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Review

The current state of the osteoarthritis drug development pipeline: a comprehensive narrative review of the present challenges and future opportunities

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***Abstract*:** In this narrative review article, we critically assess the current state of the osteoarthritis (OA) drug development pipeline. We discuss the current state-of-the-art in relation to the development and evaluation of candidate disease-modifying OA drugs (DMOADs) and the limitations associated with the tools and methodologies that are used to assess outcomes in OA clinical trials. We focus on the definition of DMOADs, highlight the need for an updated definition in the form of a consensus statement from all the major stakeholders, including academia, industry, regulatory agencies, and patient organizations, and provide a summary of the results of recent clinical trials of novel DMOAD candidates. We propose that DMOADs should be more appropriately targeted and investigated according to the emerging clinical phenotypes and molecular endotypes of OA. Based on the findings from recent clinical trials, we propose key topics and directions for the development of future DMOADs.

Keywords: clinical phenotype, clinical trials, disease-modifying osteoarthritis drugs (DMOADs), drug development, molecular endotype, osteoarthritis (OA)

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Information source

We conducted a literature search in PubMed, Scopus, Embase, Web of Science, and Clinicaltrials.gov. An electronic search using keywords was performed; keywords included 'DMOAD', 'Osteoarthritis', 'Clinical trial', 'Preclinical study', 'Therapeutic agent'. References were selected for inclusion if the investigated DMOAD candidate demonstrated evidence of structural and/or functional improvement for osteoarthritis (OA) at the pre-clinical stage.

For this comprehensive narrative review, we excluded candidate disease-modifying osteoarthritis drugs (DMOADs) for which there have been no recent updates in terms of clinical trial progress for more than 5 years.

Introduction

OA is the most common form of arthritis in adults and is a leading cause of chronic pain and functional decline leading to long-term physical disability.[1] The knees are most frequently affected by OA, followed by the hips and the hands.[2] There is increasing evidence to suggest that global prevalence rates of OA are expected to increase in line with increasing life expectancy and growing levels of obesity.[3] Despite the limitations in our understanding of OA pathogenesis, it is increasingly recognized that OA is not a homogeneous disease and can be broadly divided into several subtypes, known as phenotypes, based on clinical presentation.[4–6] OA disease progression is typically assessed by changes in joint space width (JSW) measured on plain radiographs. Increased JSW is

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widely accepted to be a surrogate maker of cartilage degradation and structural progression. In recent years, advances in diagnostic imaging combined with an improved understanding of molecular alterations in the intra-articular environment have suggested that OA is a disease of the joint as an organ.[7] Disease progression is not restricted to the articular cartilage compartment and involves all joint tissues, featuring inflammation in the intra-articular environment, articular cartilage degradation, subchondral bone changes, and synovitis.[7–10]

There is increasing evidence to suggest that there are intrinsic and extrinsic factors that contribute to OA progression. Extrinsic factors refer to factors outside the joint and its surrounding area. These include repeated physical micro-trauma, which have been recognized as traditional causes of OA. Intrinsic factors are related to the joint itself, such as aging, gender difference (varus-valgus malalignment at the knee), obesity, and inflammation.[11,12] In recent years, intrinsic factors have also been recognized as major factors of OA progression. Altered joint biomechanics, metabolism, and low-grade inflammation play critical roles in the pathogenesis of OA and research efforts have focused on the development of DMOADs that act on these contributing pathways.[13,14]

Due to aging societies, the global prevalence of OA has grown.[15] In the United States, one-third of adults aged ⩾60 years currently show evidence of symptomatic OA, and the number of patients with OA is predicted to exceed 70 million by 2040.[16] Thus personal and societal medical costs for the treatment and management of knee OA are increasing rapidly.[17,18] Despite the rising global burden, current therapeutic agents for OA are limited with non-pharmacological and pharmacological treatment strategies designed to alleviate pain and improve function.[19–23] Currently, there are no DMOADs that have been approved and licensed by the regulatory agencies. In late-stage disease, and in cases of persistent joint symptoms, patients may require joint replacement surgery.[24] However, despite optimal management, up to 20% of patients experience no/little symptom improvement following knee arthroplasty.[25] Subsequently, the question arises as to what must be done in cases where all rational treatment options have been exhausted along the treatment algorithm. To overcome these limitations, there is an unmet and growing need for the development of therapeutic agents that can prevent further structural deterioration, restore joint structure, and improve symptoms. Disease-modifying OA drugs (DMOADs) have the capacity to fulfill such requirements. Although several DMOAD candidates have been evaluated in clinical trials until the 2020s, there are no DMOADs that have been approved by regulatory agencies, for a variety of reasons such as safety (i.e. adverse side effects), an unfavorable risk-to-benefit ratio, and ultimately the failure to demonstrate convincing patient benefits, including symptom modification and structural protection.[26,27]

In this narrative review, we summarize the current definition of DMOADs and provide an update of the pre-clinical and clinical results of novel DMOAD candidates. We categorize each of the respective candidates according to their developmental stage. Based on the available data from pre-clinical, translational, and clinical studies, we suggest key topics and directions for the development of future DMOADs.

DMOADs definitions and evaluating outcomes used for current OA clinical trials

To our knowledge, there is no updated definition for DMOADs. Furthermore, there are no regulatory guidelines for the assessment of clinical outcomes for DMOADs. Instead, with reference to the 'guidelines for the development of OA drugs', as described by the US Food and Drug Administration (FDA), OA drugs should meet the following criteria:[28]

> 'The ultimate goal of treatments related to inhibition of structural damage or targeting the underlying pathophysiology associated with OA is to avoid or significantly delay the complications of joint failure and the need for joint replacement, and also to reduce the deterioration of function and worsening of pain'.

Based on published literature about DMOADs and FDA guidelines, we can summarize the definition of DMOAD as follows:[26]

'DMOADs should 1) delay or reverse the progression of the disease, and 2) provide the patient with long-term medical improvements'. In essence, the efficacy of DMOADs in OA refers to their clinical benefit and an improvement in how a patient (1) feels or experiences pain or other symptoms, (2) functions or physically performs

with their affected joint(s), and (c) survives or maintains a healthy joint(s).

The process of developing candidate OA drugs is highly complex, time-consuming, and challenging. OA drugs can be divided into two groups: those that impact on structure and those that improve symptoms. However, the criteria for DMOAD development require the establishment of endpoints that can satisfy both of these conditions. There are two reasons why structural outcomes are not used in the evaluation of OA drug efficacy. First, there is no clear definition regarding the course of OA progression, and there is no consensus regarding outcomes that accurately reflect the extent of disease progression. In the Kellgren and Lawrence (K&L) classification system, which is a current standard commonly used to assess radiographic structural OA severity, the disease is diagnosed based on the presence of joint space narrowing (JSN) and the presence or absence of osteophytes which are observed in the event of excessive bone remodeling at the joint margins (Table 1).[29] While K&L scoring is frequently used to define radiographic knee OA, limitations of this scoring method have been reported, and modified grading systems have been developed and applied to overcome these limitations.[29–32]

The classification of OA based on K&L grading has been commonly used to assess the extent of structural improvement/worsening in the joint space and surrounding joint tissues. It has the advantage of being quickly processed and can be applied in both research and clinical settings. There are, however, several conceptual and technical challenges associated with using radiography to assess OA severity. For example, due to limitations in resolution, it is not possible to differentiate degradation of the joint cartilage or menisci, and the relationship between radiographically assessed structural changes and knee symptoms is not well established.[33,34] Due to the inability to visualize and assess changes in soft tissues on radiographs, it has been suggested that at least 1–3 years of follow-up are required to identify significant trends, but for many patients, the actual period of clinical OA progression is less than 52 weeks.[35,36] It is not clear whether observing significant changes in joint structure and/or symptoms within 1 year reflects the true nature of OA when the disease itself has likely developed and progressed over several years. As imaging technology has improved, magnetic resonance imaging (MRI) has been highlighted as an alternative imaging modality to overcome the previous limitations.[37,38] MRI has several advantages over conventional radiography. For instance, MRI can be used for the assessment of peri-articular soft tissues and for identifying bone marrow lesions (BMLs), and synovial inflammation. More sophisticated MRI techniques exist which use intravenous contrast agents which allow for the differentiation of effusion and synovitis.[39,40] However, there are also several limitations to using MRI for OA assessment. First, MRI is much more expensive and time-consuming than conventional radiography, and there is still debate regarding optimal MRI measures which may be used for the assessment of OA progression.[41] In summary, conventional radiographic imaging is convenient and commonly used, but it does not reflect all the changes in the joint, and while MRI overcomes these limitations, high costs and operating times also prevents widespread use in clinic. For these pragmatic reasons, radiography and MRI need to be combined for the objective assessment of structural changes and the evaluation of novel therapeutics in OA clinical trials. However, MRI is costly and has not been approved as a gold standard by the regulatory agencies.

