achieved, although mainly in small animal models, with interventions applied at an early disease stage. Less convincing data were obtained with the delivery of regenerative factors. Multidisciplinary efforts towards tackling the discord between *in vitro* and *in vivo* release, combined with adaptations in the regulatory landscape may be needed to enhance safe and expeditious introduction of more and more effective controlled release-based treatments with the OA and CLBP patients.

Contents

Abbreviations: ACLT, anterior cruciate ligament transection; BMP, bone morphogenetic protein; CLBP, chronic low back pain; CT, computerized tomography; CXB, celecoxib; DALY, disability-adjusted life years; DMM, Partial medical meniscectomy; MM, medical meniscectomy; ECM, extracellular matrix; FDA, Food and Drug administration; GAG, glycosaminoglycans; IL-1RA, interleukin-1 receptor antagonist; IV, intravenous; IVD, intervertebral disc; IVDD, intervertebral disc degeneration; MRI, magnetic resonance imaging; MS, microspheres; NGF, nerve growth factor; NP, nucleus pulposus; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PEA, polyesteramide; PEG, polyethylene glycol; PLCA, polycaprolactic acid; PLGA, poly(lactic acid-co-glycolic acid); PRP, platelet-rich plasma; PTH, parathyroid hormone; TAA, triamcinolone acetonide; TGF, transforming growth factor; YLD, years lost to disability.

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1. Introduction

While traditionally the focus and financial efforts of biomedical research on chronic diseases worldwide has been directed towards diabetes, oncology, cardiovascular and neurodegenerative research [1–3], gradually the burden of disease has been increasing in other non-communicable chronic conditions. Amongst the diseases with most impact globally are osteoarthritis (OA) and chronic low back pain (CLBP). A systematic analysis of the global burden of diseases in 2016 concluded that back pain was the leading cause of loss of years lost to disability (YLD) in 1990 through 2016 (57.6 million of total YLDs)[4]. While back pain has occupied the first position since, OA increased over the studied period gaining in position and was in 2016 the 12th leading cause of YLD [4]. Notably, long-term trends investigation in knee OA prevalence demonstrated that this had doubled since the mid-20th century [5] and it is to be expected that the prevalence and burden of OA will even rise further in the coming decades due to ageing [6]. Clinically the most commonly affected joint is the knee, followed by the hand and hip joint, with women being overrepresented [7]. While most low back pain is termed non-specific, CLBP in 40% of the cases is attributed to disc degeneration [8,9] and in 15-45% to lumbar facet joint degeneration [10]. Both OA and intervertebral disc (IVD) degeneration are whole organ diseases, involving aberrations of the different anatomical tissues wherein cross-talk among the involved tissues further aggravates the degenerative process. While there are distinct anatomical and physiological differences between a synovial joint and the IVD, they share similarities in the underlying pathological degenerative processes that result in impaired structural and biomechanical function with pain and impaired mobility as main symptoms [11].

1.1. The articular joint and intervertebral disc are analogous structures undergoing similar pathophysiological processes during disease

Joints are vital structures of the skeleton allowing for motion. Most joints such as the knee or shoulder are synovial joints. The synovial joint cavity, formed by the joint capsule firmly attached to the adjoining bones, separates the bones. The synovial fluid nourishes the hyaline cartilage covering the articular surfaces of the bones and acts as a lubricant during joint movement. In contrast, the IVD does not have a joint cavity. It is an amphiarthrodial joint adjoining the vertebral bodies of the spine and consists of three distinct and interdependent specialized tissues: the central viscous nucleus pulposus (NP), the outer fibrillar annulus fibrosus, and the cartilaginous end-plates that anchor the disc to the adjacent vertebral bones. Both joints are challenging environments due to limited nutrition of vital anatomical structures: the articular and end-plate cartilage are not vascularized and receive their nutrition via diffusion. Within this context, the IVD is the largest avascular organ of the body: diffusion of nutrients and metabolites towards the center of the disc occurs through small capillaries superficially penetrating the outer annulus and diffusion of nutrients through the end-plates [12].

Despite distinct differences at the anatomical level, synovial joints and the IVD support complex loading conditions during daily human activity. The challenging biomechanical function of the healthy IVD is facilitated by the NP, constrained by the surrounding annulus fibrosus and cartilaginous end-plates, which together enable the development of a high hydrostatic pressure within the NP and allows the IVD to withstand forces of compression and torsion. The ability of synovial joints and the IVD to withstand challenging biomechanical forces in different directions is supported by a tissue-specific architecture of the matrix components (see Fig 1). Cartilage and the NP are rich in extracellular matrix (ECM) with relatively low cell densities. The healthy ECM is rich in proteoglycans entrapped within a network of collagen fibres. Proteoglycans consist of a protein core to which a multitude of glycosaminoglycan (GAG) side chains are attached, negatively charged mucopolysaccharides. Through the attraction of cations, a highly hydrated tissue is formed. The ratio of GAG:collagen is different in these tissues, with much higher ratios in the healthy IVD (24:1) compared to the articular cartilage (4:1)[13]. The fibrillar collagen network of cartilage (articular and endplate) oriented along the direction of the biomechanical forces is cross-linked and thereby stabilized to withstand the internal swelling pressure generated by the negatively charged GAGs. For the IVD, the swelling generated by the GAG-rich NP is constrained by the surrounding annulus fibrosus and endplates.

In the OA and CLBP field, more and more researchers are acknowledging that these diseases share many pathophysiological characteristics between them. Although similar does not imply the same, identifying the common grounds may help the development of novel therapies, just as differences will do. The pathogenesis of OA and IVD degeneration is complex, involving mechanical, inflammatory, and metabolic factors. At the ECM level, the ratio of GAG:collagen changes for both tissues (cartilage 2:1; NP 5:1) [14], while both are marked by scant collagen turnover [15,16] underlining their limited reparative capacity. Regardless of the cause, an imbalance between matrix degradation by activated matrix degrading enzymes and matrix anabolism ultimately leads to structural changes, failure of the joint/disc as an organ and its inability to meet the biomechanical demands, thereby generating a vicious circle. The vicious cycle is maintained and further aggravated by (pro)inflammatory processes [17,18], which are further stimulated by by-products of the ongoing matrix breakdown [19]. Within this context, the degenerating cartilage and the NP are further challenged by a low cellular density and a metabolically harsh condition for the resident cells, including low oxygen tension and low levels of nutrients that may result in relatively high local concentrations of lactic acid with negating effects driving further catabolism [20,21].

Both OA and disc-related CLBP refer to symptomatic diseases, as radiographic OA/disc degeneration is more common than symptomatic disease. OA and IVD degeneration are diseases of the whole joint and alterations occur in the different joint-specific tissues wherein cross-talk among the involved tissues further precipitates the degenerative process and has also strongly been related to pain. An important entity in this is the subchondral bone which is also affected during joint/disc degeneration. The cross-talk between bone and cartilage/disc is well-acknowledged in both the pathological processes, as is the need to address disease-modifying therapies for both the articular joint [22] and the IVD [23]. It is well-recognized for example that bone marrow lesions and bone cysts in OA [24], and edematous or fatty degenerative changes in the vertebral bodies adjacent to the affected IVD as visualised by MRI (the so-called Modic changes)[25], are strongly related to pain. Regardless of the cause, patients experience pain as the most debilitating symptom. Initially, it is intermittent and mainly related to weight-bearing. As the disease progresses the pain may become persistent and in the long term can even result in sensitization where either neuropathic or central pain mechanisms are at play [26,27]. This

