OSTEOARTHRITIS — AN UNTREATABLE DISEASE?

Heike A. Wieland, Martin Michaelis, Bernhard J. Kirschbaum and Karl A. Rudolphi

Abstract | Osteoarthritis is a painful and disabling disease that affects millions of patients. Its aetiology is largely unknown, but is most likely multi-factorial. Osteoarthritis poses a dilemma: it often begins attacking different joint tissues long before middle age, but cannot be diagnosed until it becomes symptomatic decades later, at which point structural alterations are already quite advanced. In this review, osteoarthritis is considered as a disease of the whole joint that may result from multiple pathophysiological mechanisms, one of which is the dysregulation of lipid homeostasis. No proven disease-modifying therapy exists for osteoarthritis and current treatment options for chronic osteoarthritic pain are insufficient, but new pharmacotherapeutic options are emerging.

SYNOVITIS
Inflammation of the synovium, the tissue that produces joint-lubricating fluid.

In 1999, the Secretary-General of the United Nations, Kofi Annan, signed a declaration to launch the Bone and Joint Decade 2000–2010 for the treatment and prevention of musculo-skeletal disorders[1]. Osteoarthritis (OA) is one of the most common forms of musculo-skeletal disease encountered in all countries of the globe (TABLE 1)[2]. In Europe, a joint is replaced due to OA every 1.5 minutes. The situation is even worse in the United States, where a total of ~500,000 joint replacements are performed per annum[3,4]. According to conservative estimates, the diagnosed symptomatic cases of OA alone represent a huge population (BOX 1).

The clinical symptoms of OA are pain and functional impairment that includes joint stiffness and dysfunction (BOX 1, FIG. 1). In 80% of patients with OA, movement is limited to some degree. This leads to impaired performance in the workplace, and 25% of patients cannot perform their main activities of daily life, which often leads to social isolation and depression[5].

The principal morphological characteristic of OA is a slowly developing degenerative breakdown of cartilage with only episodic SYNOVITIS (FIG. 2). In addition, changes occur in the bone, synovium and muscle. On the basis of radiographic and clinical parameters, it has been shown that the prevalence of OA increases with age, affecting a large proportion of all people above the age of 65 years[2,6]. By contrast, rheumatoid arthritis (RA) mainly affects younger people and is a fast-developing, generalized inflammatory disease driven by autoimmune processes. Interestingly, the prevalence of RA is much lower than that of OA[2,7] (TABLE 1), but until now the field of RA has attracted more scientific and public attention than OA.

In a population-based study, substantial discordance has been reported between radiographically diagnosed OA of the knee and knee pain[8]. In some patients, signs of structural alteration are asymptomatic, whereas other patients report joint pain in the absence of radiographically detectable alterations. The latter discrepancy probably results from the fact that joint-space width is too insensitive as a determinant for structural alterations. In future, more precise measurements (for example, magnetic resonance tomography) will lead to a better correlation between structural processes and symptoms.

In contrast to RA, no drugs are available with proven disease-modifying efficacy in OA. The only registered systemic oral drug therapy for OA is symptomatic treatment using analgesics or anti-inflammatory agents, such as acetaminophen (also known as paracetamol) or cyclooxygenase (COX) inhibitors. Until recently, when rofecoxib (Vioxx; Merck) was withdrawn from the market (September 2004), treatment

Therapeutic Department Thrombosis & Osteoarthritis, Aventis Pharma Deutschland GmbH, a company of the Sanofi-Aventis group, Industrial Park Höchst, 65926 Frankfurt, Germany. Correspondence to H.A.W. e-mail: Heike.Wieland@sanofi-aventis.com
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of OA was dominated by COX2 inhibitors[9]. After nearly 4 years of selective COX2 inhibitors being available in the United States and Europe, it is evident that significant unmet need still exists in the treatment of OA. COX2 inhibitors not only fail to provide adequate pain relief, but also cause gastrointestinal complications common to other non-steroidal anti-inflammatory drugs (NSAIDs). In addition, cardiovascular concerns remain[10,11]. In some countries, intra-articular hyaluronic acid preparations are registered as drugs and in other countries as medical devices for symptomatic relief.

Table 1 | **Osteoarthritis epidemiology***

Country	2002	2007	2012
United States	13.2	14.4	15.5
Europe	14.5	15.2	15.8
Japan	6.6	6.9	7.2
OA total prevalent cases	34.3	36.5	38.6
RA total prevalent cases	2.8	3.1	3.4

*Number (in millions) of diagnosed total prevalent cases of OA (see REF. 7 for more details). Adapted from REF. 7. OA, osteoarthritis; RA, rheumatoid arthritis.

Inadequate current treatment options

There is an urgent need to improve the options to treat OA. First, structure-modifying efficacy has not been demonstrated beyond doubt for any of the existing drugs. Second, existing drug therapies for OA reduce the symptoms (mainly pain), but are only moderately effective and often leave patients with a substantial pain burden. Concomitantly, the side-effect profiles of current OA treatments during chronic application are raising considerable concerns[10,11] (discussed later).

Lack of structure-modifying drugs. To date, no drugs are available that have shown a significant structure-modifying effect in state-of-the-art placebo-controlled, randomized clinical studies[14]. Therefore all claims of pharmacotherapeutic or nutraceutical efficacy of substances such as glucosamine sulphate, chondroitin sulphate and hydrochloride are so far anecdotal. Most clinical studies on these compounds have been performed with glucosamine sulphate. In these studies, there was either no proven effect or, if effects were observed, the radiographic method chosen was criticized, especially for deficient standardization and inadequate positioning of the joints (see later). In fact, there is ongoing debate among experts as to which positioning method is best for objectively demonstrating a beneficial effect on cartilage destruction. Modern imaging techniques, such as magnetic resonance imaging (MRI), might help to solve this problem in the future. In addition, the National Institutes of Health (NIH)-sponsored Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) could help to clarify whether or not these substances are efficacious. This large, randomized, placebo-controlled study is designed to test the short-term (6 months) effectiveness of glucosamine and chondroitin in reducing pain and improving function in a large number of patients with knee OA in comparison to the COX2 inhibitor celecoxib (Celebrex; Pfizer). The study will also evaluate the impact of glucosamine and chondroitin sulphate on the progression of knee OA following an additional 18-month treatment regimen. The results of the study are expected in 2005 (for further information, see Online links).

Pain relief is only partial. Acetaminophen has been in frequent use for pain relief for more than 100 years (FIG.3). Interestingly, its mechanism of action still remains unknown. Given in recommended doses, acetaminophen is very safe. It is recommended as a first-line oral analgesic for knee OA[15] and in many individuals it induces pain relief as well as an NSAID. Recent meta-analyses of available clinical studies, however, reveal that acetaminophen is less effective than NSAIDs and COX2 inhibitors[16–18].

NSAIDs are effective for treating pain in OA and should be considered for patients who do not respond to acetaminophen (FIG. 3)[15]. The principal target for NSAIDs are the isoforms of cyclooxygenase, COX1 and COX2. COX1 is constitutively expressed in many cell types, whereas COX2 is induced at the site of inflammation, although it is also constitutively expressed in the kidney, for example[19]. It has been proposed that the anti-inflammatory and analgesic benefits of NSAIDs derive from inhibition of prostaglandin synthesis. Prostanoids contribute to the development of peripheral sensitization through protein kinase A-mediated phosphorylation of sodium channels in nociceptor terminals, which increases excitability and thereby reduces the pain threshold. In addition to this peripheral action, NSAIDs might also act in the central nervous system (CNS)[20].