Although the correlation between structural changes and symptoms is important in OA, assessment of joint structure by itself is not sufficient for evaluating the efficacy of new DMOADs. When evaluating an OA patient's quality of life, outcomes related to functional improvement are far more relevant than just structural improvement. Starting with the knee grading system suggested by Donoghue in 1995, a number of outcomes have been widely used to assess a patient's pain intensity or motor ability The Arthritis Impact

Table 1. Summary of K&L grades.

Grade 0	No radiographic features of OA are present
Grade 1	Doubtful JSN and possible osteophyte lipping
Grade 2	Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	Multiple osteophytes, definite JSN, sclerosis, and possible bony deformity
Grade 4	Large osteophytes, marked JSN, severe sclerosis, and definite bony deformity

JSN, joint space narrowing; K&L, Kellgren and Lawrence grade; OA, osteoarthritis.

Measurement Scale (AIMS) was devised to assess health-related quality of life in patients with rheumatoid arthritis (RA) in 1980.[42] Since then, various tools and patient-reported outcome measures (PROMs) have been developed to capture a patients symptom state, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), modified versions of KOOS, painDETECT, and the International Knee Documentation Committee (IKDC) scoring system.[43]

The main factors to consider when selecting a suitable outcome for a clinical trial are reliability, validity, and relevance to the mode of action of the drug or intervention. For instance, using outcomes known to have high concurrent validity can overcome the difficulty of interpretation and, most importantly, increase confidence in the observed results. For example, the WOMAC pain subscale is known to have a high level of reliability for the assessment of knee pain in OA, while also having high concurrent validity with Lequesne algofunctional index (LAI) and Short Form-36 (SF-36).[44,45] Table 2 summarizes the key features and correlation between several functional assessment outcomes that are commonly used in the evaluation of OA.[46,47]

One of the greatest obstacles to understanding and interpreting treatment effects in OA clinical trials is the powerful placebo effect which has been previously described.[48] In a large meta-analysis of randomized clinical trials ($N = 198$), significant effects on pain relief and functional improvement were observed among the placebo arm groups.[49] Most candidate drugs have demonstrated treatment effects that do not surpass the placebo effect and thus fail to demonstrate statistically significant and clinically relevant improvements; to the extent that some groups have even suggested using placebo for treating the symptoms of OA.[50] Based on the OA assessment criteria described above, the items required to meet the conditions for a DMOAD have been summarized in Table 3.

In addition, in recent years, biochemical markers measured in serum and synovial fluids have gained popularity as a means of assessing the OA disease state and predicting clinical outcomes. Using biochemical markers to evaluate OA progression is an attractive approach due to the ease and convenience of collecting biospecimens, and the ability to perform immunoassays. One of the main weaknesses of plain radiography is the inability to capture early OA. By the time OA is diagnosed and confirmed radiographically, the disease has already reached a relatively advanced stage.[51] Current thinking suggests that once OA has reached an advanced stage, the ability to prevent further disease progression and even promote structural repair may be significantly reduced.[52] OA can be treated more effectively if it is diagnosed at an earlier stage and there are ongoing efforts to identify biochemical markers that enable an earlier clinical diagnosis.[53] The biochemical markers which have shown promise as suitable candidates for clinical evaluation include pro-inflammatory factors and products of cartilage matrix degradation.[54] In particular, some of the most researched factors are matrix breakdown products released following the degradation of type II collagen and aggrecan, which are the major structural components of articular cartilage matrix. C-reactive protein (CRP) and c-telopeptide of type II collagen (CTX-II) are two biochemical markers that have been assessed in recent clinical trials.[55,56]

However, the majority of biochemical markers that have been studied to date for the assessment of clinical outcomes have significant limitation because they do not accurately reflect clinical symptoms in most patients.[57] Biomarkers are typically measured in serum or urine, but the metabolic products from the affected joint space are greatly diluted in these systemic biofluids.[35] In addition, biomarkers are sensitive to biological changes, such as circadian rhythms, diet, and physical activity.[58] Despite these limitations, biomarker research is thriving because of the proliferation of omics tools and technologies. Biochemical markers offer the advantage of broadening our understanding of the molecular events that occur in the early phases of OA pathogenesis, potentially highlighting the window of opportunity for targeted early interventions. They can also help to expand and diversify the diagnostic platforms and methods that employ biochemical markers. For example, if we can identify a biomarker that reproducibly and consistently increases in terms of expression levels in serum before a patient begins to feel pain, early treatment can be initiated to slow disease progression and preserve long-term joint function. This strategy can be especially helpful for targeting early

Table 2. Main features of outcomes used for the clinical assessment of the knee joint.

Assessment	Response options	Subscales	Total items/ scoring	Validity/responsiveness	Notes
AIMS	5-point scale	Nine subscales (mobility, physical activity, dexterity, household activity, social activities, activities of daily living, pain, depression, and anxiety)	45 items/0~60 score	Good validity and responsiveness in patients with arthritis	The first established assessment specifically designed for arthritis outcomes studies
AIMS2	5-point scale	12 subscales (AIMS with arm function, social support, and work)	101 items/0–60 score	Similar validity and responsiveness with AIMS	Better psychometric properties and the advantage of including patients' improvement compared with AIMS Difficult to use for daily treatment due to long postal surveys
HAQ-DI	4-point scale/ VAS	Three subscales (disability, pain, and health status)	22 items/0–66 score	Good construct validity, internal consistency and reliability Content validity and responsiveness were limited	An effective, reliable, and sensitive instrument capable of quantitative analysis Patient-reported assessments indicator used across various diseases including arthriti
WOMAC	5-point scale/ VAS	Three subscales (pain, stiffness, and function)	24 items/0–96 score (derived from a 5-point scale)	Well validity and good test–retest reliability	The most widely used assessment for OA; The target population is limited to elderly population
KOOS	5-point scale	Five subscales (pain, symptoms, activities of daily living, sports activity, and quality of life)	42 items/0–100 score	Adequate validity, internal consistency, test–retest reliability, construct validity, and responsiveness for age- and condition-relevant subscales	An assessment that includes younger patient groups Generally used for injury-related symptoms assessment
OKS	5-point scale	Two subscales (pain and function)	12 items/0–48 score	Proven to be valid and sensitive to clinically important changes over time, specifically in patients undergoing a total joint replacement	An assessment to determine the need for joint replacement surgery

(Continued)

Table 2. (Continued)

Assessment	Response options	Subscales	Total items/ scoring	Validity/responsiveness	Notes
IKDC	Yes or no; 5/10-point scale	Three subscale (symptoms, sports activity, and function)	10 items/0–100 score	Good internal consistency, test–retest reliability, content and structural validity, and responsiveness	A major assessment used in research and clinical trials
LAI	Multiple-choice/5-point scale	Three subscales (pain, maximum distance walked, and activities of daily living)	11 items/0–24 score	Similar validity and good test–retest reliability compared with WOMAC	An assessment used to evaluate severity of OA in elderly population. Measuring mainly the type of pain and the duration of stiffness
OARSI Physical Performance Measures	Physical performance–based analysis	Physical performance	5 items/ distance or time	Good known-groups validity, acceptable reliability compared with KOOS	Performance-based physical function assessment Consists of three minimum core set (30-s chair stand test, 40-m fast-paced walk test, and stair climb test) and two recommend set (Timed up & go test and 6-minute walk test)
SF-36 ASHI	Yes or no; 2~6-point scale	Eight subscales (physical functioning, bodily pain, general health, vitality, role physical, role emotional, social role functioning, and mental health)	11 main, subdivided into 36 items/0–100 score	Associated with poor criterion validity and reproducibility	An assessment used to evaluate the changes in clinical severity of arthritis Measuring both physical health and mental health at the same time

AIMS, Arthritis Impact Measurement Scale; ASHI, Arthritis-Specific Health Index; HAQ-DI, Health Assessment Questionnaire Disability Index; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; LAI, Lequesne algofunctional index; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OKS, Oxford Knee Score; SF-36 ASHI, Short-Form Health Survey of Arthritis-Specific Health Index; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

OA and potentially modifying it with the right interventions. As such, there have been large collaborative biomarker studies conducted by public–private partnerships involving many investigators with expertise in clinical trial design, biochemical markers, imaging, and statistics. The Foundation of National Institutes of Health (FNIH), which performs related research in this area, has compiled a list of important biochemical marker candidates based on the results of previous clinical studies. The FNIH consortium has already collected and analyzed relevant data, with the aim of uncovering biochemical markers that can reflect structural and symptomatic changes in response to an appropriate intervention in a clinical trial.[59,60] Table 4 summarizes a list of candidate biochemical markers that can potentially be investigated as an outcome of OA due to changes in expression levels in clinical studies.[60]

Several candidates for OA have been examined or are currently in the process of being assessed in clinical trials using evaluating outcomes that have been selected to assess the mechanisms of action. In the next section, we will describe the two main therapeutic mechanisms of DMOAD candidates.