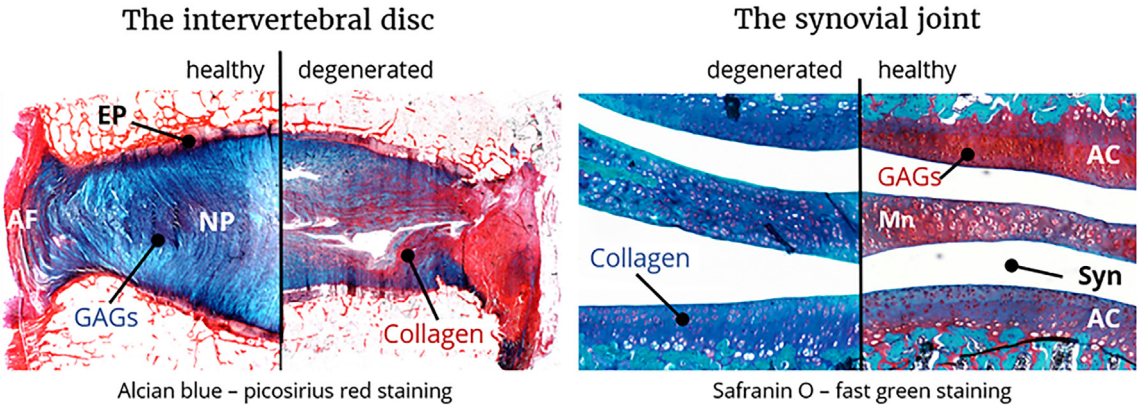

Fig. 1. The articular joint and intervertebral disc are analogous structures undergoing similar pathophysiological processes during disease.

multidimensional pain, including both sensory and emotional experiences associated with actual or potential tissue damage, affects the mobility and quality of life of these patients.

1.2. Current treatments

OA and CLBP are initially treated conservatively, typically entailing a combination of lifestyle changes, physiotherapy and oral analgesics (See Fig. 2). Specifically in knee OA, alternatives for OA such as braces [28], intra-articular injections of hyaluronan [29], or ingestion of glucosamine or chrondroitin sulphate [30] have thus far shown in a meta-analysis to be of insufficient clinical relevance. Focusing further on pain medication, the historical first-line medication acetaminophen (paracetamol) was shown to have a very small effect and preference was given to NSAIDS [31]. However, until now a plethora of oral NSAIDS has been employed for the treatment of OA and chronic low back pain, all with limited clinical improvement [32,33], while prolonged intake is associated with gastrointestinal and cardiovascular adverse effects [34]. Other analgesic strategies for OA and CLBP include local applications, including either ointments or local injection (intra-articular, epidural, intra-discal) of medication, mostly analgesics and anti-inflammatory drugs such as corticosteroids and NSAIDs. Opioids are being increasingly used in patients with severe pain, without solid evidence that they are more effective over other medication, while they carry a considerable risk of addiction, evidenced by the current opioid epidemic [35,36].

When all these treatments fail, surgery is the remaining option to treat IVDD-related CLBP, including IVD replacement or spinal fusion, although neither are very frequently applied and their effectivity is subject to debate [37]. In an analogous fashion, end-stage treatment of OA involves joint prosthesis surgery (Fig. 2). However, end-stage patients suffering from OA have to overcome a period of debilitating pain for at least a decade until the optimal timing is reached for joint replacement, with considerable socio-economical effects [38].

1.3. Recently emerging approaches towards non-surgical treatment of osteoarthritis and intervertebral disc-related chronic low back pain

Apart from low molecular weight analgesic drugs as a first resort to relieve the chronic pain associated with OA and IVD degeneration, various novel treatments are also being evaluated in clinical trials as an alternative to surgical intervention [39–43]. Firstly, for both OA and CLBP, a variety of stem cell-based trials has been initiated, although without convincing benefit for either disease as yet [44,45]. Whether this is a matter of optimization by using supportive biomaterials, or other

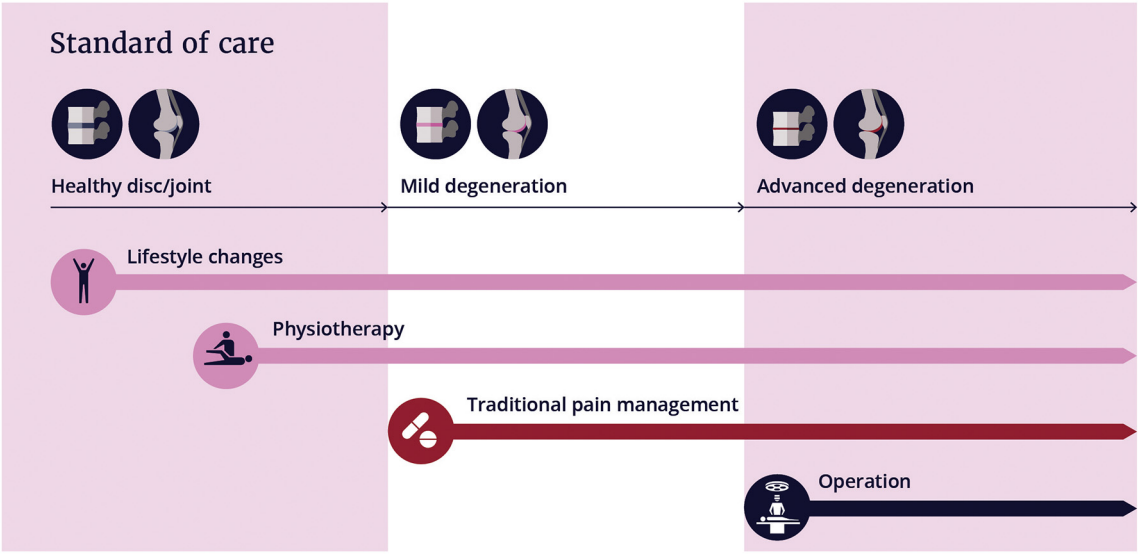

Fig. 2. The standard of care of osteoarthritis and chronic low back pain. Treatment consists of conservative treatment in the early stages. When all these treatments fail, surgery is the remaining option to treat IVDD-related chronic low back pain. Prior to becoming eligible for joint prosthesis in end-stage also osteoarthritis patients need to overcome a period of debilitating pain for at least a decade.

types of cells such as tissue-specific progenitors, embryonic or induced pluripotent stem cells are better alternatives, still needs to be settled. In terms of novel systemic drugs, mainly for OA, an extensive search for different druggable targets of disease is ongoing. Among these, inflammatory cytokine and enzyme inhibitors are frequently used as therapeutic agents, but until now these agents showed no or only limited efficacy and an increased risk of adverse events [39–41]. One of the more promising treatments currently in late-stage clinical trials is a Nerve Growth Factor (NGF) antibody which shows very effective pain reduction in patients, albeit at the expense of a higher risk for progressive OA [42,43].

1.4. Local disease needs local treatment

Although still most drugs used to treat degenerative joint diseases are administered systemically, these diseases are ideally suited for local treatment, as commonly one or more well-defined sites accessible by injection are affected. A major advantage of locally administered drugs is the possibility to achieve high concentrations at the site of administration, while avoiding the often serious side effects associated with systemic treatment [46] (Fig 3A). For chronic low back pain associated with IVD degeneration, local treatment most likely even represents the only effective option, as access to the large non-vascularized IVD is very limited. Indeed, in IVDs of several animal species, the local tissue concentrations measured within 1 hour after 2–3 IV injections of antibiotics are only a fraction of the plasma levels; 5–20% depending on the drug characteristics [47–49]. Also for IV administered vancomycin, IVD drug peak levels and concentration over time were strongly reduced compared to plasma levels, as demonstrated by the low values of the area under the curve (AUC) for the IVD [50]. Although the synovial joint is lined by a well-vascularized joint capsule, also in joints a limited synovial fluid penetration was shown. Drug concentrations in the synovial fluid reach only 23–50% of the levels found in the circulation for most systemically administered drugs, including antibodies, antibiotics and small molecule drugs [51–55] even after several days of continued intake [54,55]. Also in this compartment, peak drug levels and AUCs of orally taken drugs are reduced compared to plasma [56]. Because synovial fluid levels rather than plasma levels of anti-inflammatory drugs were shown to correlate to relief of clinical symptoms in arthritis [57,58], concentrations attained locally may often fall well beyond those required for efficacy, as was shown for example for the orally administered NSAID celecoxib [59].