The relative efficacy of different NSAIDs given to patients with knee OA was determined in a recent review, which indicated that there was no substantial efficacy-related evidence to distinguish between equivalent

Box 1 | **Epidemiology and pathology of osteoarthritis**

Osteoarthritis (OA) is the most common form of arthritis[2,12], and affects millions of people (TABLE 1). It can occur in any joint but is most common in certain joints of the hand, knee, foot and hip (FIG. 1). If severe, the pathological changes result in radiological changes, such as loss of joint space, subchondral bone sclerosis and presence of osteophytes (bony spurs mostly located at the joint margins). These changes can result in joint symptoms such as pain, stiffness and loss of function. The symptoms vary with time and between joint sites and individuals. Incidence and prevalence are therefore difficult to determine. The main risk factors for OA are age, obesity and any form of joint trauma. In some families, OA seems to be inherited[13]. People born with slight defects that make their joints fit together incorrectly or move incorrectly, such as bowlegs or a congenitally abnormal hip, might be more likely to develop OA. Because of the ageing of populations in the developed world, the prevalence of OA is expected to increase. Nevertheless, many elderly people do not suffer from OA, which indicates that it is not a universal feature of ageing. Pain or discomfort, limitation of activity and reduced participation in daily activities are the main health indicators associated with OA. OA is the most common reason for total hip- and knee -joint replacement. The considerable prevalence of OA in middle-aged subjects imposes a considerable burden in terms of lost working time and early retirement.

recommended doses of NSAIDs[21]. The NSAID administered should therefore be selected on the basis of safety, patient acceptance and costs[21].

Selective COX2 inhibitors were introduced in 1999. The rationale behind their development was the assumption that COX2 inhibitors should have an improved side-effect profile compared with non-selective COX-inhibiting NSAIDs[22] — that is, a lower risk of gastrointestinal complications — while providing equivalent efficacy. In fact, in terms of analgesic efficacy and improvement of function in OA patients, selective COX2 inhibitors do indeed seem to be as good as comparable NSAIDs[23,24].

Opioid analgesics, such as tramadol, are useful alternatives in patients in whom NSAIDs, including COX2-selective inhibitors, are contraindicated, ineffective and/or poorly tolerated[15]. The increased risk of adverse side effects, particularly in the elderly, has to be taken seriously.

Glucosamine and chondroitin products are widely used for pain management in OA patients and are recommended by the European League Against Rheumatism (EULAR)[15]. Although their long-term use seems to be safe, their efficacy remains controversial[25–27]. An ongoing independent clinical trial funded by the NIH is expected to clarify their clinical relevance and to provide appropriate recommendations[28].

Topical drug application to treat OA is thought to deliver high local drug concentration with a reduced risk of systemic side effects. Topical NSAIDs are superior to placebo in reducing knee OA pain for 2 weeks, but not when given over a period of 3–4 weeks[29]. Their efficacy during longer-term treatment is unknown. Topical salicylates and capsaicin have been used in a small number of trials and demonstrated a lower efficacy than topical NSAIDs[30].

Another form of local administration used to treat pain in OA patients is intra-articular injection. Long-acting corticosteroids are recommended for the treatment of flare of knee pain[15]. They achieve maximum efficacy within less than 1 week, and their benefit lasts for 2–4 weeks[31,32]. Although there are concerns that steroids might speed up the progression of OA when injected repeatedly, the evidence on this issue is inconclusive. Attempts to predict responders to steroid injections have not delivered a clear picture — for example, the presence of effusion has been reported to be predictive of greater benefit with steroids by some researchers, but not by others[33].

Hyaluronic acid (HA) is a physiological component of synovial fluid and cartilage. Numerous functions have been attributed to HA, including lubrication, inhibition of prostaglandin E_2 (PGE_2) synthesis and effects on cell–cell interactions[34,35]. HA levels are diminished in OA joints, and intra-articular injections of exogenous HA therefore aim to compensate for this deficiency[35].

There is only a small effect in the treatment of knee OA compared with placebo injection[36], and so it has recently been suggested that the EULAR recommendation for the use of HA preparations[15] should be re-evaluated and that further independent trials using intent-to-treat analysis are needed[36].

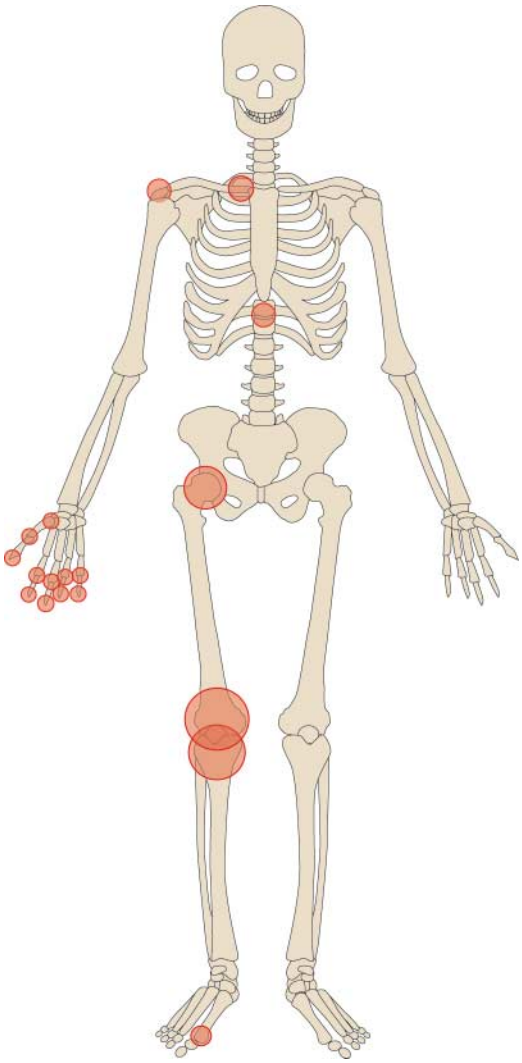


Figure 1 | **Common target sites for osteoarthritis.** The most common target joint affected by osteoarthritis (OA) is the knee joint, whereas hip, shoulder, spine and toe are less frequently affected. OA has a slow, insidious onset and mostly affects only one or a few joints (in contrast to rheumatoid arthritis, which is a systemic multi-joint disease). OA is a leading cause of disability and has a substantial economic impact[2].

Tissues involved in OA

Cartilage: redressing the imbalance. In normal joints, a firm, visco-elastic tissue — the cartilage — covers the end of each bone. Cartilage acts as a smooth, gliding structure and as a cushion between the bones (FIG. 2), thereby preventing biomechanical damage caused by severe loading. It is mainly composed of collagen and proteoglycan and of cartilage cells, the chondrocytes. The dense network of aggrecan (aggregating chondroitin sulphate proteoglycan) and collagen fibres is essential for the biomechanical properties of the cartilage.