Therapeutic mechanisms of DMOAD candidates

Although there are several hypotheses regarding the pathogenesis and progression of OA, it is clear that an imbalance between anabolic and catabolic activity within the joint leads to increased tissue degradation leading to structural collapse of the joint space and subchondral bone due to excessive production of pro-inflammatory, catabolic, and pro-apoptotic factors. Degradation of joint structures results in restricted movement, and sensitization of peripheral and central sensory pathways causes pain.[61] Based on these mechanism, approaches to OA drug development can be broadly divided into two types, induction of anabolic factors and inhibition of catabolic factors.

Induction of anabolic factors

In order to slow down the disease progress, intra-articular injections of cells (i.e. chondrocytes and stem cells) and cell-derived factors that stimulate chondrogenic differentiation may be supplied exogenously to support cartilage regeneration and repair. Representative therapeutic candidates known to induce structural improvement effects in the articular cavity include growth factors and bone morphogenetic proteins (BMPs).

Table 3. Practical understanding of current EMA or FDA guidance on DMOAD.

Structure improvement	Symptom improvement
Radiographic indicator (JSN) MRI indicator (cartilage volume and thickness) Non-cartilage indicator (BML, synovitis, andv effusion)	Pain indicator Function indicator Delay of surgical intervention
To obtain approval, both conditions must be met.	

BML, bone marrow lesion; DMOAD, disease-modifying osteoarthritis drugs; EMA, European Medicines Agency; FDA, US Food and Drug Administration; JSN, joint space narrowing; MRI, magnetic resonance imaging.

Inhibition of catabolic factors

Reducing the increased levels of local pro-inflammatory and pro-apoptotic factors in the joint space is considered to be a useful strategy for inhibiting further structural degradation in OA. Therefore, numerous clinical trials have been conducted to evaluate the efficacy of drugs that suppress the activity of pro-inflammatory cytokines (i.e. tumor necrosis factor alpha and interleukin 1 beta) or growth factors associated with pain, such as nerve growth factor (NGF). Among these, NGF inhibitors have been shown to suppress OA pain. Therefore, several drug development programs have focused on targeting NGF signaling. For instance, tanezumab is a humanized recombinant monoclonal immunoglobulin G2 antibody that works by inhibiting the binding of NGF to its receptors, thereby reducing pain in OA. However, in March 2021, the FDA's Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSARM) rejected tanezumab as a drug for OA. During clinical trials, several adverse events, including rapidly progressing OA (RPOA), were reported, and the risks of using tanezumab appeared to outweigh the benefits. Once again, this highlights the requirement for long-term safety as well as efficacy when developing DMOADs.

In the next section, we will describe several DMOAD candidates that have conducted more than Phase II clinical trial. By summarizing the mechanism and clinical progress of each candidate material, we would like to identify their strengths and limitation.

Table 4. Representative candidates for OA biomarkers.

Category		Biomarker candidates
Joint composition	Cartilage matrix	CTX-II, NTXs, COMP, MMPs, Col10neo, PIIANP, PIIBNP, AGNx1, HA, and so on.
	Synovial matrix	Col3-ADAMTS, C3M, and so on.
	Bone matrix	Pyridinolin, deoxypyridinolin, and so on.
Pathological mechanism	Inflammation	CRP, IL-1β, IL-6, IFN-γ, TNF-α, endothelin, clusterin, MCP1, and so on.
	Obesity	Leptin, adiponectin, insulin, ghrelin, HGF, uric acid, and so on.
	Oxidative stress	Nitrotyrosine, Coll2-1NO2, and so on.
	Angiogenesis	CXCl10, FGF1/2, PDGFAA/BB, ANG1, and so on.
	Others	Autoimmunity-IgG autoantibodies against TSP-4, COMP and CLEC3A Crystal formation-fetuin-A, Sensitization-neurotrophic factor
Metabolic change	Carbohydrate metabolism	Glycolysis, citric acid cycle, and so on.
	Amino acid metabolism	Taurine, hypotaurine, arginine, proline, and so on.
	Fatty acid metabolism	Acylcarnitines, glycerolipids, and so on.

AGNx1, ADAMTS-degraded aggrecan; ANG, angiopoietin; C3M, collagen type III degraded by matrix metalloproteinase; CLEC3A, C-type lectin domain family 3 member A; Col10neo, collagen type X neoepitope; COL3-ADAMTS, collagen type III cleavage product derived from ADAMTS; Coll2-1NO2, nitrated epitope of the a-helical region of type II collagen; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; CTX-II, C-terminal cross-linked telopeptide of collagen type II; CXCL10, C-X-C motif chemokine 10; FGF, fibroblast growth factor; HGF, hepatic growth factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MMPs, matrix metalloproteinases; NTX, N-telopeptide crosslinks; OA, osteoarthritis; PDGF, platelet-derived growth factor; PIIANP, PIIBNP, N-terminal propeptide of type II collagen, splice variants IIA and IIB, respectively; TNF, tumor necrosis factor; TSP, thrombospondin.

DMOAD candidates undergoing clinical trials

Induction of anabolic factors

Recombinant human fibroblast growth factor-18 sprifermin). Sprifermin, also known as recombinant human fibroblast growth factor 18 (rhFGF18), is a recombinant form of human fibroblast growth factor 18 (FGF18) produced in a bacterial expression system as a therapeutic fusion protein.[62] The efficacy of sprifermin for cartilage regeneration has been demonstrated in a number of pre-clinical animal models, including an ovine defect model and a surgical rat model.[63,64] Based on these pre-clinical studies, several clinical trials have been conducted. In 2008, a phase I clinical trial of intra-articular sprifermin initiated with 168 patients and one of the secondary endpoints (cartilage thickness measured by MRI) showed a statistically significant effect.[65] Following the completion of a phase I clinical trial, a 5-year dose-ranging, randomized, placebo-controlled phase II clinical trial (FORWARD) was initiated in 2013. To assess structural improvements, the loss of cartilage thickness in the central medial compartment of the femur was measured by MRI as the primary endpoint while the cartilage thickness was assessed in the rest of the femur (excluding the central medial compartment) as the secondary endpoint. To assess the extent of functional improvement, changes in the WOMAC and VAS scores were included as secondary endpoints.[66] The results after 2 years of follow-up were presented at the American College of Rheumatology annual conference in 2017. In the first 2 years, sprifermin treatment showed statistically significant improvement in total joint cartilage thickness from baseline compared with the placebo group, but the outcomes obtained

were of uncertain clinical importance. In addition, the results after 3 and 5 years of follow-up revealed a decrease in overall cartilage thickness between years 2 and 3, and the secondary endpoints for functional improvements showed no decrease in pain compared with that of the placebo group. These results were published in JAMA in 2019.[67] Taken together, sprifermin is still a promising pro-regenerative therapeutic candidate, but it cannot qualify as a DMOAD because it does not appear to have any significant impact on OA pain symptoms. The clinical development of sprifermin has since been halted. Further development of this asset will require phenotyping and stratification of patients in future clinical trials. Selecting patients who possess the right phenotype for pro-regenerative treatments may be a necessary pre-requisite for demonstrating functional improvement following administration of sprifermin.[62]