In the knee, intra-articular injection of corticosteroid suspensions for OA are commonly used in clinical practice and it is one of the few effective pain treatments, active for several weeks after injection [60]. Also in CLBP, intradiscal injection of corticosteroids is being applied, albeit not a standard of care treatment as there is still controversy over its efficacy [61]. This may at least in part have arisen due to a large number of clinical trials being based on a corticosteroid formulation of which the major excipient, polyethylene glycol (PEG), is toxic for IVD tissue, as shown in rabbits injected with the same amount of vehicle as present in the drug formulation [62]. These effects, also described for human paraspinal injection of drug formulations with relatively high PEG concentrations [63], were not seen using a corticosteroid formulation with saline only [62]. Later trials in which corticosteroids in other vehicles (benzyl alcohol, carboxymethylcellulose, polysorbate 80 [64]/the former plus parahydroxybenzoate, propyl parahydroxybenzoate, and PEG at lower dosages [65]/EDTA [66]) were injected intradiscally, showed CLBP relief for over several months. The improvement did seem to be most pronounced in patients with Modic changes in their spines [64–66]. Among more targeted and novel types of drugs, local Tumor Necrosis Factor (TNF) inhibition was suggested to at least temporarily relieve pain in both OA [67], sciatica [68] and discogenic chronic low back pain [69], as did SM04690, a low molecular weight Wnt pathway inhibitor in early phase OA trials [70,71]. A clinical trial investigating the safety of intradiscal administration of the latter drug for IVD degeneration was, however, terminated without publication of the results (ClinicalTrials.gov/NCT03246399). Trials on intradiscal injection of a peptide derived from biglycan (YH14618) and an oligonucleotide nuclear factor-kB decoy (AMG0103) are still ongoing [72]. Interestingly, both an intra-articularly administered growth factor, rhFGF-18 (recombinant human fibroblast growth factor 18; sprifermin) [73–75], and the small molecule cathepsin K inhibitor MIV-711 [76] were recently found to induce structural improvement in human OA patients, without being accompanied by the expected relief in clinical symptoms.

2. Biomaterial-based local drug delivery: new trick for old drugs

Despite the encouraging results from local injection of drug formulations as treatment for degenerative joint disease, still efficacy of any drug, old or new, locally administered as bolus will likely be limited,

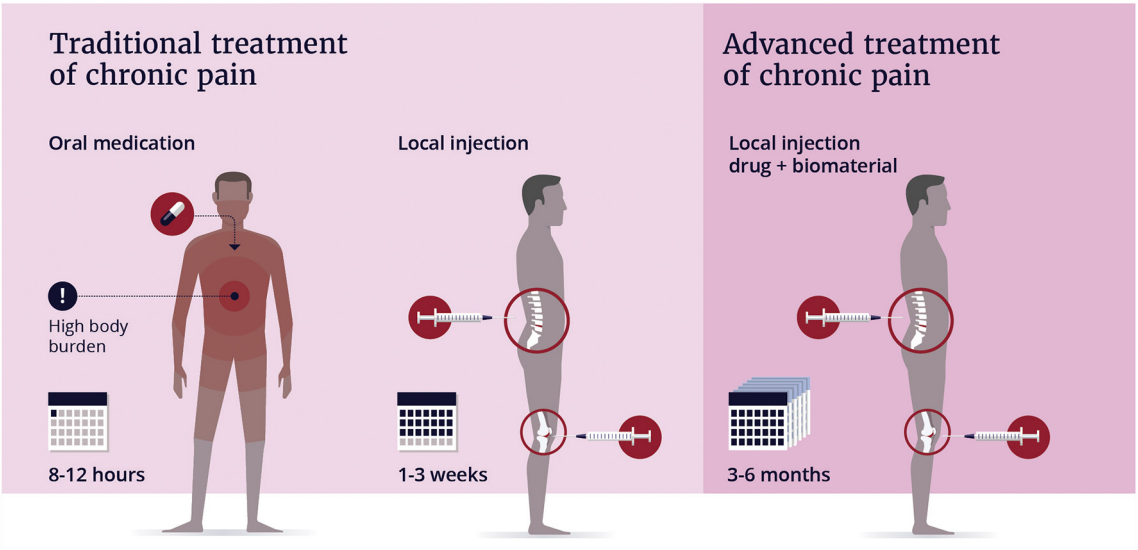

Fig. 3. A. The standard of care of pain in degenerative joint diseases consists of oral medication associated with systemic side effects or local applications with limited efficacy. B. Advances on local controlled drug delivery employing biomaterials hold promise for effective and prolonged pain management.

in particular in the articular joint characterized by full clearance within several days [77,78]. In contrast, in the IVD drug retention will be longer, again related to the IVD's blood supply limited to the outer layers of the annulus fibrosus and hence slow clearance rates. Unfortunately, as yet little is known on the retention of intradiscally administered drugs. From the trials on effective intradiscal corticosteroid injections, return of clinical symptoms was observed within 3–6 months, suggesting indeed substantially longer drug exposure than in the articular joint [64]. Still, more extended exposure to therapeutic bioactive molecules is desirable for both diseases, while repetitive reinjections are unfavorable due to the enhanced risk of infection, especially considered a risk factor for patients undergoing prosthetic surgery [79,80], and possibly reduced patient compliance [81]. Therefore, the use of biomaterial-based controlled release systems to achieve long term therapeutic drug levels while minimizing the number of repetitive injections is indicated in OA and disc-related CLBP (Fig 3B).

2.1. Vehicles for local drug delivery

What type of delivery vehicles are suited best as local drug depots for treating joint degeneration-associated disease depends on several factors. Degradability is a prerequisite, as undisruptive removal of an empty depot from neither the IVD nor the articular joint is possible. Tissue location and the physicochemical properties of the therapeutic compounds will further dictate the choice of delivery platforms in terms of their required physical and chemical properties. For example, using hydrogels, networks of hydrophilic polymers, as drug release depots in the articular joint may yield some challenges. Firstly, exposure to the daily biomechanical loads of the joint may cause hydrogel fragmentation, as was suggested in an elegant study using a triiodobenzoyl endcapped PEG-PCLA hydrogel (Fig 4A)[82]. This may hamper reproducibility of release profiles, which can be overcome by injection in locations with limited biomechanical loading, such as in local cartilage defects [83,84] or inside the surrounding tissues. Moreover, the highly hydrated nature of hydrogels and thus high permeability particularly for low molecular weight hydrophilic drugs, often limits release duration to one or a few days at most [82,83]. The confined environment of the IVD may be more suited for hydrogel-mediated drug release, as, although fragmentation of injected hydrogels also occurs here (Fig 4B), clearance may be slower due to the limited vascularity [12]. On the other hand, hydrogels are very suitable for the release of small drugs and large protein therapeutics. Hydrophobic low molecular weight drugs can be released in a sustained manner from hydrogels crosslinked via hydrophobic domains, which can be loaded with and act as depots for hydrophobic drugs whereas the release of proteins can be modulated by the crosslink density of the hydrogel network [85–87].

In contrast, polymeric microspheres based on relatively hydrophobic polymers can release drugs up to several months, even in the articular joint [88], although the release, of course, varies with the type of polymer used. A variety of poly(lactic acid-co-glycolic acid) (PLGA)-based microsphere drug formulations have been approved by the FDA [89,90]. However, loading of proteinaceous drugs in microspheres formulations entails some challenges. Many common solvent-based drug loading protocols can compromise conformation and hence activity of protein [91–94], [95]. Fortunately, technologies have recently been developed that avoid the use of organic solvents by loading pre-formed porous polymeric particles with proteins using trapping agents [96,97]. Microsphere-based release usually displays a burst, although this can be dampened by their incorporation in hydrogels [98–100].