In OA, a multitude of biological molecules drive cartilage breakdown, and thereby hinder attempts at repair and disrupt cartilage homeostasis. The underlying mechanisms act in a self-sustaining vicious cycle (FIG. 4). The timing of and extent to which the changes in cartilage

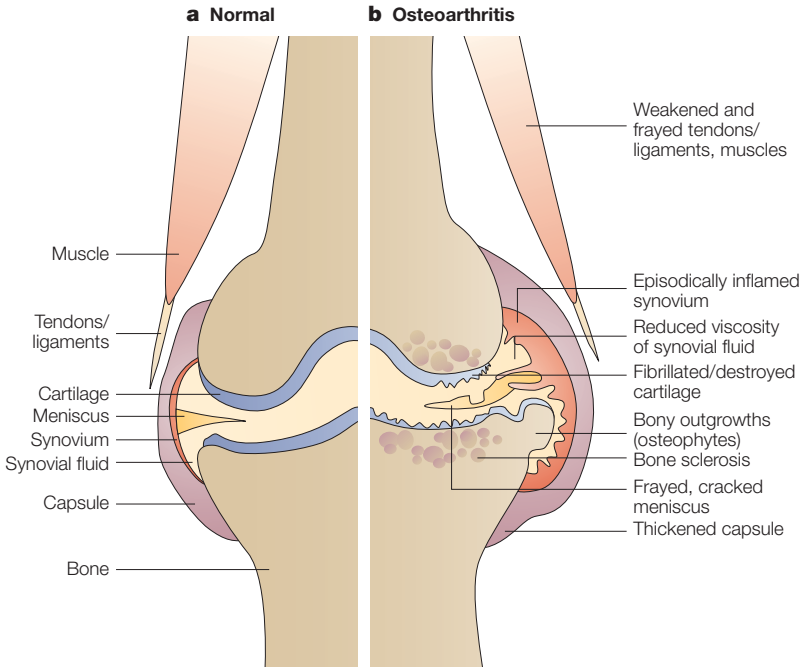


Figure 2 | **Articular structures that are affected in osteoarthritis. a** | Healthy tissue is shown: normal cartilage without any fissures, no signs of synovial inflammation. **b** | Early focal degenerate lesion and 'fibrillated' cartilage, as well as remodelling of bone, is observed in osteoarthritis. This can lead to bony outgrowth and subchondral sclerosis.

homeostasis occur is influenced by trauma to the joint, and hereditary and other factors (FIG. 4). As the cartilage breaks down, changes occur in the underlying bone, which thickens with the formation of bony outgrowths from the calcified cartilage layers and the bone surface. Finally, the synovium becomes inflamed as a result of cartilage breakdown. Chondrocytes produce mediators associated with inflammation, for example, cytokines and chemokines[37,38], and proteolytic enzymes that can cause further damage to the cartilage (FIGS 4,5a). Key contributors to catabolic processes include, for example, matrix metalloproteinases (MMPs) and interleukin-1β (IL-1β), growth factors and free radicals, among others[37,39]. Insulin growth factor 1 (IGF1) and bone morphogenetic proteins (BMPs) are endogenous anabolic factors that stimulate cartilage generation and remodelling[40–43]. The endogenous attempt to repair the cartilage defects can lead to the subsequent activation of an overwhelming biochemical cascade; in particular with increased amounts of growth factors. A compound that mimicked cartilage-repair mechanisms in a dose-dependent manner could act as a useful chondroprotective agent, provided it stimulated cartilage locally and did not affect regions within intact cartilage.

LEPTIN and its receptor have been identified in human cartilage and display stimulatory effects on proteoglycan synthesis in rats[44,45]. The location and the extent of leptin expression were related to the degree of cartilage damage and paralleled the expression of the growth factors IGF1 and transforming growth factor-β (TGFβ)[44]. The intra-articular injection of leptin into rat knee joints induced the synthesis of IGF1 and TGFβ in cartilage at both the messenger RNA and the protein levels, and strongly stimulated the anabolic functions of chondrocytes, as indicated by increased proteoglycan production[44].

A change in the equilibrium of anabolic versus catabolic processes can cause a net catabolic increase and, therefore, cartilage degradation (FIG. 4). Lohmander *et al.*[46] reported an increase in the numbers of fragments of collagen type II soon after injury and arthritis. One of the major factors during breakdown is the pro-inflammatory cytokine IL-1β, which is expressed by both chondrocytes and synoviocytes. Intracellularly, the pro-form of IL-1β is converted by interleukin-1 converting enzyme (ICE, also known as caspase 1) to produce the active form of IL-1β. The pathophysiological importance of IL-1β has been elucidated by both pralnacasan (Vertex/Sanofi-Aventis), an ICE inhibitor that reduced joint damage in two murine models of OA[47], and also by gene transfer of a biological IL-1β receptor antagonist[48]. IL-1β activates proteases, such as MMPs (FIG. 5a). These enzymes cleave collagen (MMP1, MMP8 and MMP13) and proteoglycans (MMP3) and also convert pro-MMPs into the active form (MMP3) (FIG. 5a). They are differentially induced in human osteoarthritic tissue and human synovial fibroblasts[49,50], as are other degradative proteases such as cathepsins and aggrecanases (a disintegrin-like metalloprotease with thrombospondin type motifs, ADAMTS1/ADAMTS4/ADAMTS5). Peroxisome proliferator-activated receptor-γ (PPARγ), a member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors, can exert anti-IL-1β effects and downregulates MMP1[51,52]. IL-1β and tumour-necrosis factor-α (TNFα) induce overexpression of COX2 and PGE_2 in the joint[53,54]. COX2 expression is at least partly mediated by the nuclear factor-κB (NF-κB) pathway in synovial fibroblasts[55,56] and in chondrocytes[53], as shown by pharmacological inhibition[57] and by overexpression of a dominant-negative inhibitor of NF-κB (IκB) mutant[58]. Stimulation of the NF-κB pathway by IL-1 or TNFα results in phosphorylation of the IκB kinase. The subsequent degradation of this kinase unmasks the latent NF-κB, which translocates into the nucleus, thereby again increasing the expression of cytokines, MMPs and COX (FIG. 5a). As mentioned before, disrupted homeostasis seems to result in a self-sustaining vicious cycle, thereby inducing severe structural modification (FIG. 4). This account leaves open the nature of the 'entry' and 'exit' points of this vicious cycle, neither of which are yet known. Nevertheless, the likelihood of identifying a disease-modifying drug is now greater than ever because the pathophysiological jigsaw is becoming more and more complete[59].

Bony changes. One of the hallmarks of OA are the pathological structural changes that occur in the subchondral cortical and trabecular bone and subarticular structures (FIG. 2). A significant increase in bone turnover and remodelling (that is, both bone formation and resorption) of the bone–cartilage interface occurs early in the course of the disease, especially in areas underlying damaged cartilage areas. The cortical subchondral plate thickens, and the trabecular bone becomes increasingly

LEPTIN
A polypeptide hormone ligand related to the family of interleukin-6 cytokines encoded by the obese (*ob*) gene and secreted by adipocytes.