Transforming growth factor β1 induction (Tissue-Gene-C, TG-C). Transforming growth factor β1 (TGF-β1), a member of a protein superfamily with over 35 members expressed in multicellular organisms, controls a number of important processes in both healthy and diseased states, including cell proliferation, tissue formation and repair, and inflammation.[68] Regarding structural improvements in chondrocytes, TGF-β1 is known to mediate the synthesis of the cartilage structural components such as proteoglycans and type II collagen by binding to chondrocyte receptors.[69] TG-C is a new cell-based gene therapy that utilizes the biological activity of TGF-β1 to improve cartilage structure and induce anti-inflammatory effects. TG-C is a 3:1 mixture of human chondrocytes (HCs) derived from a donor with polydactyly and GP2-293 cells engineered to over-express a gene that secretes TGF-β1, which is known to play important roles in cartilage differentiation and immune regulation.[70] The efficacy was analyzed in pre-clinical studies in a rat mono-iodoacetate (MIA) model, and the intra-articular TG-C administration group showed long-term pain relief and structural improvements. In these studies, TG-C administered by intra-articular injection changed the largely M1 macrophage-dominant pro-inflammatory environment to an M2-macrophage-dominant anti-inflammatory environment. Interleukin (IL)-10 and TGF-β1 play critical roles in this process.[71] In a 24-month phase II clinical trial on 102 patients in the United States, TG-C treatment did not cause any severe adverse effects. The primary endpoints of IKDC and VAS showed a statistically significant pain relief effect compared with that of the placebo, and the OMERACT-OARSI response rate also showed statistically significant effects after 6, 12, and 18 months.[72] Based on these clinical trial results, the investigators have received FDA approval for a phase III clinical trial, which is currently ongoing.[73]

BMP-7. BMPs are a group of proteins known to contribute to the differentiation of various cell types. Since they were first classified in 1965, more than 20 additional BMP subtypes have been found to date. BMPs play important roles in bone and cartilage differentiation processes, especially in the developmental stage, such as bone formation, hematopoiesis, and epithelial cell differentiation.[74,75] Focusing on these properties, several pre-clinical studies have been conducted to verify the efficacy of BMPs in OA models. These pre-clinical studies derived BMP classes with exceptional cartilage regeneration ability, which were then used in clinical trials of patients with OA. Among BMPs, BMP-7 has received particular attention as a potential candidate, and several studies have shown that BMP-7 has beneficial effects on chondrocytes. When BMP-7 was applied to an animal model with a surgically induced joint defect, regeneration of the injured cartilage was observed.[76,77] Based on these results, a clinical trial was conducted in 2007 to assess the safety when 0.03, 0.1, 0.3, or 1.0 mg of BMP-7 was intra-articularly administered to 33 patients with OA. No adverse reactions were reported in this clinical trial, and there was an improvement trend in the WOMAC pain score, which was a secondary endpoint outcome. Structural progression was assessed using radiography, which did not reveal any ectopic bone formation.[78] Based on the results of this safety assessment, a phase II clinical trial that enrolled 355 patients was conducted to assess BMP-7 efficacy, but the results have not yet been published[79] and no further progress has been reported in the literature.

Angiopoietin-like protein agonist (LNA-043). There are studies attempting to develop new therapies using candidate drugs that have demonstrated a cartilage-specific anabolic effect in the pre-clinical studies; one such candidate is LNA-043, an angiopoietin-like protein (ANGPTL) protein 3 agonist. The ANGPTL protein family is known to have various biological functions and is involved in the development, physiology, and pathology.[80–82] Based on these molecular mechanisms, a

phase I clinical trial was conducted in 2015 that enrolled 28 patients with OA awaiting total knee arthroplasty to assess the safety of LNA-043. As a result, intra-articular administration of LNA-043 showed no notable adverse effects.[83] Following this safety assessment, a randomized, double-blind, placebo-controlled, multi-center phase II clinical trial with 550 patients was initiated in 2021.[84] Each dose of LNA-043 was administered to patients, after which various outcomes over the course of 2 years will be measured. Cartilage thickness and proportion of participants demonstrating structural progression are included as endpoints to analyze structural improvement-related efficacy. In addition, WOMAC and OARSI physical performance–based assessment are used as functional improvement evaluating outcomes.

IL-10 induction (XT-150). IL-10 is an anti-inflammatory cytokine with the potential to decrease the expression of pro-inflammatory cytokine such as IL-1 beta and tumor necrosis factor (TNF) alpha and suppress matrix metalloproteinases (MMPs) activity in the joint microenvironment.[85] In chondrocytes, IL-10 is able to modulate inflammatory responses and cell apoptosis.[86] These molecular properties of IL-10 suggest that it may be used as a therapeutic for modifying the environment in the joint by the introduction of exogenously administered IL-10. XT-150 is a naked plasmid DNA-based IL-10 gene therapy that expresses a long-acting IL-10 variant and was specifically developed for the treatment of OA and neuropathic pain. XT-150, absorbed by synovial immune cells, aims to reduce inflammatory factors over a long period of time XT-150 treatment increased IL-10 expression levels in the knee joint and the treatment reduced OA-related pain behavior in a canine model of OA.[87] To evaluate the pain relief effect and safety of XT-150, in humans, a 1-year randomized, blinded, placebo-controlled phase II clinical trial with 290 participants was initiated in 2020.[88]

Inhibition of catabolic factors

Wnt pathway inhibitor (lorecivivint). Lorecivivint was developed as an inhibitor of the Wnt pathway, a signaling pathway that affects chondrocyte, osteoblast, and synovial cell differentiation. The Wnt pathway is known to influence cartilage degeneration and the onset of OA.[89,90] *In vitro* studies have demonstrated that lorecivivint modulates the Wnt pathway by inhibiting intranuclear kinase CLK2/DYRK1 activity, thereby suppressing inflammation. Moreover, when lorecivivint was intra-articularly applied to the joint in a MIA-induced rat OA model, MIA-induced pain was alleviated and cartilage structure was preserved.[91] Based on these pre-clinical studies, a phase II clinical trial was conducted with 455 patients in 2015, where a single dose of the drug at one of three different doses (0.03, 0.07, and 0.23 mg/2 mL) was intra-articularly administered and patients were followed up for 1 year. Using WOMAC, the patient global assessment was measured as an index of functional improvement and the primary endpoint. As a result, only the medium-dose group showed a significant decrease in WOMAC pain score, and there was no significant difference between the low- or high-dose groups.[92] In addition, a phase IIb clinical trial with 695 patients showed pain relief and functional improvement in both the low-dose (0.07 mg/2 mL) and high-dose (0.23 mg/2 mL) groups for 24 weeks. Post hoc analysis revealed that the low-dose treated group showed improved responses in pain and function compared to the placebo group, and this improvement lasted for 24 weeks.[93] However, the medial JSW used to assess the extent of structural improvement did not show significant improvement.[94] Based on these results, a phase III clinical trial was initiated in 2020 to evaluate long-term safety and efficacy in 500 patients.[95]

Cathepsin K inhibitor (MIV-711). Cathepsin K is a cysteine protease involved in bone resorption; it degrades type I/II collagen and aggrecan found in cartilage, and thus there have been attempts to develop OA therapies using candidate drugs that inhibit cathepsin K activity.[96,97]

MIV-711, a selective cathepsin K inhibitor has been evaluated as a DMOAD candidate in animal models and clinical trials.[97,98] The investigators confirmed subchondral bone structural improvement in an anterior cruciate ligament transection (ACLT) rabbit model and a partial medial meniscectomy canine model.[98] Even though no significant improvement in cartilage structure was observed, μCT analysis showed that MIV-711 can induce structural recovery in the subchondral bone. Biomarker analysis also showed that expression of bone resorption–associated biomarker, urine HP-1, or urine CTX-I were decreased in both animal models. Based on these pre-clinical studies, a 6-month, multicenter, randomized, placebo-controlled, double-blind, three-arm phase IIa clinical trial was conducted in 2017 to

assess the efficacy, safety, and drug tolerance of MIV-711 for patients with knee OA, and the intermediate results were published.[99] The patients in this clinical trial were orally administered 100 or 200 mg MIV-711 or a placebo four times a day for 26 weeks. The numerical rating scale (NRS) pain score, which quantifies the degree of pain a patient feels between 0 and 10, was measured as the primary endpoint, and the changes in bone area and cartilage thickness were measured using MRI as secondary endpoints to assess structural improvement. The pain relief effect of the drug was not significantly different from that of the placebo group. When the structural improvement effects were compared, the 100 mg group showed a statistically significant improvement in the medial femur cartilage compared with that of the placebo group, but neither 100 mg nor 200 mg showed significant effects on the tibia cartilage.[100] In a phase IIa clinical trial published in the Annals of Internal Medicine in December 2019, the investigators reported no statistically significant pain relief effect for patients treated with MIV-711 but observed a decreased trend in bone remodeling and cartilage loss in the MIV-711 groups compared with placebo. The authors concluded that MIV-711 may be effective for structural improvement but that further studies are required.[101] In addition, in the case of odanacatib, selective cathepsin K inhibitor targeting osteoporosis patients, it has been reported that cardiovascular risk increases due to administration.[102] In the case of MIV-711, no cardiovascular risk-related adverse events have been reported, but it can be a major precaution in the development of drugs targeting cathepsin K.