Nanoparticle-mediated drug delivery is a topic receiving a lot of attention but may be less suitable for achieving a clinically meaningful

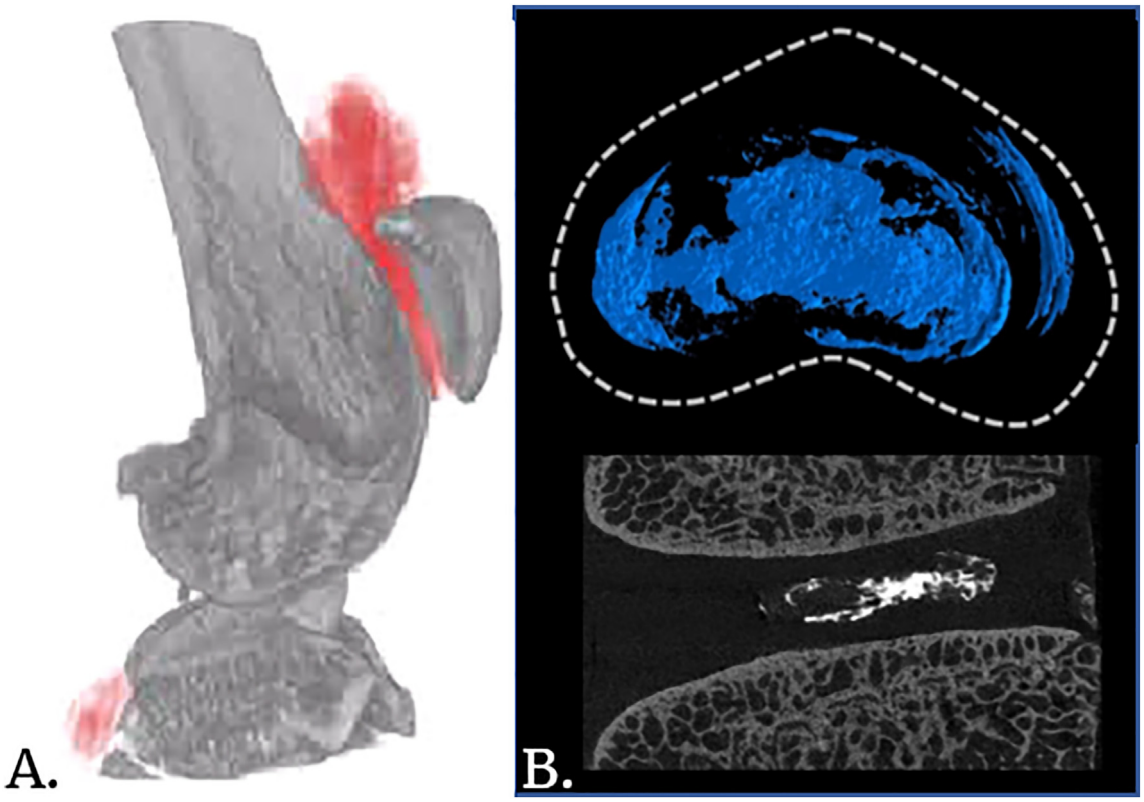

Fig. 4. Local delivery in the confined joint space. A. Reconstructed 3D microCT image of a rat knee joint 24 hours after intra-articular injection of a PEG PCLA-based hydrogel with triiodobenzoyl endcaps (in red) illustrating fragmentation of the hydrogel in the joint cavity. Adapted from Sandker et al. 2013 [82] ; B. Detection of a radiopaque hydrogel comprised of N-carboxyethyl chitosan, oxidized dextran and teleostean in the degenerate disc visualized in axial views of 3D mCT reconstructions (top) and 2D sagittal mCT slices (bottom). Adapted from Gullbrand at al. 2017 [194].

prolonged local drug presence. Particles <10 μm are known to be phagocytosed by the monocyte-macrophage system [101] including the synovial lining macrophages [102], and nanoparticles (10–200 nm) are also taken up via endocytosis by a variety of cells. The extent of uptake depends on the cell type but also on the size and surface characteristics of the nanoparticles [103,104]. Moreover, they are also cleared via the microvascular pathway [102], altogether resulting in shorter retention compared to microsphere counterparts, as shown for chitosan nano- vs microparticles [105]. Therefore, this review focusses on the literature on the efficacy of microsphere or hydrogel-mediated local drug delivery systems.

2.2. Preclinical promises of drug delivery in OA and IVDD

In contrast to oncology [106], contraception [107] and ocular disease [108,109], for treatment of degenerative joint disease until now only one controlled release-based treatment has received regulatory approval. This is a microsphere formulation based on PLGA, releasing the off-patent corticosteroid drug triamcinolone acetonide (TAA) [110,111]. In the preclinical arena, several other drug delivery platforms releasing existing or novel drug candidates have been investigated until now, with encouraging results up until *in vivo* or relevant *ex vivo* models. Most of these formulations target the inflammatory or catabolic processes in degeneration (Table 1) and some aim to achieve regeneration of the affected tissue (Table 2). The studies discussed in this paper comprise only those formulations that reached further in the translational chain involving small/large animal models and relevant *ex vivo* models by showing an effect on disease parameters, as an absence of effects cannot be clearly attributed to sub-optimal release profiles, inactivity of the drug or the dose used.

2.2.1. Inhibition of inflammation and degeneration

Among anti-inflammatory drugs, NSAIDs have been a common choice of drugs to be loaded in delivery systems for intra-articular controlled release. Ibuprofen delivery by PLGA [112], lornoxicam by chitosan-tripolyphosphate [113] and diclofenac by collagen-lipid [114] microspheres all inhibited synovial inflammation and/or cartilage degeneration in mono-iodoacetate (MIA) induced OA in rats. The same results were found for lornoxicam released from PLGA microspheres in papain-induced OA [115]. In a rat model of OA induced by anterior cruciate ligament transection and partial resection of the medial meniscus (ACLT/DMM) delivery of celecoxib (CXB) in polyesteramide (PEA) microspheres also inhibited synovial inflammation, and osteophyte formation and subchondral bone sclerosis as visualised by micro CT analysis. However, histological analysis showed that cartilage degeneration was unaltered [116]. This might be due to the relatively late moment of injection -4 weeks after OA induction- whereas in other intra-articular drug delivery studies in rodents, treatments were applied between 0-10 days after induction of OA [112–115,117,118] (see also Table 1). Intradiscal injection of CXB-loaded PEA microspheres in an experimental canine model of induced IVD degeneration also resulted in inhibition of inflammation, osteophyte formation and sclerosis of the subchondral bone beneath the endplate. Moreover, inhibition of IVD degeneration was found, at the histological, biochemical and structural level at 3 months post-injection, further pointing out that despite the many similarities in tissue pathophysiology, differences between the two joint types are evident also at the level of treatment response. These may also relate to differences in the blood supply and inherently the clearance rates of the drug upon administration. A reduction in NGF positivity in the NP suggested pain reduction [119]. Indeed, intradiscally released CXB from a PEG-PCLA hydrogel in a small cohort of canine patients with CLBP reduced owner-reported pain symptoms in most animals, without clear structural improvement on MRI imaging [120]. However, drug-only controls were not always included in the study design, since CXB has a very low aqueous solubility of around 1 μg/ml [121] and is not available as a suspension for injection. This precludes a conclusion on the added value of controlled release formulations over bolus injection. Notwithstanding, these findings suggest that in late stage degeneration, inflammation may not drive cartilage or IVD degeneration, but is still involved in pain. This pain can be effectively and long-term inhibited, which would be of great relevance for OA and CLBP patients worldwide, as their chronic pain is the major reason for disability.