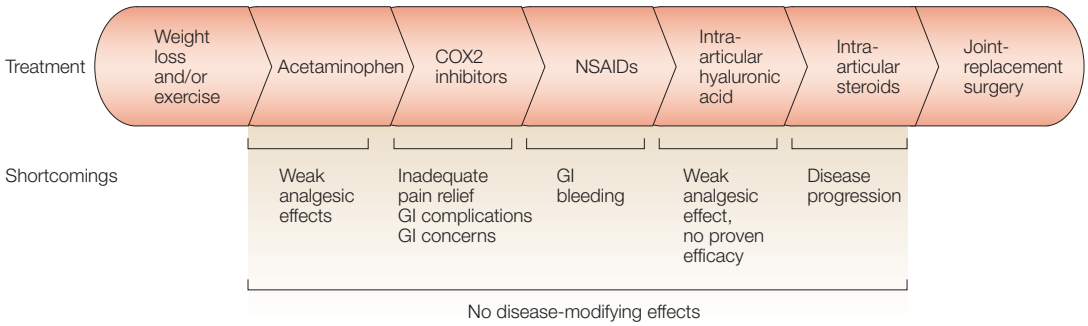


Figure 3 | **Current osteoarthritis treatment options.** The current treatment options as issued in the guidelines from the American College of Rheumatology are fairly limited. In addition to non-pharmaceutical measures such as weight loss and physical exercise they include only symptomatic treatment of limited efficacy with analgesics, non-steroidal anti-inflammatory agents or intra-articular administration of steroids or hyaluronic acid. Because no drugs exist that prevent or halt osteoarthritic joint destruction, the ultimate measure is joint replacement. COX2, cyclooxygenase 2; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

irregular[60]. The underlying pathomechanisms of this remodelling process are not fully understood, but biomechanical factors, such as localized increased load on the subarticular bone beneath areas of damaged cartilage, and pathobiochemical influences, such as enhanced release of cytokines and tissue growth factors, seem to have an important influence.

It is still a matter of debate which happens first — early cartilage destruction or bony changes. This question is difficult to answer in human patients because OA is usually only manifest in advanced symptomatic stages of the disease, but there is evidence from longitudinal animal studies of OA that cartilage destruction might in fact precede bone pathology[61].

The most prominent alterations in bone comprise sclerosis of the subarticular cancellous bone and osteophyte formation[62]. The strong increase in bone remodelling has prompted preclinical investigations of the disease-modifying potential of the bisphosphonates, including alendronate and risedronate, in animal models of OA. The results are, however, still inconsistent. Although alendronate and risedronate showed some evidence of joint protection in experimental OA in rats and rabbits[63,64], an experimental bisphosphonate, NE-10035 [2-acetylthio-ethylidene-1, 1-bisphosphonic acid, disodium salt] (Procter & Gamble Pharmaceuticals), while normalizing bone turnover, did not protect against cartilage destruction in a dog model of OA[65]. In a recently conducted large, placebo-controlled, randomized Phase III clinical study in patients with knee OA, risedronate did not show any structural or symptomatic efficacy[66].

By the early stages of OA there are also already pathological changes in the zone of calcified cartilage, which is separated from the non-calcified upper cartilage areas by a fine tissue lining (the so-called tidemark). Even below areas with minimal cartilage damage the tidemark reduplicates and spikes of granulation tissue (which resembles fibrovascular tissue) and fibrous tissue often advance into the non-calcified articular cartilage. When the disease advances, this tissue undergoes ENDOCHONDRAL OSSIFICATION, accompanied by invading blood vessels (angiogenesis), and can even fully penetrate the thinning cartilage to reach the articular surface. This process, also known as EBURNATION, is characteristic of progressive OA.

The bony outgrowths at the margins of the joint are referred to as osteophytes or, more precisely, osteochondrophytes[67]. They are also vascularized and very often seen in non-weight-bearing zones, particularly in primary OA of the hip joint. Major pathobiochemical factors promoting the formation of osteophytes seem to be TGFβ$_1$ and basic fibroblast growth factor (bFGF), which are highly expressed in osteophytes of the femoral head in OA patients[68]. Research is still under way to establish whether these structures are good or bad for the joint[69], whether they can help to stabilize the joint or in fact promote the degenerative process, and, most importantly, whether they contribute to osteoarthritic pain by mechanical impact on the innervated neighbouring joint tissues (synovium, capsule, ligament insertion sites and periphery of the meniscus). Some scientists consider osteophytes to be an adaptive process that reshapes the joint to reduce instability, thereby helping to redistribute forces to protect the cartilage. The absence of osteophytes has been linked to a higher risk of disease progression in patients with hip OA[69]. However, preclinical and clinical studies suggest that cartilage destruction positively correlates with the degree of osteophyte formation[70] and that osteophyte formation in the human knee joint is closely associated with, and is indeed more accurately predictive of, pain than the rate of joint-space narrowing[71]. So far there is no convincing clinical evidence that surgical removal of osteophytes improves or worsens OA.

Another source of osteoarthritic pain is the vascularization of areas of osteoarthritic bone remodelling, because invading blood vessels are accompanied by sensory nerve fibres, but this hypothesis awaits further clarification[72]. There is evidence that enhanced vascular pressure in subarticular bone regions (especially in the femur or tibia), venous engorgement, chemical and mechanical stimulation of sensory nerve endings in the vascular wall, or ischaemia might contribute to severe ischaemia- and pressure-induced rest or night pain in patients with advanced hip or knee OA[73].

ENDOCHONDRAL OSSIFICATION
A type of bone formation that occurs by replacement of hyaline cartilage.

EBURNATION
Spikes of granulation and fibrous tissue reach the joint surface. The tissue undergoes endochondral ossification and penetrates the thinning cartilage, eventually exposing smooth, dense bone on the articular surface.

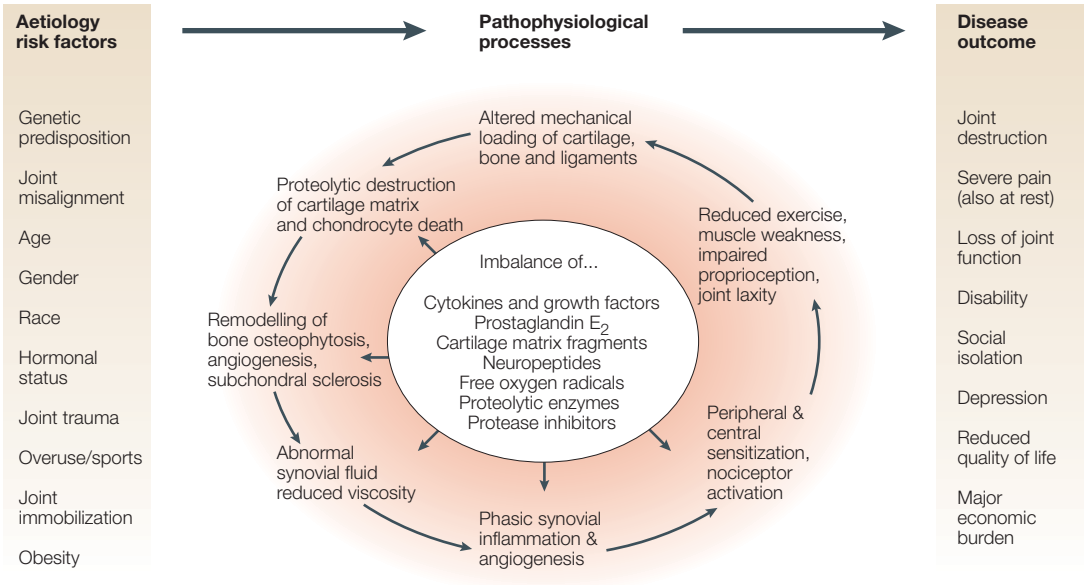


Figure 4 | **Vicious cycle of osteoarthritis.** This is a simplified scheme showing the intricate relationship between aetiological factors (left), pathophysiological processes (central) and disease outcome (right). The pathophysiological processes influence and often amplify each other in a vicious cycle. For instance, joint mis-alignment (left) can contribute to cartilage destruction and subchondral bone sclerosis. As a consequence, pain originates due to mechanical and chemical nociceptor activation, and reduces quality of life, often resulting in disability and social isolation (right). The dysregulation of certain biochemical factors shown in the inner cycle drives the disease process that finally leads to joint destruction. The individual trigger of disease onset is often unknown.