Senolytic small molecule inhibitor (UBX-0101). Senescent cells accumulate in tissues during the process of aging, and the secretion of factors involved in the development of the senescence-associated secretory phenotype (SASP) contributes to age-related pathology. Thus, if senescence cells are not properly cleared from the joint space, adjacent cells can also become affected by inflammation and apoptotic signaling. Indeed, based on the large numbers of senescent chondrocytes in cartilage isolated from patients who had undergone arthroplasty for OA, it can be hypothesized that the regulation of senescent chondrocytes affects OA progression.[103,104] UBX-0101 is an experimental senolytic that can selectively remove senescent chondrocytes by inhibiting MDM2/p53 interactions and verify that this senolytic agent increases senescent cell apoptosis and improves OA symptoms when intra-articularly injected into ACLT-induced OA mice.[105] Based on these results, a phase I clinical trial that enrolled 48 patients was initiated in 2018 to investigate the safety and efficacy of the drug; the results confirmed drug safety and showed improved WOMAC pain scores in the high-dose group.[106] In 2020, randomized, double-blind, placebo-controlled phase II clinical trial with 180 patients was completed and results have recently been released.[107] However, in August 2020, UBX-0101 failed to meet the primary endpoint on the 12-week phase II study. In the WOMAC-A, no significant difference was observed between the placebo or UBX-0101-treated group.[108] Aside from the disappointing outcomes of the short-term phase II study, another clinical trial has been conducted to compare the efficacy of repeated administration with a single administration, but no results have been released yet.[109]

IL-1 neutralization (anakinra and lutikizumab). IL-1 is a pro-inflammatory cytokine known to contribute to cartilage degeneration, and there is a long history of inhibiting IL-1 to prevent the progression of inflammatory forms of arthritis, especially RA.[110,111] As a powerful inducer of cartilage degradation, IL-1 induces the expression of genes involved in matrix destruction, such as MMPs, and is known to control the bioavailability of degradation-related factors.[112] However, the actual concentrations of IL-1 in the cartilage of OA patients are very low, thereby making it challenging to examine treatment effects and to measure using omics-based approaches. Therefore, there have been discussions regarding whether OA symptoms can be reduced by modulating IL-1. Representative clinical trials conducted to confirm the effect of local IL-1 control using intra-articular administration on improving the OA environment are as follows. In phase II clinical trial conducted in 2004 using anakinra (IL-1 receptor antagonist) for OA, no significant functional improvement was observed in anakinra-treated group.[113,114]

ABT-981 (lutikizumab) is another example of IL-1-targeted drug that has recently undergone clinical trials. Lutikizumab inhibits inflammatory activity by directly binding IL-1α and β. In a 1-year phase II clinical trial initiated in 2014, the WOMAC pain score of 350 patients was measured to analyze functional improvement, and the

extent of synovitis and effusion was found to reflect structural improvement.[115] Up to a certain point in the trial, the WOMAC pain score improved significantly in the medium-dose (100 mg) group, but there was no significant difference between the low- and high-dose groups. After 16 weeks, the WOMAC pain score decreased in all groups, and there were no significant differences compared with the placebo group. There were also no significant differences in the structural improvement.[116,117]

A disintegrin and metalloproteinase with thrombospondin motifs 5 inhibitor (GLPG1972/S201086). A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) is a representative cartilage matrix–degrading enzyme involved in the progression of OA. By degrading aggrecan, which plays an important role in maintaining the physical characteristics of cartilage, ADAMTS-5 results in a structural breakdown in the joint space and is expressed at high levels in tissue from patients with OA.[118] In the pre-clinical studies, OA was induced in ADAMTS-5-deficient mice, and the model's characteristics of cartilage degradation and pain were reduced.[119] Focusing on this cartilage-specific activity, several drugs are being developed to inhibit ADAMTS-5 activity in an effort to mitigate structural degradation of cartilage and OA progression. In 2010s, several highly selective monoclonal antibodies to ADAMTS-5 were developed.[120] GSK2394002, a humanized ADAMTS-5-selective monoclonal antibody is a representative example. In a surgical mouse OA model, systemic administration of GSK2394002 showed structural disease modification and alteration of pain-related behavior.[121] However, in safety pharmacology studies conducted in cynomolgus monkeys, GSK2394002-induced irreversible increases in arterial pressure. Due to this safety issue, no further development has been conducted.[122]

Another example of ADAMTS-5 inhibitor is GLPG1972/S201086. A pre-clinical study conducted using a meniscectomy rat OA model, oral gavage of GLPG1972/S201086 was able to regenerate damaged cartilage tissue. The regenerated cartilage showed higher proteoglycan content and reduced subchondral bone thickness compared with that of the vehicle group. *In vitro* studies showed that GLPG1972 could efficiently inhibit MMPs and ADAMTS-5 activity in OA.[123] These results were presented in EULAR 2018. In 2015, a phase I clinical trial was conducted with 41 patients to assess the safety and pharmacokinetics/pharmacodynamics of single or multiple doses of GLPG1972/S201086 for up to 14 days.[124] No specific adverse effects were observed in this clinical trial, and there was a decrease in ARGS neoepitope, which is a useful biomarker associated with cartilage degradation. The results of this clinical trial were reported at the EULAR and OARSI conferences in 2018. Based on these results, a 52-week international, multi-regional, multicenter, randomized, double-blind, placebo-controlled phase II clinical trial was started in 2018 with 938 patients.[125] Cartilage thickness in MRI was selected as the primary endpoint for structural improvement, and other MRI-related variables were also measured, such as bone area. The WOMAC, VAS, and OMERACT-OARSI responses were included to investigate effects on pain and functional improvement. In October 2020, it was reported that GLPG1972/S201086 failed to reduce cartilage loss of the central medial tibiofemoral compartment of the target knee *via* quantitative MRI, which was the primary outcome of the clinical trial.[126] They conduct additional analyses to fully evaluate the clinical results.

Pentosan polysulfate sodium. Pentosan polysulfate sodium (PPS), a semi-synthetic drug manufactured by chemical sulfonation of xylan derived from the European beech, has been used to treat blood clots and urinary tract infections for 70 years.[127] It is known to have a structure similar to that of natural glycosaminoglycans (GAGs), and it is presumed to have a protective coating effect on the damaged structure because of these structural similarities.[128]

Based on these protective effects, recent studies suggest that PPS could be used to treat other diseases. In OA environment, PPS could suppress the expression of NGF in the subchondral bone to ameliorate pain associated with OA.[129] In addition, it could stimulate the synthesis of hyaluronan and suppress the further structural collapse by forming a stable complex with TIMP-3, an inhibitor of ADAMTS-5.[130,131] Since 2020, a phase III clinical trial has been underway in the United States with 938 patients.[132] The clinical trial will evaluate both structural and functional improvement effects in OA patients.

Matrix extracellular phosphoglycoprotein (TPX-100). OA has been classically generalized as a joint cartilage disorder. However, a growing body of

literature has revealed that patients with OA show many histopathological changes in subchondral bone, which is related to disease progression.[133,134] Alongside this shift in perspective, studies have attempted to control disease progression by regulating subchondral bone. Matrix extracellular phosphoglycoprotein (MEPE), a protein expressed specifically by osteocytes and odontoblasts, inhibits bone mineralization, and thus there are hopes that it could inhibit structural changes in the subchondral bone and ultimately attenuate OA.[135] TPX-100, an amino acid peptide derived from MEPE was a representative example of MEPE-derived DMOAD candidate. *In vitro* studies have revealed that co-culture with TPX-100 could promote chondrocyte differentiation and function in mesenchymal stem cell (MSC) and intra-articular TPX-100 administration induces articular cartilage formation and type II collagen compared with vehicle group in chondral defect goat model.[136]

A phase II, randomized, double-blind, placebo-controlled, 12-month clinical trial was conducted to evaluate the safety and efficacy of the TPX-100 with OA patients.[137] According to the initial analysis released in 2018, patients treated with intra-articular administration of TPX-100 showed decreases in the KOOS and WOMAC scores, which were used to analyze functional improvements, but showed no significant differences in cartilage thickness or volume, which were used to analyze structural improvements.[138] In the additional analysis released in 2020, patients treated with TPX-100 showed a statistically significant decrease in bone shape changes in the joint as assessed *via* MRI, and this decrease in bone shape changes was correlated with changes in cartilage thickness.[139] These clinical analysis results were compiled and published in 2021, and the authors evaluated that TPX-100 has a functional improvement effect represented by WOMAC physical function and delays pathological structure change.[140]

The recent clinical progress of DMOAD candidates introduced above is summarized in Table 5. In section "DMOAD candidates in the pre-clinical development stage," we will describe the DMOAD candidates that have not yet entered clinical trial. By analyzing their mechanisms and research methods, we would like to summarize their merits and commonalities over previous candidates.