PEA-based microspheres discussed above have also been investigated as a formulation to slowly release the corticosteroid TAA [88,122–124]. In a rat model of collagenase-induced OA, this combination inhibited synovial inflammation without changes in cartilage integrity [122]. However, when applied in ACLT/DMM-induced OA, aggravation of degeneration was noted, which was caused by inhibition of tissue healing. This response was not observed in the TAA bolus-treated animals, suggesting that specifically the combination of acute joint trauma with the controlled release and hence extended presence of TAA is not safe [123].

Interestingly, in a rat model of bacterial cell wall-induced arthritis, TAA released from PEA microspheres resulted in inhibition of inflammation for up to 90 days, whereas the PLGA formulation releasing the same amount of drug lost efficacy already after 30 days [88]. Although it is difficult to extrapolate *in vitro* to *in vivo* release [125,126] and the PEA platform, in contrast to PLGA, degrades by protease activity [127], the explanation may in part be provided by the differing *in vitro* release profiles (Fig. 5). The PLGA microspheres showed a higher burst release, followed by a phase of limited release starting after the third week, which could have explained the observed loss of analgesic effect *in vivo* after 30 days. In contrast, after the burst, the PEA microspheres showed a gradual release for the remainder of the 170 days period [88]. As the efficacy of the commercial PLGA-based TAA formulation was recently shown to be insufficient to meet the primary end-point in comparison to the regular intraarticular suspension of the drug [110,111], the data on the PEA formulation indicates that there is still room for improvement in terms of release characteristics and hence pain relief of depot formulations.

As less commonly used inhibitors of inflammation, the statin fluvastatin [117] and the isothyocyanate sulforaphane [118] loaded in PLGA microspheres, the latter in turn encapsulated in a fibrin gel, also inhibited OA progression in ACLT-induced rabbit or rat joints, respectively. Unfortunately, drug-only controls were not included. More focused inhibition of inflammation with release of IL-1 receptor antagonist (IL-1RA) from PLGA microspheres slowed down ACLT-induced joint degeneration in rats, although without a significant difference with IL-1RA bolus injection. This may have been due to the fact that both formulations were injected weekly, thereby ensuring sufficient IL-1RA in both conditions [128]. An appropriate study design to reach conclusions about the therapeutic value of the PGLA formulation would rather be the comparison of a single intra-articular injection of IL-1RA-loaded microspheres with an equal dose of free protein. Successful inhibition of IL-1 activity by co-delivering IL-1RA-loaded PLGA microspheres with IL-1 in rat caudal discs was demonstrated by the prevention of IL-1-induced IVD matrix loss [129]. However, as a complete lack of IL-1 signalling was recently shown to enhance rather than prevent IVD degeneration in mice [130], IL-1-based strategies may need more finetuning for local delivery to treat chronic low back pain.

Other processes instrumental in joint degeneration and addressed by sustained release depot formulations are autophagy, vasculogenesis and hypertrophy. The autophagy agonists cordycepin [131] and sinomenium [132] released from chitosan microspheres, in turn loaded in a methacrylated hyaluronic acid or gelatine-based hydrogel, respectively, at least partially slowed down histological cartilage degeneration upon ACLT-mediated OA induction in mice. Inhibition of angiogenesis as one of the drivers of OA pathophysiology may also be a feasible approach. The drug crizotinib-loaded chitosan microspheres which in turn were embedded in a crosslinked gelatine-hyaluronic acid hydrogel,

Table 1
In vivo therapeutic efficacy of polymeric formulations for the local release of drugs targeting inflammation, autophagy or hypertrophy in osteoarthritis and IVD-related chronic low back pain. Results are arranged along the postulated mechanism of action of the drug released, relevance of the animal model, and disease.

Active compound & total administered dose (per joint/per body weight)	Carrier	Model	Timing of administration after induction	Analysis after (first) injection	Effects	Compared to local free drug	Reference
Anti-inflammatory							
Ibuprofen (0.2, 0.6, 1 mg)	PLGA MS	MIA-induced OA rat	7 d	7 w	↓cartilage degeneration	No	[112]
Lornoxicam (4 mg/kg)	PLGA MS	Papain-induced OA rat	9 d	6 w	↓synovial inflammation ↓cartilage degeneration	Yes	[115]
Lornoxicam (4 mg/kg)	Chitosan MS	MIA-induced OA rat	1 d	1, 2, 3 w	↓swelling ↓cartilage degeneration (?)[a]	Yes	[113]
Diclofenac (1 mg/kg)	Collagen-lipid MS	MIA-induced OA rat	Until OA response	3, 10, 18 w	↓swelling (MRI)	Yes	[136]
Celecoxib (CXB) (0.03, 0.23, or 0.39 mg)	Polyesteramide MS	ACLT/DMM-induced OA rat	4 w	16 w	↓synovial inflammation ↓osteophyte formation ↓ number and size of subchondral bone cysts =cartilage degeneration	No	[116]
CXB (0.01, 0.3 mg)	PEA MS	IVDD induced by partial nuclectomy in experimental canines	4 w	12 w	↓degeneration (histology, biochemistry) ↓osteophyte formation&sclerosis ↓inflammation (PGE2) ↓ NGF production (immunohistochemistry)	No	[119]
CXB (0.09 mg/IVD)	PEG/PCLA hydrogel	Canine CLBP patients*	NA	12 w	↓pain (owner questionnaires) = IVD degeneration (MRI)	No	[120]
Triamcinolone acetonide (TAA) (0.25 mg)	PEA MS	Collagenase-induced OA rat	1 w	7 w	↓synovial inflammation =cartilage degeneration	Yes	[122]
TAA (0.7, 1, 1.6 mg)	PEA MS	ACLT/DMM-induced OA rat	4 w	16 w	↑cartilage degeneration** Induction pathological calcification**	Yes	[123]
TAA (0.08, 0.8 mg)	PEA MS	IVDD induced by partial nuclectomy in experimental canines	4 w	12 w	= degeneration (histology, biochemistry) = osteophyte formation = inflammation (PGE2) ↓ NGF production	No	[124]
Fluvastatin (0.03 mg/kg)	PLGA MS	ACLT-induced OA rabbit	7 d	5 w	↓degeneration (histology)	No	[117]
Sulforaphane (0.03 mg)	PLGA MS+fibrin hydrogel	ACLT-induced OA rat	0 d	8 w	↓degeneration (histology)	No	[118]
IL-1RA (0.25 mg)	PLGA MS	ACLT-induced OA rat	7, 14, 21, and 28 d	5 w	↓degeneration (histology, urinary biomarker) ↓synovial inflammation (histology)	Yes	[128]
IL-1RA (0.03 mg)	PLGA MS	IL-1-induced degeneration tail IVDD rat	0 d	7 d	↓proteoglycan loss	No	[129]
Autophagy enhancing							
Cordycepin (5 mg/kg)	Chitosan MS loaded in methacrylated hyaluronic acid hydrogel	ACLT-induced OA mice	10 d, once a week	4/8 w	↓degeneration (histology) ↑autophagy	Yes	[131]
Sinomenium (5 mg/kg)	Chitosan MS loaded in gelatine hydrogel	ACLT-induced OA mice	10 d, 1x/week	4/8 w	↓degeneration (histology) ↑autophagy	Yes	[132]
Hypertrophy inhibitors							
Crizotinib (3.5 mg/kg)	Chitosan MS in hyaluronic acid- gelatine hydrogel	ACLT-induced OA mice	10 d, 2x/week	4/8 w	↓degeneration (histology) ↓VEGF production	Yes	[133]
Rac1 inhibitor (0.03 mg)	Chitosan MS	ACLT-induced OA mice	7 d, 1x/week (free drug 2/w)	4, 6, 8 w	↓degeneration (histology)-no difference with free drug	Yes	[134]
PTH(1-34) (45 ng in microspheres, 1.7 ng free drug)	PLGA MS	Papain-induced OA rat	0 d, 1x/2 weeks, free PTH 1x/3 d		↓degeneration (histology)-no difference with free drug	Yes	[135]