In advanced stages of OA, osteonecrotic processes lead to macroscopically and radiographically visible cysts in the subarticular bone. The pathogenesis of this osteonecrotic process is not entirely clear, but might be related to the occlusion of intramedullary arterioles and subsequent bone ischaemia. Venous occlusive disease associated with a state of hypercoagulability has also been discussed in this context[72].

An important risk factor in OA is obesity, which is often a result of leptin resistance. Besides its role in regulating caloric intake, leptin regulates bone mass and mineralization through a neuroendocrine pathway involving the sympathetic nervous system[74]. Leptin-deficient ob/ob and leptin receptor-deficient db/db mice have a high-bone-mass phenotype, and intra-cerebroventricular administration of leptin in ob/ob mice decreased bone mass and bone formation[75]. These data are in agreement with the finding that leptin-resistant obese people often have higher bone mass mineralization and are protected from osteoporosis[76]. The role of bone remodelling in OA led to the hypothesis that, regardless of its metabolic role, leptin resistance contributes to enhanced subchondral bone mass in OA.

Synovium. Although OA is not a disease driven by inflammation, some degree of episodic, non-erosive synovial inflammation is common in OA, even during early stages of the disease (FIGS 4,5b)[69]. Synovial mast cells are particularly involved and increase in number in OA[77]. Synovial inflammation is often confined to areas of the synovial membrane close to the cartilage[78]. Calcium crystal-induced inflammation has also been discussed[79]. So, in contrast to RA, synovial inflammation predominantly develops secondarily to pathological processes in cartilage and bone. In addition, sporadic reports show the existence of auto-antibodies in synovium of some OA patients, indicating that these contribute to mild chronic synovial inflammation[80]. Arthroscopic evaluations have shown that sites of synovial inflammation abut on cartilage lesions, and so enhanced synovitis could accelerate cartilage damage in OA patients[81]. The presence of synovitis is considered to be reflected by elevated levels of hyaluronan in serum[82]. The synovium is densely innervated by small-diameter sensory nerve fibres[83]. IL-1β and TNFα have the capacity to excite and also to sensitize nociceptors[84]. IL-1β and TNFα have also been shown to contribute *in vivo* to behavioural signs of inflammatory hyperalgesia[85,86]. Moreover, cytokines enhance the release of PGE_2 and histamine from chondrocytes and mast cells, which in turn can (indirectly) increase the sensitization of nociceptors[87]. Bradykinin is generated in inflamed synovium as it is in all inflamed tissue, and is able to excite and sensitize sensory nerve fibres (FIG. 5b)[88,89]. The clinical relevance of bradykinin has recently been demonstrated in a Phase II study in which intra-articular injection of a specific bradykinin B_2 receptor antagonist reduced OA knee pain more potently than placebo injection[90].

Many sensory nerve fibres that innervate the synovium contain neuropeptides, such as substance P and calcitonin gene-related peptide[91] (FIG. 4). Excitation of these nerve fibres leads to a release of these neuropeptides into the synovium. This so-called neurogenic inflammation might contribute to localized inflammation in synovium[92].

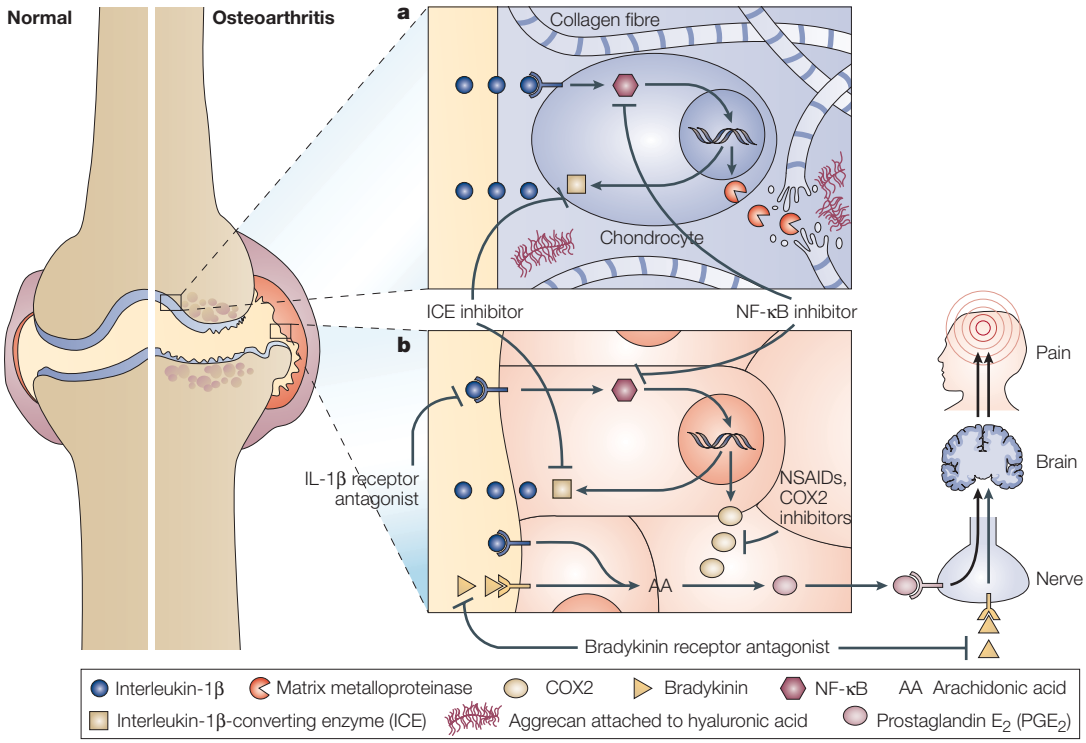


Figure 5 | **Targets for the development of disease- (a) or symptom-modifying (b) drugs for osteoarthritis. a** | Degenerative processes in cartilage, and potential targets for disease modification. A chondrocyte embedded in the network of collagen fibres and aggrecan is shown. IL-1β induces the expression of matrix proteases, which degrade the matrix components (shown on the right of panel **a**). The matrix metalloproteinases are targets with potential for disease modification. Interleukin-converting enzyme (ICE) converts IL-1β to its active form and, therefore, represents another target for disease modification. **b** | Nociception and possible ways of interfering with it. Inhibiting the production of the inflammatory cytokine IL-1β or blocking its receptors or interrupting its subsequent intracellular signalling through nuclear factor-κB (NF-κB) and the blockade of bradykinin receptors are more recent approaches to developing symptom-modifying drugs with greater efficacy than non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit the formation of the pain mediator prostaglandin E_2. COX2, cyclooxygenase 2.