DMOAD candidates in the pre-clinical development stage

Neural EGFL-like 1

Neural EGFL-like 1 (NELL-1) is a protein that contains epidermal growth factor-like repeats and is known to affect cell growth and differentiation. Under physiological conditions, NELL-1 is expressed in cartilage, inhibiting NELL-1 expression during development results in abnormal cartilage formation. Li *et al.*[141] at Peking University observed the chondrogenic effects of NELL-1 at the cell level by analyzing the effects of recombinant NELL-1 treatment on chondrocytes and MSCs. When MSCs were treated with NELL-1, there was increased proliferation of chondrocyte precursors and improved cartilage formation, differentiation, and maturation as well as enhanced differentiation of the extracellular matrix. Based on these *in vitro* results, the induction of cartilage regeneration without osteosarcoma formation was observed when NELL-1 was administered to the rabbit cartilage defect model.[142] Subsequently, in order to identify the mechanism of cartilage differentiation with NELL-1, joint structural changes at the time of NELL-1 haploinsufficient mice were identified at 3 and 18 months.[143] As a result, Nell-1-haploinsufficiency is prone to pathologic environment changes with increased pro-inflammatory cytokines in articular cartilage. When forming an inflammatory OA environment by injecting the IL-1β, NELL-1 treatment was associated with differences in the extent of aging-related or IL-1β-induced structural degradation. These chondrogenic differentiation capabilities were associated with the expression of Indian hedgehog (IHH) expression through NFATc1 pathway activation and Runx1 pathway activation by NELL-1. In molecular analysis, NELL-1 was found to activate NFATc1 in the nuclei of chondrocytes to induce expression of Indian hedgehog protein, which is involved in chondrocyte differentiation, and simultaneously activates the Runx1 pathway, which inhibits inflammation, suppressing cartilage degradation. They concluded that NELL-1 has potential as a DMOAD based on these structural improvement effects.

IL-4 and IL-10 fusion proteins

IL-4 and IL-10 are representative examples of anti-inflammatory cytokines. Although there have been attempts at exploiting these properties for obtaining therapeutic agents against inflammatory

Table 5. The list of DMOAD candidates undergoing clinical trials.

No	Candidate	Category	Mode of action	Representative clinical trial			
				Status	Duration	Main structure outcome	Main symptom outcome
1	FGF-18 (sprifermin)	Induction of anabolic factors	Promote chondrogenesis and cartilage matrix production by activation of FGF receptor 3	Phase II completed: NCT01919164[66]	2 years (F/U: 5 years)	Primary: Change of cartilage thickness by MRI	Secondary: Change of WOMAC total score
2	TGF-β1 (TG-C)	Induction of anabolic factors	Inhibit inflammatory environment in knee joint and promote cartilage matrix production by macrophage polarization	Phase III active: NCT03203330[73]	2 years	Secondary: Change of MRI Assessment	Primary: Change of WOMAC, VAS score
3	BMP-7	Induction of anabolic factors	Promote chondrogenesis and cartilage matrix production	Phase II completed: NCT01111045[79]	1 year	Not provided	Primary: Change of WOMAC score
4	Angiopoietin-like protein agonist (LNA-043)	Induction of anabolic factors	Promote chondrogenesis and cartilage matrix production by acting directly on cartilage-resident cells	Phase II recruiting: NCT04864392[84]	5 years	Primary: Change of Cartilage thickness Secondary: Proportion of participants demonstrating structural progression	Secondary: Change of WOMAC pain, function score, OARSI physical performance measures score
5	IL-10 transgene plasmid DNA (XT-150)	Induction of anabolic factors	Regulate the joint inflammatory environment by IL-10 production	Phase II active: NCT04124042[88]	1 year	Not provided	Primary: Responder Rates in KOOS/WOMAC score Secondary: Pain interference, patient global assessment
6	Wnt inhibitor (lorecivivint)	Inhibition of catabolic factors	Promote chondrogenesis, chondrocyte function and anti-inflammatory effect by inhibition of CLK2 and DYRK1A pathway	Phase III recruiting: NCT04520607[95]	1 year	Secondary: Change of mJSW in the target knee	Primary: Change of NRS pain score Secondary: Change OF NRS function score
7	Cathepsin K inhibitor (MIV-711)	Inhibition of catabolic factors	Inhibition of cathepsin K activity which involved in breaking down of collagen in bone and cartilage	Phase II completed: NCT02705625[99]	6 months	Secondary: Change of bone area of the target knee, femur cartilage thickness by MRI, change of serum CTX-I and II level	Primary: Change of NRS Pain Score Secondary: Change of WOMAC pain, difficulty and stiffness score
8	Senolytic small molecule inhibitor (UBX-0101)	Inhibition of catabolic factors	Promote the selective elimination of senescent cells by inhibition of p53/MDM2 interaction	Phase II completed: NCT04129944[107]	12 weeks (F/U: 24 weeks)	Not provided	Primary: Change of WOMAC pain score Secondary: Change of WOMAC function, NRS score

(Continued)

Table 5. (Continued)

No	Candidate	Category	Mode of action	Representative clinical trial			
				Status	Duration	Main structure outcome	Main symptom outcome
9	IL-1 inhibitor (Anakinra)	Inhibition of catabolic factors	Inhibit the activity of IL-1 by binding competitively to the IL-1 type I receptor	Phase II completed: NCT00110916[114]	4 weeks	Not provided	Primary: Change of WOMAC score Secondary: Change of PGA
10	IL-1 neutralization (ABT-981)	Inhibition of catabolic factors	Inhibit the activity of IL-1α and β by dual variable domain immunoglobulin (DVD-Ig) of the IgG1/k subtype neutralization	Phase II completed: NCT02087904[115]	1 year	Primary: Change of synovitis/effusion volume by MRI evaluation Secondary: Change of BML, cartilage volume by MRI	Primary: Change of WOMAC pain score Secondary: Change of WOMAC function, index knee IOCPA score, knee pain intensity, PGA of Arthritis, Number of OMERACT-OARSI response
11	ADAMTS-5 inhibitor (GLPG1972)	Inhibition of catabolic factors	Inhibit the activation of ADAMTS-5, which is cartilage degrading enzyme	Phase II completed: NCT03595618[125]	1 year	Primary: Change of cartilage thickness by MRI Secondary: Change of bone area by MRI, JSW by X-ray	Secondary: Change of WOMAC, VAS score, number of OMERACT-OARSI response
12	PPS	Inhibition of catabolic factors	Inhibit the activation of ADAMTS-5, which is cartilage degrading enzyme by increasing the affinity between ADAMTS-5 and TIMP-3	Phase II and III Not yet recruiting: NCT04809376[132]	24 weeks	Not provided	Primary: Change of WOMAC NRS score Secondary: Change of WOMAC index, NRS score, PGIC score, WPAI score, number of OMERACT-OARSI response
13	MEPE (TPX-100)	Inhibition of catabolic factors	Regulate the subchondral bone remodeling by inhibition of bone mineralization	Phase II completed: NCT03125499[138]	3 years	Primary: Change of patellar cartilage thickness by MRI Secondary: Change of non-patellar cartilage volume by MRI	Secondary: Change of patient-reported outcome measures

ADAMTS-5, A disintegrin and metalloproteinase with thrombospondin motifs 5; BML, bone marrow lesion; BMP, bone morphogenetic protein; CTX-I, C-terminal cross-linked telopeptide of collagen type I; DMOAD, disease-modifying osteoarthritis drugs; DNA, Deoxyribonucleic acid; FGF, fibroblast growth factor; ICOAP, Intermittent and constant osteoarthritis pain; IKDC, International knee documentation committee; IL, interleukin; JSW, joint space width; KOOS, knee injury and osteoarthritis outcome score; MEPE, Matrix extracellular; MRI, magnetic resonance imaging; NRS, numeral rating scale; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OMERACT, Outcome Measures in Rheumatology Clinical Trials; PGA, patient global assessment; PGIC, Patients' Global Impression of Change; PPS, Pentosan polysulfate sodium; TGF, Transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster universities osteoarthritis Index; WPAI, work productivity and activity impairment.

disease, administration of IL-4 or IL-10 alone has not shown significant effects in multiple clinical trials. In the late 90s, clinical trials using each protein for RA were conducted, but they did not progress beyond phase II trials. Thus, combination therapy using multiple anti-inflammatory agents has been considered for overcoming these limitations. In an *in vivo* RA model, IL-4 and IL-10 combination therapy showed a synergistic effect.[144] However, the combined administration of single cytokines is limited by the characteristic low bioavailability of low molecular weight molecules, which restricts its applications.