MS: microspheres; MIA: mono-iodoacetate; ACLT: anterior cruciate ligament transection; DMM: partial dissection of the medial meniscus; PEA: polyesteramide; PCLA: Polycaprolactone; PLGA: poly(lactic acid-co-glycolic acid); IVDD: intervertebral disc degeneration. '=' means no change
[a] Not quantified. *Not compared to vehicle. **Not seen with TAA bolus suspension.

reduced VEGF expression by chondrocytes, and slowed down the progression of OA induced by anterior cruciate ligament transection (ACLT) in mice [133]. Inhibition of hypertrophy by chitosan microparticles releasing a Rac1 inhibitor, or by PLGA microspheres releasing the 1-34 amino acid polypeptide of parathyroid hormone (PTH), also protected cartilage from destruction in ACLT-induced OA in mice [134] and in papain-induced OA in rats [135], respectively. In both studies, the effect of a bolus injection of the free drug was similar, but as the frequency of injection and even the injected dose was not the same as for the drug delivery system, the results do not allow to draw conclusions. Moreover, the controlled release drug formulations of cordycepin, sinomenium, crizotonib, Rac1 inhibitor and PTH1-34 were injected at

Table 2
In vivo and *ex vivo* therapeutic efficacy of polymeric formulations for the local release of regenerative agents for cartilaginous tissues in OA and disc-related chronic low back pain. Data are arranged according to increasing level of complexity of the released active and disease.

Active compound&total administered dose	Carrier	Model	Timing of administration after induction	Analysis after (first) injection	Effects	Compared to locally administered free drug	Reference
Kartogenin	Chitosan MS	ACLT-induced OA rat	6 w & 9 w	8 w	↓degeneration (histology)	Yes	[105]
Tri-butanoylated N-acetyl-D-galactosamine (1.5 mg)	PLGA MS	MMT-induced OA rat	1 w	3 w	↓degeneration (histology)	Yes	[152]
BMP-7 (1.6 or 16 μg/200 mg tissue, 17 μg/ml free drug	PEA MS	Human degenerated NP tissue culture	NA (no induced model)	4 w	= degeneration (histology)	Yes	[149]
BMP-2/BMP-2/7 heterodimer (0.1 or 0.7 μg)	Fibrin/hyaluronic acid hydrogel	Chondroitinase-induced IVDD goat	12 w	12 w	= disc height loss = degeneration (histology/MRI)	No	[150]
GDF-5 (dose unknown)	PLGA MS	Aspiration-induced IVDD in rats	4 w	8 w	↓disc height loss ↓proteoglycan loss ↓degeneration (histology)	No	[154]
PRP (100 μl)	Gelatine MS	ACLT-induced OA rabbit	4 w, 1x/3 w	6 w	↓degeneration (macroscopy/histology)	Yes	[138]
PRP (5 μl hydrogel)	Gelatine MS	Stab-induced IVDD in rabbit	2 w	2, 4, 8 w	↓disc height loss ↓degeneration (histology)	Yes	[139,140]

MS: microspheres; ACLT: anterior cruciate ligament transection; PEA: polyesteramidePLGA: poly(lactic acid-co-glycolic acid); IVDD: intervertebral disc NP: nucleus pulposus; MMT: medial meniscus transection. '=' means no change

least once a week. Since in clinical practice this frequency of injection would not be acceptable for the patient, further studies should investigate the long term effects of single injections.

2.2.2. Regenerative approaches

To a much lesser extent, regenerative factors such as growth factors or small molecule drugs have been applied in controlled release systems in the joint and the IVD in preclinical OA and IVDD models (Table 2). Although there is only limited evidence for its efficacy upon direct articular injection in OA patients [137], platelet-rich plasma (PRP) loaded in gelatine hydrogel inhibited cartilage degeneration in ACLT-induced OA in rabbits, with injections administered 4 and 7 weeks after induction [138]. Also in stab-induced IVD degeneration in rabbits, injection of this drug formulation protected against loss of disc height, extracellular matrix and water content [139,140]. In neither study, direct injection of PRP had any effect. Hence, the myriad of factors in PRP may after all have some activity when slowly released from the gelatine hydrogel and thus present in the disc for a longer period of time. Also, several BMPs have been locally administered, incited by their potent actions on chondrocyte and IVD cell-mediated extracellular matrix production, although mainly administered in their free form and not as sustained release formulation [141–144]. Direct injection of BMP-7 resulted in efficient inhibition of degeneration in stab- or compression-induced IVDD in rabbits [145–147] and rats [148], respectively, with even signs of regeneration as indicated by the increase in disc height over time in the treated discs. Also in an *ex vivo* bovine IVD organ culture model, BMP-2/-7 heterodimers increased matrix production after nucleotomy. However, injection of BMP-7 releasing polyesteramide microspheres did not affect the matrix content of cultured NP explants from human degenerated IVDs [149]. Similarly, no effect on IVD tissue integrity was found of intradiscal delivery of BMP-2 or BMP-2/-7 heterodimers conjugated to a fibrin/hyaluronic acid gel in a goat model of chondroitinase-ABC induced IVD degeneration. As free growth factor was not taken along as control, it is not clear whether their residual specific activity upon conjugation and release may have been compromised, thereby limiting the effects [150]. However, a high dose of BMP-7 added directly to the culture medium of human degenerated NP tissue could not enhance the production of ECM either [149], nor was any effect noted of intradiscal injection of BMP-7 in a canine model of spontaneous mild IVD degeneration. Extradiscal bone formation showed the injected growth factor was active [151]. In line with these findings, intradiscal injection of rhBMP-7 did not progress beyond

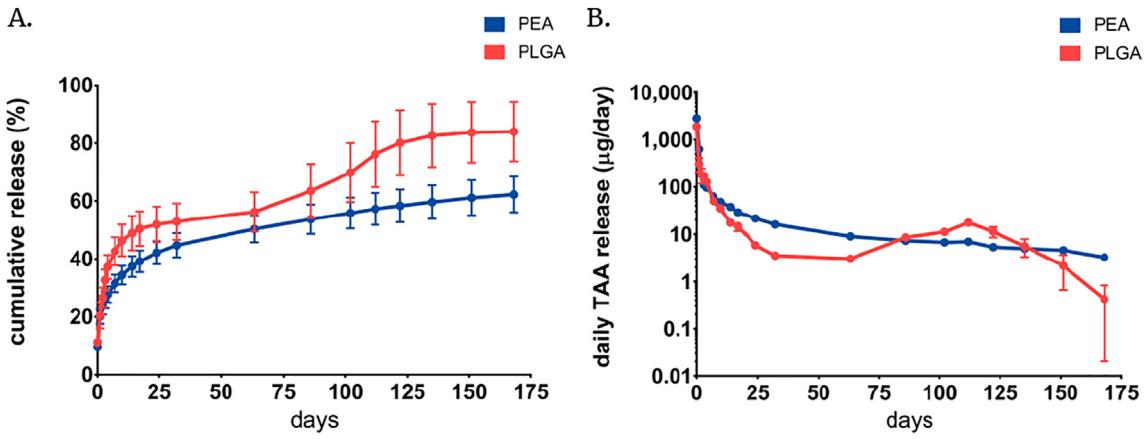

Fig. 5. Release profiles of triamcinolone acetonide released in vitro in PBS from PEA or PLGA micro-spheres over 24 weeks. A. Cumulative triamcinolone acetonide (TAA) release from PLGA (red) or PEA (blue) microspheres and B. daily TAA release from PLGA (red) or PEA (blue) microspheres. Data represent mean ±standard deviation (SD) of three microsphere batches per polymer. Adapted from Rudnik-Jansen et al. 2019 [88].

Phase II clinical trials in humans [72]. Altogether it appears that in large 'animal' models with more or less established IVD degeneration, as opposed to the acute IVD damage in the rat and rabbit models described above, regeneration may be more challenging.