Muscles, tendons and ligaments. Many patients with knee OA experience atrophy of muscles surrounding the involved joint, in particular the quadriceps muscle (FIGS 2,4)[93]. Exercise can reduce knee pain, although the effect documented varies among studies[94]. Slemenda *et al.*[95] examined the association between quadriceps strength, OA and knee pain. Interestingly, not only participants with radiographic evidence of OA and knee pain had quadriceps muscle weakness, but also those without knee pain. Patients who had undergone meniscus resection were found to have bilateral quadriceps weakness[96]. Quadriceps weakness might therefore be a primary risk factor for knee dysfunction and progression of joint degeneration. O'Connor and Vilensky[97] discuss whether generalized neuromuscular dysfunction is the primary aetiological factor in a subgroup of OA patients. Muscle weakness, and subsequently enhanced laxity of the joint, might also be a consequence of chronic OA pain.

However, in OA patients with mis-aligned and lax knees, greater quadriceps strength was associated with increased likelihood of OA progression[98].

Sources of pain

Chronic pain in osteoarthritic patients depends primarily on the activation of sensory neurons that innervate the affected joint[99]. With the exception of cartilage, all joint tissues, including subchondral bone and synovium, are densely supplied by small-diameter nociceptive neurons (FIGS 4,5b). Excitation of nociceptors occurs as a result of OA-related morphological and/or biochemical alterations — for example, enhanced levels of inflammatory mediators, such as bradykinin, were generated during localized inflammation in synovium and increased vascular pressure in the subarticular bone (FIG. 5). Moreover, receptive endings of nociceptors are sensitized, which results in enhanced impulse traffic from the joint to the spinal cord (FIG. 5b). This enhanced nociceptive input in turn leads to altered processing in the spinal cord and higher centres (central sensitization), which results in a multiple amplification of pain sensation[100,101]. Finally, OA-related morphological alterations can also directly affect sensory neurons, although neuropathic alterations have not yet been clearly demonstrated in OA patients and the clinical features of OA pain are different from classical descriptions of neuropathic pain.

Systems biology of osteoarthritis

Osteoarthritis is a disease of the whole joint in which all articular structures are affected (FIG. 2). OA is therefore obviously not a simple disease entity. However, the different conditions covered by this term are linked by a common pathological concept (FIG. 4).

A recent publication by the Food and Drug Administration (FDA) entitled *The Critical Path to New Medical Products*[102] has proposed that, among other strategies, a systems biology approach could be taken to avoid further delays in the development of new medical entities reaching patients — an approach that is expected to address many biological problems in drug discovery[103]. In particular, the development of disease-modifying drugs for OA suffers from a lack of pathophysiologically validated animal models and of clinically proven reference drugs. This dilemma is causing a 'catch-22' situation, because if a drug does not work in an animal model of OA, this could be because its mechanism of action is irrelevant for OA. However, it cannot be ruled out that the animal model might be irrelevant and that the drug would work in human patients.

An over-reactive repair mechanism with a self-sustaining process involving angiogenic and inflammatory factors also contributes to the progression of the disease. Angiogenesis coincides with chondrocyte hypertrophy, because hypertrophic chondrocytes release angiogenetic growth factors. In addition, endochondral ossification occurs alongside angiogenesis[104,105]. Inhibition of these processes might be a method for reducing both pain and joint damage[104].

Other diseases that affect the joints, such as Paget's disease, which affects bone turnover, and others (for example, Wilson's disease), can trigger a predisposition to OA[106]. The inverse relation between osteoporosis and OA[107] is still not unequivocally explained. Bisphosphonates, which suppress increased bone turnover in osteoporosis, have been evaluated as treatments for OA because of the increased bone turnover in the subchondral region. Indeed, treatment with alendronate reduces cartilage degeneration and osteophyte formation in animal models of OA[63].

One risk factor for OA is obesity (FIG. 4). This risk factor must include more than just mechanical load, otherwise it would be difficult to explain why obesity increases the risk not only of knee OA, but also of hip and hand OA[12]. This pattern of joint involvement points to the hypothesis that joint damage might be caused by a multitude of systemic factors, including metabolic triggers such as leptin[108,109].

Changes in body fat, but not body weight, have been reported to correlate with symptomatic relief in knee OA[110]. Leptin is released by adipose tissue and leptin receptors are present on cartilage[45]. If leptin was an anabolic factor[44], the leptin resistance observed in obese individuals could disturb the homeostasis in cartilage. If leptin was to stimulate osteophytes through TGFβ production, then increased leptin levels in obesity could represent the link between adipocytes and changes in the joint[111,112]. Interestingly, adipocytes share a common mesenchymal stem-cell precursor with osteoblasts and chondrocytes[113].In general, this again supports the above-mentioned systems biology approach of regarding OA as a generalized metabolic joint disease with inflammatory and angiogenic components.

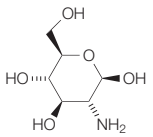
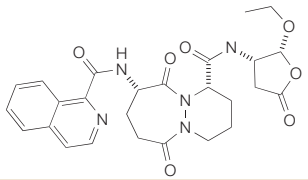
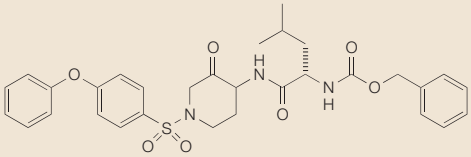
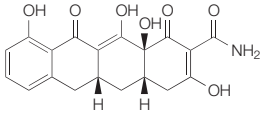
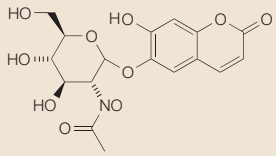
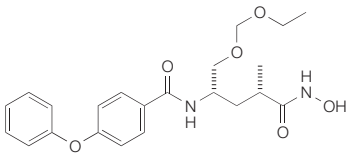
Novel approaches to OA therapy

Structure-modifying drugs. Structure-modifying drugs interfere with key targets in a catabolic pathophysiological cascade that leads to joint destruction. Although OA is increasingly recognized as a disease of the whole joint, the major target tissue in the development of disease-modifying anti-osteoarthritis drugs (DMOADs) is still the articular cartilage. New drugs under development are shown in TABLES 2,3. Pralnacasan, the first orally bioavailable and highly selective ICE inhibitor, reduced joint destruction in two mouse models of OA[47] and has recently been studied in Phase II clinical trials. However, the clinical investigation has been put on hold because of liver changes detected during the toxicology studies lasting 9 months and more in dogs. Much research effort has also been directed towards identifying small-molecule inhibitors of MMPs that act downstream in the pathophysiological cascade. So far, these compounds have failed in the early clinical phase, mainly because of intolerably painful musculo-skeletal side effects, such as tendonitis, which seem to be caused by the relatively broad-spectrum MMP inhibition of these compounds[114]. There are, however, still some MMP inhibitors with more selective specificity profiles in preclinical or early clinical development. Some are more selective for collagenase 3 (MMP13) inhibition, which seems to be the most important MMP expressed in OA cartilage[50]. The selectivity profile should exclude inhibition of collagenase 1 (MMP1), for instance[115], which has been held responsible for the musculo-skeletal side effects.