To address this issue, Steen-Louws *et al.*[145] generated a ~70-kDa fusion protein combining the two cytokines and demonstrated the immunosuppressive function of the fusion protein *in vitro, in vivo*, and *ex vivo*. The research team first compared IL-4/10 receptor expression in cartilage from patients with OA and healthy patients and identified elevated receptor expression in cartilage from the former. Next, to investigate the effects on the actual intra-articular environment, they cultured cartilage explants and observed a decrease in proteoglycan turnover when treated with the fusion protein. Expression of the inflammatory cytokines IL-6 and IL-8 was also found to be decreased, which in turn, resulted in decreased expression of MMPs, vascular endothelial growth factor, and NGF, which are catabolic factors and pain mediators. When the proteins were administered intra-articularly to a canine OA model, pain behaviors improved.[146] Based on these results, the research team concluded that IL-4/10 combination therapy has potential as a DMOAD.

Alpha-2-macroglobulin

During the pathogenic course of OA, structural degradation due to protease activity is an important factor in cartilage degradation. Accordingly, one strategy for DMOAD development is slowing the progression of OA through protease inhibitors, and alpha-2-macroglobulin (A2M) is one example. A2M is a unique type of protease inhibitor with a bait region and a four-arm structure, and it is known that due to its unique structure, it can block almost all kinds of protease.[147] *In vitro* OA condition, A2M could inhibit cartilage degradation through inhibition of endoprotease, MMPs, and ADAMTS activity.[148,149] In *ex vivo* and *in vivo* pre-clinical experiments, A2M showed anti-catabolic activity acting by binding macrophage receptors and inhibiting MMP-2 and MMP-9 activity.[150] The ratio of A2M and protease is considered a key element in regulating the catabolic environment in the joint space, but in nature, the concentrations of A2M in the joint space are extremely low. When chondrocytes that were degraded by IL-1β were subsequently treated with recombinant A2M, decreased expression of catabolic factors such as ADAMTS and MMPs was observed by enzyme-linked immunosorbant assay (ELISA).[151] In a further experiment, intra-articular A2M was administered to Wistar rats with ACLT-induced arthritis, and the results showed a significant decrease in the extent of cartilage injury, decreased expression of factors related to cartilage degradation, such as MMPs and Col X, and increased expression of factors related to Col 2 synthesis.[150] Although there have been no clinical trials for OA treatment using A2M, a clinical trial was recently conducted at New York University to examine whether A2M expression in the synovial fluid can be used as a biochemical marker in patients with OA.[152] If this trial shows a significant correlation between A2M expression and OA progression, the potential to control OA *via* A2M modulation can be revisited.

Mitoprotective therapy (SS-31)

While studying the causes of various forms of OA, changes in metabolic regulation were found to affect the course of the disease. For example, in post-traumatic OA (PTOA), mitochondrial dysfunction can cause apoptosis of chondrocytes *via* oxidative stress.[153,154] Szeto-Schiller peptide (SS-31) is a recombinant peptide that prevents mitochondrial dysfunction due to oxidative stress by binding with cardiolipin, a mitochondrial phospholipid, to improve the production of adenosine triphosphate (ATP) and inhibit apoptosis. This peptide has been evaluated in a clinical trial for atherosclerosis.[155] To investigate the utility of this peptide in PTOA, a PTOA signal was induced in cartilage extracted from bovine knee cartilage, SS-31 was applied to the cartilage, and then outcomes were observed after 1 week; the survival rate was found to be similar to that of uninjured cartilage.[156] Although there have not been any reports on its application in an OA model because chondrocyte apoptosis due to mitochondrial dysfunction is also observed in OA, SS-31 is expected to be applicable for OA treatment.

Novel chondrogenic factors

In cartilage regeneration strategies using chondrocytes differentiated from stem cells, the treatment efficacy depends on how effectively the exogenous stem cells can be induced to differentiate into chondrocytes. Human synovium-derived stem cells (hSSCs) show higher chondrogenic potential compared with other stem cells and have thus been considered as a potential source for cartilage regeneration.[157] To achieve better efficiency, strategies were developed to not only administer stem cells but also supply factors with chondrogenic potential in combination with stem cells, in an effort to induce stem cell differentiation in the appropriate direction. Sakaguchi *et al.* used a COL2-GFP-ATDC5 monitoring system to screen 2,500 natural and synthetic small compounds and identified a thienoindazole derivative (TD-198946) as a compound with high chondrogenic potential. In OA environment, TD-198946 could recruit native MSC from subchondral bone and enhance GAG production *via* PI3K/Akt signaling.[158,159] These results may provide a new strategy for stem cell–based OA therapy.

The recent pre-clinical studies of these DMOAD candidates introduced above are summarized in Table 6.

Discussion

With increasingly aging populations, the demand for fundamental treatments which alter the course of progression in OA is growing. The history of OA drug development has grown alongside our understanding of the disease. In the past, OA was regarded as a result of cartilage degradation, so evaluation outcomes were dependent on the degree of cartilage degradation, and treatment strategies also focused on cartilage. However, as the research progresses, it has become clear that OA is not only a disease caused by cartilage but also by complex degradation of various tissues in the joint, and recent treatment strategies have comprehensively targeted the intra-articular environment totally. As our understanding of OA disease mechanisms develops, the need for treatments that go beyond conventional management of symptoms has grown. However, symptomatic treatments need to be administered continuously because they do not eliminate the root cause of the symptoms, and treatments that were initially effective may show gradually diminishing returns as the disease progresses. Ultimately, the last option remaining for patients is arthroplasty – replacing the knee joint with a prosthesis.[160] Moreover, even though arthroplasty is the most effective method for pain and knee dysfunction and provides the longest sustained effects, distress during the postoperative recovery period impose burden on patients and concerns regarding complications are unavoidable.[161–163] Subsequently, there is a demand for less-invasive treatment methods and alternatives to joint arthroplasty that provide prolonged benefit to the patient. With advances in technology, researchers are able to inspect the changes in joints of patients with OA in multiple ways. This forms the background for the emergence of DMOADs, which are defined as fundamental OA treatments that reconstruct the intra-articular structures and improve the patient's quality of life.

Since the 2000s, numerous studies have been conducted to identify candidates that can satisfy the two criteria of DMOADs: inhibit disease progression and induce long-term symptom improvements. Several clinical trials have focused on pathological changes in the subchondral bone of patients with OA and tested the applicability of drugs which were used for other diseases, such as osteoporosis or RA. However, the results of these clinical trials did not meet the primary endpoint in clinical trials. Oral formulations such as bisphosphonates that have systemic effects failed to produce significant results due to toxicity problems, adverse events, and/or lack of efficacy. Thus, candidate drugs that have been highlighted as potential DMOADs are specific to intra-articular metabolism or are administered intra-articularly to act locally. Pre-clinical studies and clinical trials have been conducted using various candidates, including candidates that promote chondrogenesis or inhibit cartilage degradation in the joint space. However, despite some successes, any of the DMOAD candidates have not received regulatory agencies' approval. One major reason affecting the current situation is the ambiguity of OA assessment criteria. Notably, in the FDA assessment of OA drugs guidelines, no structural evaluating outcomes have been defined or implemented to facilitate the development of DMOADs. This is directly related to clinically meaningful benefits; as clinicians would claim, patients do not complain about their structural evaluation result, but rather joint symptoms and pain. For this reasons, FDA declared that they do not use structural endpoints in approval decisions

Table 6. The list of DMOAD candidates in the pre-clinical development stage.