In general, the relative instability of growth factors and costs of (patented) recombinant proteins may make their clinical application less attractive. Alternatively, small molecules with regenerative activity may be delivered. Kartogenin has been shown to have promise as a regenerative small molecule, through activation of CBFb-RUNX1 leading to enhanced chondrogenesis. Delivered by chitosan microspheres in ACLT-induced OA in rats, indeed histological degeneration was inhibited [105]. Also, tri-butanoylated N-acetyl-D-galactosamine glucose as PLGA formulation was shown to inhibit OA progression in an MMT-induced rat model of OA. This carbohydrate-based drug candidate both enhances chondrogenesis by inhibiting Wnt/β-catenin signalling and inhibits inflammation by interfering with NF/kB signalling [152]. A second alternative to regenerative protein drugs may be provided by polymeric-based plasmid DNA delivery, such as shown by combined nano-microparticle approaches delivering antifibrotic or anabolic genes in induced IVDD [153] and OA [154]. Although not within the scope of this review, delivering cells genetically modified to produce regenerative factors is also a possibility to ensure the prolonged local presence of active factors [155].

2.3. Limitations of local microparticle and hydrogel depots for treatment of osteoarthritis and chronic low back pain

Although locally administered drug-loaded microspheres or hydrogels in general will provide the longest drug exposure, one disadvantage is the lack of spatial control of release inside the joint. Especially in the articular osteoarthritic joint, different therapeutic agents will be required for different joint tissues. For example, degenerated cartilage requires growth factor activity for regeneration, but the synovial capsule exposed to growth factors is prone to osteophyte formation [156]. In the synovial lining, inflammation may be the most prominent process involved in disease [157,158], requiring an especially high dose of the administered anti-inflammatory drug either in its free form or as polymeric formulation at this location. Nanosized delivery systems allow targeted delivery by attachment of molecules (e.g. small molecules or antibodies) that preferentially bind to particular cells in the diseased target tissue [159–161]. Incorporation of nanoparticles in microspheres or hydrogels may overcome their limited release profiles and combine the best of both worlds [162,163], although the complexity in terms of pharmaceutical production and quality control of these systems may slow down their progress to the clinic.

Additionally, OA and CLBP pain can encompass nociceptive, inflammatory and neuropathic pain, and involves joint nociception, peripheral and central sensitization (as reviewed in Fu 2018 [164]). Nociceptive pain in OA is strongly associated with bone marrow lesions and synovitis, disease hallmarks that can be efficiently eliminated with local delivery of anti-inflammatory drugs, although peripheral and central sensitization may take time to reduce [165]. Chronic neuropathic pain, with a prevalence of 23% in patients with knee or hip OA [166] and 8% in patients with chronic low back pain without leg involvement [167], cannot be targeted by anti-inflammatory drugs nor agents that restore tissue integrity, and in addition may not always be localised easily. Combined formulations with neuropathic analgesics such as gabapentin or opioids is an option. However, at more remote locations, and to modulate the central sensitization process, separate injections or even systemic administration of neuropathic analgesics will be needed.

3. Hurdles to widespread clinical implementation

The number of drug delivery formulations showing success in animal models of osteoarthritis and IVD degeneration is in sharp contrast to the number of drug delivery based products available for the patient, showing several hurdles still need to be overcome. These include a lack of understanding *of in vivo* release and optimal timing of the intervention, but also the regulatory hurdles and risks that are specific for local controlled drug delivery approaches.

3.1. Unpredictability in vivo release

One hurdle towards efficient development of effective drug formulations is the frequently observed discrepancy between *in vitro* and *in vivo* release profiles. Typically the loading and release profiles of drug delivery formulations are tested and fine-tuned *in vitro* in simple buffers such as PBS, with or without detergent, with regular sampling over time [125,126,168]. However, these test systems deviate substantially from the *in vivo* conditions. An important *in vivo* determinant of local release of hydrophobic drugs is for example the presence of drug binding interstitial fluid proteins. This was illustrated by the enhanced release of encapsulated drugs by immersion in natural or mimicked body fluid compared to PBS [169,170]. Also, the rate of *in vivo* fluid exchange is not very likely to be reflected by changing buffers at predefined time points and will differ between different tissues and organs and maybe even degenerative state of the tissue. For example, in a non-vascularised structure such as the IVD, fluid exchange will be minimal and hence retention higher than in the joint [12]. Indeed, TGF injected in rabbit IVDs was still detectable after 28 days [139], while injection of a cytokine mix containing TGF in human OA knees demonstrated clearance within 3 days [171]. In addition, in contrast to many other body locations, the biomechanical loading of the articular joint and IVD also likely contributes, most possibly in an organ-specific manner, to fluid flow and in addition may enhance penetration of the drug into the tissue [172]. Furthermore, under these well-defined *in vitro* conditions degradation of the polymers present in the formulation only occurs by chemical hydrolysis, while some are also enzymatically cleaved as shown e.g. for the PEA-based microspheres [127]. Within this context, the joint/disc-specific characteristics with respect to enzyme activities affecting release profiles and biomaterial degradation remain to date unknown. Finally, the biomaterial response, a process known to depend on defined physicochemical properties of the biomaterial used, to the carrier will affect release by modulating erosion and the formation of a fibrous capsule [173].

Drug delivery and release from locally administered formulations *in vivo* could become controllable and thereby tailorable if the relative contribution of abovementioned factors governing local drug concentrations can be established and are taken into account during formulation development and testing (Fig 6). To this end, medium to high throughput systems mimicking the tissue-specific *in vivo* conditions are essential to determine the role and interrelationship of each factor. Moreover, advanced imaging modalities that realtime follow drug presence *in vivo* over time [122], detect local fluid flow [174] or can delineate the preferential tissue for drug accumulation, such as mass spectrometry imaging [175], are crucial tools to validate these findings and provide mechanistic insights into, and control of, *in vivo* local drug release and retention upon administration of sustained release polymer-based formulations. Study designs should in addition always ensure the inclusion of a direct injection of free drug as control, to establish the effect and added value of using polymeric controlled release on all outcome parameters.

3.2. Early vs late intervention

As mentioned above and also depicted in Tables 1 and 2, most of the encouraging results with local administration of polymeric drug formulations in OA and IVD degeneration were obtained in early stages of degeneration. This implies that most likely progress of degeneration was prevented rather than reverted. This is further supported by the complete prevention of osteophyte formation by CXB-loaded microspheres in induced OA in rats [116] which are normally already present in