The proof of disease-modifying effects in patients remains a major challenge. Measurement of the rate of joint-space narrowing on serial radiographs taken in a weight-bearing position in randomized, placebo-controlled Phase III studies lasting minimally 1 year (United States) or 2 years (Europe) is the only outcome measure accepted by the FDA and the European Medicines Agency (EMEA) for the approval of drugs claimed to structurally modify hip and knee OA. Quantitative assessment of articular cartilage thickness and volume by modern magnetic resonance imaging (MRI) techniques is rapidly developing and could supplement or even replace joint radiography in the not-too-distant future as a more sensitive method. Time-to-indication of joint replacement is also under discussion as a clinical outcome parameter. Health authorities might approve drugs that reduce the rate of joint-space narrowing without significant improvement of function and/or pain provided that in further studies symptomatic benefit (pain relief and functional improvement) will be shown. Therefore 'pure' structure-modifying drugs that do not provide symptomatic benefit would lose their registration and not remain on the market. Primary idiopathic OA has a very slow progression rate. Structure-modifying drugs therefore have to be administered over a very long period of time, which imposes very high demands on their safety.

Emerging therapies for chronic OA pain. Several COX2-selective inhibitors are undergoing clinical development for OA (TABLES 2,3). Because they can hardly be expected

Table 2 | **Disease-modifying drugs currently in clinical trials for osteoarthritis**

Drug	Class	Phase	Company	Chemical structure
Glucosamine	Non-pharmaceutical	III	NIH	
VX-765	ICE inhibitor	I	Vertex	Unavailable
Pralnacasan	ICE inhibitor	II	Vertex/Sanofi-Aventis	
SB-462795	Cathepsin K inhibitor	I	GlaxoSmithKline	
Doxycycline	Antibiotic	III	FDA/NIH	
CPA-926	Inhibits MMP expression	II	Kureha	
ONO-4817	MMP inhibitor	I	Pfizer	
S-3536	MMP inhibitor	I	Shionogi	Unavailable
PG-530742	MMP inhibitor	II	Procter & Gamble	Unavailable
CP-544439	MMP inhibitor	I	Pfizer	Unavailable

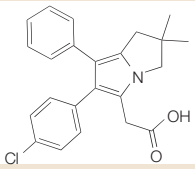
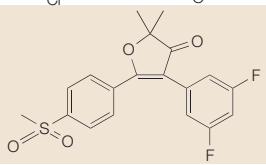
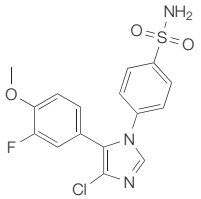
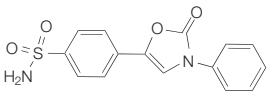
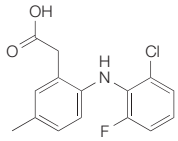
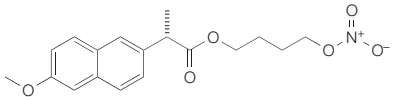
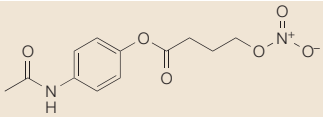
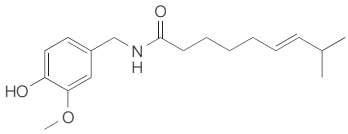
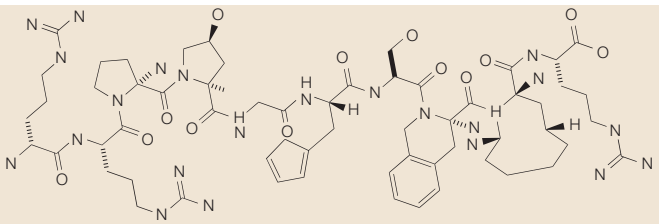
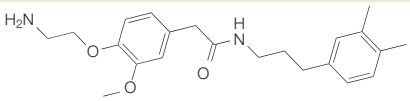
FDA, Food and Drug Administration; ICE, interleukin-1β-converting enzyme; MMP, matrix metalloproteinase; NIH, National Institutes of Health.

to be significantly more efficacious than approved COX2 inhibitors, a beneficial safety profile is the most important factor for product differentiation. The most advanced COX2 inhibitor in development is lumiracoxib (Prexige; Novartis), which has a novel chemical structure in that it lacks a sulphur-containing group but has a carboxylic acid moiety. It is highly selective and has a short plasma half-life (3–6 hours). In the large, recently published trial Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), a three- to four-fold reduction in ulcer complication (primary endpoint) in comparison with ibuprofen and naproxen was found with a treatment period of 52 weeks[116]. Its application for approval in the European Union (EU) is currently on hold to await the outcome of a safety review of COX2 inhibitors.

NSAIDs have adverse gastrointestinal effects, and it has recently been suggested that some selective COX2 inhibitors are also associated with serious gastrointestinal complications (see above). NSAIDs and COX2 inhibitors reduce the levels of prostaglandins, but their use can cause arachidonic acid to be processed through the 5-lipoxygenase (5-LO) pathway, which leads to increased production of pro-inflammatory and gastrotoxic leukotrienes[117]. Licofelone (Merckle) is a competitive inhibitor of 5-LO, COX1 and COX2. Licofelone decreases the production of both leukotrienes and prostaglandins, thereby reducing inflammation and pain with low gastrointestinal toxicity, and is currently being developed for the treatment of OA[118].

A range of standard NSAIDs, including naproxen, diclofenac and aspirin, have been coupled to a nitric oxide (NO)-donating moiety. They are able to release NO over prolonged periods of time and have shown reduced gastrointestinal and cardiorenal toxicity[119]. The mechanism that prohibits the ulcerogenic activity of the

Table 3 | **Symptom-modifying drugs currently in clinical trials for osteoarthritis**

Drug	Class	Phase	Company	Chemical structure
Licofelone	COX/LOX inhibitor	III	Merckle	
PAC-10549	COX2 inhibitor	I	Pacific	
Cimicoxib	COX2 inhibitor	I	Uriach	
GW-406381	COX2 inhibitor	II	GlaxoSmithKline	Unavailable
LAS-34475	COX2 inhibitor	II	Almirall	
CS-502	COX2 inhibitor	II	Sankyo	Unavailable
Prexige	COX2 inhibitor	III	Novartis	
Medinox	NSAID	I	Medinox	Unavailable
NO-naproxen	NO analgesic	II	NicOX	
NCX-701	NO analgesic	II	NicOX	
ALGRX-4975	NO analgesic	I	AlgoRx	
ADL-100116	Peripheral κ-opioid agonist	I	Adolor	Unavailable
AD827	Cytokine synthesis inhibitor	I	Arakis	Unavailable
HOE140	Bradykinin B_2 receptor antagonist	II	Sanofi-Aventis	
DA-5018	Capsaicin analogue	I	Dong-A	

COX2, cyclooxygenase 2; LOX, lipooxygenase; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug.

parent NSAID is not fully established. It has been assumed that NO exerts local protective actions, including mucosal vasodilatation[120]. An ongoing Phase II development programme for NO-naproxen (AstraZeneca) has been stopped, and development rights have been returned to the originator company, NicOx[120]. In addition to beneficial gastrointestinal safety aspects, these agents might reduce cardiovascular risk because of their NO-donating capability. This was indicated in a small study on patients with OA of the knee, in which NO-naproxen caused a slight fall in systolic blood pressure, in contrast to a slight increase with naproxen and rofecoxib[121]. Additional studies are needed to further distinguish these compounds from NSAIDs.