No	Candidate	Category	Mode of action	Nonclinical study results
1	NELL-1	Induction of anabolic factor	Promote chondrogenesis by NFATc1, IHH pathway and inhibit inflammatory effect by Runx 1 pathway	Intra-articular injection of NELL-1 significantly reduced IL-1β stimulated inflammation and damage to articular cartilage *in vivo* OA model
2	IL-4 and 10 fusion protein	Inhibition of catabolic factor	Inhibit proteoglycan turnover and inflammatory cytokine (IL-6, IL-8), catabolic, pain mediator (MMPs, VEGF, NGF)	Simultaneous administration of IL-4/10 fusion protein shows significant suppression of inflammatory responses that is not reached by administration of either cytokine alone
3	A2M	Inhibition of catabolic factor	Regulate the balance of protease/A2M and Inhibit the expression of endoproteases such as ADAMTS and MMP	Co-culture with IL-1b treated chondrocyte, A2M suppresses catabolic cytokines and MMPs. Intra-articular injection of A2M shortly after joint injury provides chondral protection in ACL injury of the knee by reducing these catabolic enzymes
4	Mitoprotective therapy (SS-31)	Inhibition of catabolic factors	Protect the mitochondrial cristae and promote oxidative phosphorylation by interacting with cardiolipin	Preserve chondrocyte viability similar to uninjured controls in *ex vivo* POTA model
5	Novel chondrogenic factor (TD-198946)	Induction of anabolic factors	Promote chondrogenic potency of stem cell by Runx1 mediated GAG synthesis	Co-culture with TGF-β3 treated hSSC, TD-198946 promoted chondrocyte differentiation and production of cartilaginous matrices. Expression of SOX9, S100, and type 2 collagen is increased

A2M, alpha-2-macroglobulin; ACL, anterior cruciate ligament; ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; DMOAD, disease-modifying osteoarthritis drugs; GAG, glycosaminoglycans; hSSCs, human synovium-derived stem cells; IHH, Indian hedgehog; IL, interleukin; MMPs, matrix metalloproteinase; NELL-1, neural EGFL-like 1; NFATc1, nuclear factor of activated T cells 1; NGF, nerve growth factor; OA, osteoarthritis; POTA, post-traumatic arthritis; SOX, SRY-Box transcription factor; VEGF, vascular endothelial growth factor.

because it is not clear what clinical benefits are offered to the patient by changes in the currently used structural criteria.[28] Sprifermin is a representative example of a biological drug caught in this dilemma; even though sprifermin showed significant differences in structure improvements, there was no significant effect on patients' pain or functional improvement in phase II clinical trial.[67]

It is frequently asked, how is it that structural improvements were observed, but there was no change in patient symptoms? It is the result of dissociation between classic evaluating outcomes and actual clinical outcomes for OA. In the past, pain in OA patients was considered to be the product of cartilage degradation, and from this perspective, radiation evaluation such as K&L grading system were used for OA severity evaluation. However, the clinical data that have been accumulated to date demonstrate a lack of agreement between radiographic changes in the joint and patient pain levels.[164,165] For instance, some patients with a low K&L grade (with wider joint space) can experience severe pain, while some patients with a JSN experience little pain. These dissociations suggest that OA is not the only problem with cartilage degradation. Currently, OA is recognized not simply as a result of intra-articular cartilage degradation but as the product of complex interactions between several tissues in the joint.[166–169] In keeping with this shift in perspective, studies have aimed to elucidate the pathogenesis of OA and identify clinical outcomes focusing on various tissues, including knee joint cartilage and subchondral bone, synovium, menisci, ligaments, and peri-articular muscles and nerves. Alongside these pre-clinical studies, there has been growing recognition of the need for more effective assessment outcomes that can combine structure and function to achieve more successful clinical trials and reduce medical expenses.

For this purpose, the FNIH biomarker consortium has been exploring potential biomarker

candidates since 2012.[170] This collaborative effort has helped expand our understanding of the pathogenesis of OA. It has spawned a wealth of research, ranging from studies which have examined the correlations between OA severity and structural joint changes measured with advanced imaging technology, including MRI, to studies evaluating the clinical usability of biochemical markers identified in pre-clinical studies.[171–174] Nevertheless, as of 2022, there are no established general methods that can simultaneously evaluate patient structural and functional improvements. When a disease is diagnosed based on a complex assessment of changes in multiple tissues, it raises the question of specifically which outcomes should be assessed in which tissues. Taking these limitations into account, FDA has not only positioned itself as a supervisor – suggesting basic criteria for OA drugs – but is also searching for new criteria while engaging manufacturers in discussions about endpoints.

Cartilage degradation is a hallmark feature of OA, but it is important to recognize that OA is a disease of all joint tissues that this is not the answer to all problems and to prepare comprehensive assessment criteria that extend beyond cartilage-focused approaches and consider the state of the joint as a whole. Summarized below are some research directions for achieving these goals.

First, in pre-clinical studies, we should utilize the most appropriate OA models to investigate mechanisms and the relationships between symptomatic and structural changes in the tissues of the joint during OA development. This will require complex analyses based on multifaceted data, as the differentiation of chondrocytes and the degeneration of the cartilage matrix is not controlled by a single factor or pathway but involves the actions of multiple factors, including genetic and environmental factors, inflammation, and injury; moreover, many aspects remain poorly understood. For example, if two OA animal models with similar levels of cartilage degradation show different pain behaviors, we may be able to identify new therapeutic targets for testing candidate DMOADs by investigating differences in the subchondral bone or peripheral nerves in the infrapatellar fat pad (IFP) or by conducting analysis at the mRNA level. As shown in the case of TD-198946 above, target screening can be used to identify new factors other than the traditionally known cartilage differentiation-related factors; therefore, this line of research should be continued in the future to reveal new therapeutic targets.

Second, it is necessary to improve the accuracy and sensitivity of tools employed as outcome measures in OA clinical studies. Currently, evaluation parameters are exclusively focused on the cartilage compartment, but recent research shows that various other tissue compartments other than cartilage are involved.

Another example is inflammatory OA, where the distribution of macrophage polarization could be considered as another parameter to investigate as an indicator for OA progression. Macrophages are largely subdivided into M1 and M2 phenotypes. In the case of M1 macrophage, it secretes various inflammatory cytokines and induces catabolic action, but M2 macrophages are known to secrete anti-inflammatory cytokines and contribute to tissue remodeling.[175] Meanwhile, in healthy joints, the level of macrophages in the synovial fluid is low, but an increase of macrophages, especially the M1 subtype, is observed in the blood and synovial membrane of OA patients.[176] In the synovium of OA patients, expression of M1 cytokines including IL-12, IL-1, and TNF-α are increased, while M2 cytokines such as IL-10 are decreased. Excessive production of inflammatory cytokines can cause overexpression of MMPs and aggrecanase, which promote further joint structure degradation.[177] Moreover, Daghestani *et al.*[178] showed that the expression level of M1 macrophages in the synovial fluid and serum was positively correlated with the severity of OA symptoms. Based on these results, it would appear that the development of therapeutic strategies that target macrophage polarization and inflammatory cascades can be a promising option in OA, especially in the context of inflammation. If the correlation between the distribution of macrophage polarization pattern and the symptoms of OA can be defined, this can be used to evaluate the efficacy of DMOAD candidates targeting the inflammation in OA.

In order to incorporate inflammatory changes, such as macrophage polarization, as an evaluation parameter in OA clinical trials, more mechanistic evidence is needed to establish the correlation between inflammation and OA symptoms. Presently, we cannot quantify the correlation between M1 macrophage expression level and OA progression and are not aware of the degree of expression of M2 macrophages necessary to

improve the OA inflammatory environment. Moreover, inflammation influences the pathogenesis of OA, but not all OA subtypes are driven by inflammation. Therefore, we propose that evaluation of disease progression should not rely exclusively on inflammatory status. Nevertheless, we think that the specific factors that can comprehensively encompass multiple phenotypes can be applied to the objective evaluation of DMOAD candidates in future clinical trials. To develop an optimal molecular endotype-based approach for evaluating the progression of the disease and the accessing the efficacy of candidate DMOADs, a closer linkage between pre-clinical and clinical studies can be achieved with refinement of translational models in the future.

In summary, we need more research to define and classify OA at the earliest possible stage of pathogenesis. We need to focus on the definition of DMOADs and bring all the major stakeholders, from academia, industry, regulatory agencies, and patient organizations together to develop an updated consensus definition that is fit for purpose and captures all the currently available knowledge. This will allow us to improve OA drug development and the design of novel platform clinical trials to assess DMOAD efficacy and safety. Furthermore, DMOADs should be more appropriately targeted and investigated according to the emerging clinical phenotypes and molecular endotypes of OA, creating entirely new therapeutic subtypes (i.e. theratypes) that can be targeted with different drugs.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Heungdeok Kim: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Thomas A. Perry: Data curation; Validation.

Nigel K. Arden: Data curation; Validation.

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