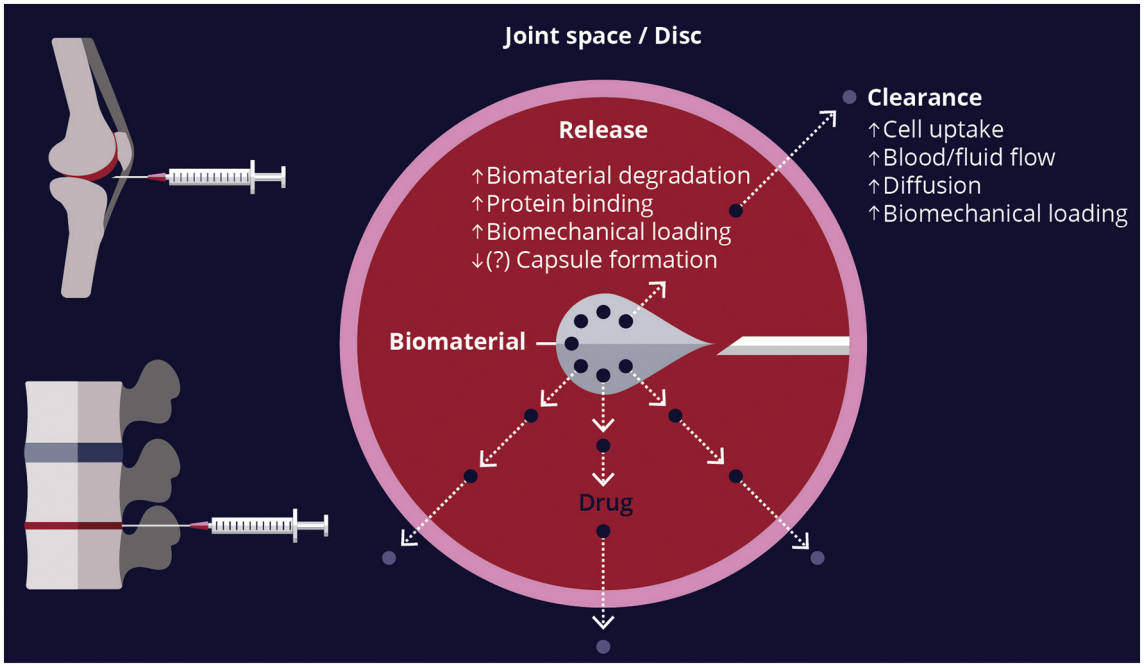

Fig. 6. In vivo drug release from locally administered formulations could become tailorable towards effective local levels over extended periods of time if the relative contribution of the factors influencing drug release and clearance of the drug and biomaterial can be established and are taken into account during formulation development and testing.

established OA. Possibly, the biochemical and/or biomechanical environment of the affected joint differs in tissues where degeneration was recently induced, compared to those where degeneration has been established over longer periods of time [176]. The former is more alike the situation in the rodent and rabbit OA/IVDD models, or the bovine *ex vivo* IVD degeneration model. The latter is more typical for canine and human patients with naturally occurring disease. In addition, also the phenotype of joint and IVD cells themselves may have changed, either or not related to the process of senescence [177–179]. Senescent cells are not only non-regenerative but also produce and release inhibitory signals such as pro-inflammatory molecules preventing tissue repair [180]. Early intervention may therefore be more effective. Some preliminary support for this approach was provided in a small study on patients with acute ACL tears, who when treated with one intra-articular dose of IL1RA preceding ACL surgery, showed better recovery than those receiving placebo [181]. This type of joint trauma is associated with post-traumatic OA [182], providing a well-defined patient population for preventive local drug delivery. Larger studies over a prolonged period of time [183] need to then show whether the development of OA is indeed inhibited. However, this pertains to a relatively limited patient population. For other forms of OA and for CLBP patients, early intervention would require the identification of reliable biomarkers or predictive characteristics to identify patients in the early stages of disease, as most patients will present with late-stage disease.

Nevertheless, even in advanced spontaneous disease as occurring in humans and canine patients, at least long term pain relief can be achieved by local [120] and also probably corticosteroid [124] delivery. As pain is the major cause for loss of quality of life, this would already represent a major step towards successful treatment.

3.3. Regulatory and safety issues

Bringing advanced drug delivery systems to the clinics will also require a shift in mind-set from a regulatory perspective. Although local sustained drug release is essentially safe at the systemic level, local prolonged exposure may have local side effects that are not induced upon systemic administration or direct local injection of the drug. This was for example demonstrated in ACLT/DMM-induced OA in rats. In this study, PEA microsphere-delivered TAA aggravated joint damage, in contrast to the same dose as a bolus, due to interference with tissue healing [123]. The latter was further supported by the observation that the treatment did not induce these effects in healthy rat joints or in collagenase-induced OA in rats [122] (Fig 3). Hence novel safety tests should be developed and incorporated in the standard regulatory guidelines of institutes such as the FDA and the EMA. On the other hand, the approval of established drugs administered locally in different formulations, modes of application or disease areas, currently requires extensive and expensive testing focussed on systemic toxicity. However, for local drug delivery products, this extensive testing is not justified as the risks associated are inherently low due to the low and short systemic exposure to drugs using this technology [116,122,123,184].

Also, the mode of administration entails specific risks, especially for CLBP related to IVD degeneration. One of the main differences between the articular joint and the IVD is the fact that the joint capsule does not have an important mechanical function, in contrast to the annulus fibrosus of the IVD. Hence, injection may compromise the annulus fibrosus integrity in IVD and induce disc herniation. Indeed, intradiscal injection has been suggested to be harmful, as provocative discography as a means to diagnose disc-related pain resulted in enhanced IVD degeneration[185]. However, as was pointed out later by several researchers in the field, this is most likely due to the overpressurization of the IVD using high volumes of radiopaque agents [186,187]. The latter were in addition shown *in vitro* and *in vivo* to be toxic to IVD cells [188]. As such, it may not be the injection per se, but rather the procedure coupled to the injection that may be harmful, like provocative discography. Within the concept of local controlled drug delivery, the key elements to be embedded within the therapeutic strategy need to respect disc integrity by employing: (a) safe carriers and biomaterials, (b) relatively small volumes to be injected and (c) relatively small needle diameter size to minimize tissue injury. By adhering to these rules, in preclinical studies in canines that are susceptible to developing disc degeneration and disease, additional degeneration was not observed with a 6 months follow up period, not even in mildly degenerated

IVDs injected with vehicle controls as compared to non-injected IVDs [151,189,190]. Nevertheless, injecting the IVD will be more of a challenge than intra-articular injection. Over-the-needle systems that enable down-scaling the size of the needle entering the disc and injection volumes that do not interfere with the intradiscal pressure should be considered from a practical perspective to enable widespread safe clinical implementation of local drug delivery, particularly in the degenerated intervertebral disc. As such the combined use of carriers that, in addition to delivering drugs targeting degeneration or pain, also can seal off the injection site in the annulus fibrosus may confer further safety on this treatment strategy [191].

Finally, both prevention and treatment of disease will still likely require multiple injections. Although the intervals between injections will be longer compared to free drug, this may pose a problem in some patients with an increased risk for infection, e.g. due to a high Body Mass Index (BMI ≥ 25kg/m^2) [192]. Also in late-stage OA disease, prior intra-articular corticosteroid injections present a slightly higher risk of joint infection upon prosthesis surgery, which is inversely related to the time interval between surgery and the last injection [79,80]. This is likely related to the immune-suppressive effect of corticosteroids, as multiple intra-articular injections with hyaluronic acid are not associated with high infection rates if hygiene guidelines are observed [193]. Altogether, development of drug delivery systems that allow for release over one or more years, such as in contraceptive uterine devices, will at least partially provide a solution to these chronic diseases. More research will define the exact risks involved and their magnitude, which will allow balancing the risks of local versus systemic treatment against clinical need.

4. Perspectives

Drug delivery systems that locally release their payload hold great promise for efficient and safe treatment of osteoarthritis and chronic low back pain. Long term pain relief is within immediate reach and a better understanding of pathology combined with novel drug targets and drugs may in the future lead to permanent solutions such as regeneration. Rational design of drug formulations based on the understanding of local conditions affecting release and retention will greatly enhance the efficacy of the therapeutic effects and also costs of development. In addition, care must be taken to use appropriate *in vivo* or *ex vivo* models of established disease where the aim is to treat rather than to prevent. Taking the differences between the articular joint and the IVD in health and disease into account will further allow for smart development of effective treatments.

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A cross-section of an intervertebral disc (human) and a knee joint (rat) in health and disease. The synovial joint cavity (Syn) contains synovial fluid that nourishes the articular cartilage (AC) covering the articular surfaces of the bones; Mn: meniscus. The intervertebral disc does not have a joint cavity; it consists of the central nucleus pulposus (NP), the outer fibrillar annulus fibrosus (AF), and the cartilaginous end-plates (EP) that anchor the disc to the adjacent vertebral bones. The challenging biomechanical function of the synovial joints and the IVD during daily activity is supported by a healthy extracellular matrix rich in glycosaminoglycans (GAGs) enclosed within a network of collagen fibres. The ratio of GAG:collagen changes with degeneration due to considerable loss of GAG in both cartilaginous tissues (NP and AC) as illustrated by the two stainings commonly used to study this on histopathology.

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