Icatibant (HOE140; Sanofi-Aventis) is a specific and potent bradykinin B_2 receptor antagonist that is currently undergoing Phase IIa trials for the treatment of signs and symptoms of OA. It is a decapeptide and is administered via intra-articular injection. In the first placebo-controlled proof-of-mechanism study in patients with knee OA, one dose of HOE140 provided greater pain relief than placebo injection and the compound was well tolerated[90].

Biomarkers for progress in treating OA

Considerable efforts are being devoted worldwide to developing biomarkers for OA[82] (TABLE 4). In general, a biomarker is an endogenous molecule that is indicative or reflective of a specific biological or pathological process — that is, an identifiable consequence or endpoint of a process and a pharmacological response to therapeutic intervention. Ideally, a biomarker could serve as a surrogate marker that can substitute for a clinical endpoint — that is, a primary outcome measure which, by expert definition, is a characteristic or variable that measures how a patient feels, functions or survives.

Biochemical markers of OA reflect the disease process leading to joint destruction. Most of the currently investigated OA biomarkers are derived from the matrix of the articular cartilage. Biomarkers of specific molecular/cellular processes involved in disease progression would help define the pathogenesis of OA and could allow early diagnosis before the disease is too far advanced and help identify patients at risk. During treatment, biomarkers for OA could help to identify sub-populations of patients — for example, fast progressors or those undergoing an active phase of inflammation — or assist in the stratification of genetically distinct patients or patient populations that have uniform biomarker characteristics. This could enable specific therapies to be targeted to specific patient groups. In drug development, OA biomarkers could help confirm drug efficacy as secondary outcome parameters in preclinical and clinical studies, and could be used to identify therapeutic doses and to evaluate the toxic effects of drugs in development to treat OA.

In OA, a number of proteases degrade the cartilage matrix that is essential for the function and integrity of the articular cartilage. This generates molecular fragments that are subsequently released from the cartilage into the synovial fluid. From the joint fluid, these fragments of degenerated cartilage — products of joint metabolism — are transported into the circulation, from where some are cleared by the kidney and are excreted in urine. The concentrations of some markers also show circadian rhythms, which necessitates a very thorough standardization of sample timing. The situation is further complicated by the fact that these molecules can be metabolized in the liver or kidney, and exchanged between the plasma and the interstitial fluid and other non-articular sources, which can influence their systemic serum and urine levels. The complex kinetics and the metabolism of the individual molecular fragments therefore contribute to the high intra- and inter-individual variability of biomarkers and render their measurements difficult to interpret. Nevertheless, progress has been made concerning the potential application of biomarkers for identifying individuals with OA who are at risk for disease progression.

There is strong evidence that primary idiopathic OA involves phases of advanced progression often associated with inflammatory flare-ups[81]. Recent evidence indicates that biochemical markers and/or markers of inflammation might serve to diagnose these phases. These also include the type II collagen crosslinking C-telopeptide region fragments (CTX-II)[122], the ratio of two type II collagen collagenase-generated cleavage epitopes in the helical region of collagen (C1,2C to C2C)[123], and the ratio of the collagen II propeptide to collagen cleavage epitopes or cartilage oligomeric matrix protein (COMP)[124].

The important question of whether or not biomarkers could serve as surrogate outcome measures in randomized clinical trials of DMOADs can only be answered with the help of an efficacious disease-modifying drug, something that is not yet available. The high variability of the marker concentration within and between patients necessitates logistic regression or principal component analyses to distinguish patient populations with different severity of OA or different rates of disease progression.

Perhaps we should devote more effort to identifying novel diagnostic tools and specific treatment options targeted at these progression phases and develop drugs with additional anti-inflammatory components. In addition, it is important to develop drugs that act on strategic signalling crossroads of the pathophysiological network, rather than drugs that only interfere with the final stage of the pathophysiological cascade (that is, proteolytic cleavage). Such drugs could offer both symptomatic relief and reduce joint damage. The final outcome of this intermittent treatment paradigm could still beneficially affect disease progression, thereby avoiding or delaying joint replacement.

Conclusions and outlook

Although OA is an enormous burden for patients, drug development for OA presents a tremendous challenge and opportunity both to industry and academia.

Table 4 | **Osteoarthritis biomarker candidates**

Biomarker	Disease process	Source
Collagen II c-telopeptides (CTX-II)	Cartilage degradation	Urine
Collagen II collagenase generated cleavage products (C2C, C1,2C)	Cartilage degradation	Urine, serum, synovial fluid
Collagen II propeptides	Collagen II synthesis	Synovial fluid, serum
Cartilage oligomeric matrix protein (COMP)	Cartilage turnover	Serum, synovial fluid
Aggrecan epitope 846	Cartilage turnover	Synovial fluid, serum
C-reactive protein	Synovitis	Serum
Hyaluronan	Synovitis	Serum, synovial fluid
Carboxy-terminal helical collagen-I telopeptide fragments (CTX-I)	Bone remodelling	Urine
Osteocalcin, bone sialoprotein	Bone remodelling	Serum

Recently, success rates from first-in-human studies to registration have been studied for a 10-year period for 10 large pharmaceutical companies in the United States and Europe[125]. The rate of success varies between different indication areas. Cardiovascular and arthritis/pain have the highest success rates by phases of development, whereas others — for example, oncology and disorders of the central nervous system — have a much higher attrition rate. COX inhibitors have contributed a great deal to this high success rate in arthritis/pain in the past. Now there is an urgent need for novel approaches. A single compound that unifies every aspect necessary for the efficient treatment of OA — that is, one that not only reduces the degenerative processes and pain, but regenerates cartilage through anabolic processes — will most probably never exist. However, biomarkers of joint destruction and inflammation and specific combinations thereof, as well as novel imaging modalities, will allow earlier diagnosis and the differentiation of subforms of OA. This will enable prophylactic and disease subgroup-specific interventions. There will be novel drugs developed for osteoarthritic pain with improved efficacy and safety profiles. Intra-articular therapy will gain more importance with the advent of specially developed slow-release formulations. This could also enable the application of novel drugs or biologicals that help to regenerate cartilage but which would otherwise be intolerable if applied systemically. An integrated view of OA is emerging with novel interesting targets. The adequate treatment of OA might well require a combination of drugs with different mechanisms of action. Taken together, there is reason for optimism that not only improved symptomatic therapies but also structure-modifying treatment of OA will become available within 20 years.

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Competing interests statement
The authors declare competing financial interests: see Web version for details.

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CORRECTION

OSTEOARTHRITIS — AN UNTREATABLE DISEASE

Heike A. Wieland, Martin Michaelis, Bernhard J. Kirschbaum and Karl. A. Rudolphi

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In Table 2 (p. 339) of the article, a structure is cited for SB-462795. We have been informed that, although available in the public domain until recently, this structure does not relate to SB-46275. The structure for SB-46275 has not yet been disclosed and, therefore, should be replaced with 'unavailable' in Table 2.