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Review

The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics

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SUMMARY

Osteoarthritis (OA) is an age-related condition and the leading cause of pain, disability and shortening of adult working life in the UK. The incidence of OA increases with age, with 25% of the over 50s population having OA of the knee. Despite promising preclinical data covering various molecule classes, there is regrettably at present no approved disease-modifying OA drugs (DMOADs). With the advent of next generation sequencing technologies, other therapeutic areas, in particular oncology, have experienced a paradigm shift towards defining disease by its molecular composition. This paradigm shift has enabled high resolution patient stratification and supported the emergence of personalised or precision medicines. In this review we evaluate the potential for the development of OA therapeutics to undergo a similar paradigm shift given that OA is increasingly being recognised as a heterogeneous disease affecting multiple joint tissues. We highlight the evidence for the role of these tissues in OA pathology as different "hallmarks" of OA biology and review the opportunities to identify and develop targeted disease-modifying pharmacological therapeutics. Finally, we consider whether it is feasible to expect the emergence of personalised disease-modifying medicines for patients with OA and how this might be achieved.

The unmet clinical need in OA for a personalised disease-modifying therapeutic

Osteoarthritis (OA) is an age-related condition and the leading cause of pain, disability and shortening of adult working life in the UK. The incidence of OA increases with age, with 25% of the over 50s population having OA of the knee[1]. Despite this prevalence, and in contrast to rheumatoid arthritis[2], there are currently no effective Disease-Modifying OA Drugs (DMOADs) which have met regulatory approval.

Clinical management of OA typically entails a limited combination of pharmacological and non-pharmacological treatment options to reduce pain and increase tolerance for functional activity[2]. Unfortunately, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) either do not modify the disease course or have been associated with serious renal and cardiovascular effects and gastrointestinal bleeding in the clinic[3]. Patients with knee OA can be offered intra-articular corticosteroid injections which can be effective in some patients in providing pain relief, but the benefit is short-lived and frequent injections can damage the articular cartilage. Recent studies have reported structural benefits with dietary Glucosamine supplementation in patients with knee OA[4]. Some of these supplements therefore hold great promise, and may in the future be part of a holistic treatment approach. However, currently they are not recommended by OARSI and ACR[5]. Ultimately therefore, many patients with knee or hip OA will undergo surgery to replace the diseased joint.

In stark contrast, our understanding and subsequent treatment of cancer has changed dramatically over the last 10–15 years. The emergence of molecular biology combined with next generation sequencing approaches has enabled a paradigm shift from labelling cancer by anatomical location and tissue type, to being defined by its molecular genetics phenotype. Importantly, this paradigm shift has facilitated the emergence of personalised therapeutics. The importance of developing personalised therapeutics was highlighted during the clinical studies of Iressa (Gefitinib), developed by AstraZeneca for patients with non-small cell lung cancer (NSCLC) to

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target the epidermal growth factor receptor (EGFR). Initial clinical trials with Gefitinib were conducted with a large mixed patient cohort and did not show overall efficacy. However, retrospective analysis revealed that the drug was efficacious in approximately 10% of patients whose lung cancer exhibited activating EGFR mutations[7]. This illustrates the importance of improved profiling of patient populations so that patients are stratified to find the right drug for the right patient. This personalised medicine approach also facilitates smaller, more targeted trial designs with a greater chance of meaningful outcomes.

Furthermore, because of our understanding of cancer biology as a multi-faceted disease, therapeutics have been developed which are designed to target different hallmarks of cancer biology, from tumour cell growth and apoptosis, tumour metabolism to anti-angiogenic drugs which target the tumour vasculature, for example the VEGF antibody Avastin (bevacizumab). These different therapeutic strategies offer a multitude of potential therapeutic targets and also are now opening the door to the study of combination therapeutics which will likely lead to a further step-change in drug efficacy[8].

In this review we evaluate the potential for the development of OA pharmacological disease-modifying therapeutics to undergo a similar paradigm shift given that OA is increasingly being recognised as a heterogeneous disease and one that involves the whole joint, encompassing multiple tissue types including cartilage, bone, adipose and skeletal muscle. We briefly highlight the evidence for the role of these tissues in OA pathology and review the opportunities within each of these tissues to identify and develop targeted disease-modifying therapeutics (Fig. 1 & Table I). We also consider whether it is feasible to expect the emergence of personalised disease-modifying medicines for patients with OA and how this might be achieved.

Biological effect areas in OA for identifying potential therapeutic targets

Targeting cartilage matrix degradation

OA is characterised by the degradation of cartilage matrix components, including cartilage specific type II collagen and the proteoglycan aggrecan[9], ultimately resulting in the loss of cartilage structure and function. Targeting cartilage matrix degeneration is a well explored area for drug target discovery, and therefore the majority of what could be termed “low-hanging fruit” have already been picked. However, given that there are thought to be several key anabolic and catabolic pathways enzymes that are dysregulated in OA cartilage[10], there remains the opportunity to identify and validate new drug targets. In addition, there are also the untapped opportunities to explore and identify novel combinations from combining existing known targets. For example by combining therapeutics that are anti-catabolic with those that activate anabolic signalling pathways. As in cancer drug discovery, these are areas which should be investigated to identify a novel efficacious combination from combining known targets.

Matrix metalloproteinases (MMPs), a diverse family of zinc-dependent proteolytic enzymes involved in the maintenance of the extracellular matrix[11], were initially seen as attractive drug targets for the treatment of OA[12] and indeed other therapeutic areas including cardiovascular disease and cancer[13–15]. However, despite several candidates showing good efficacy in preclinical

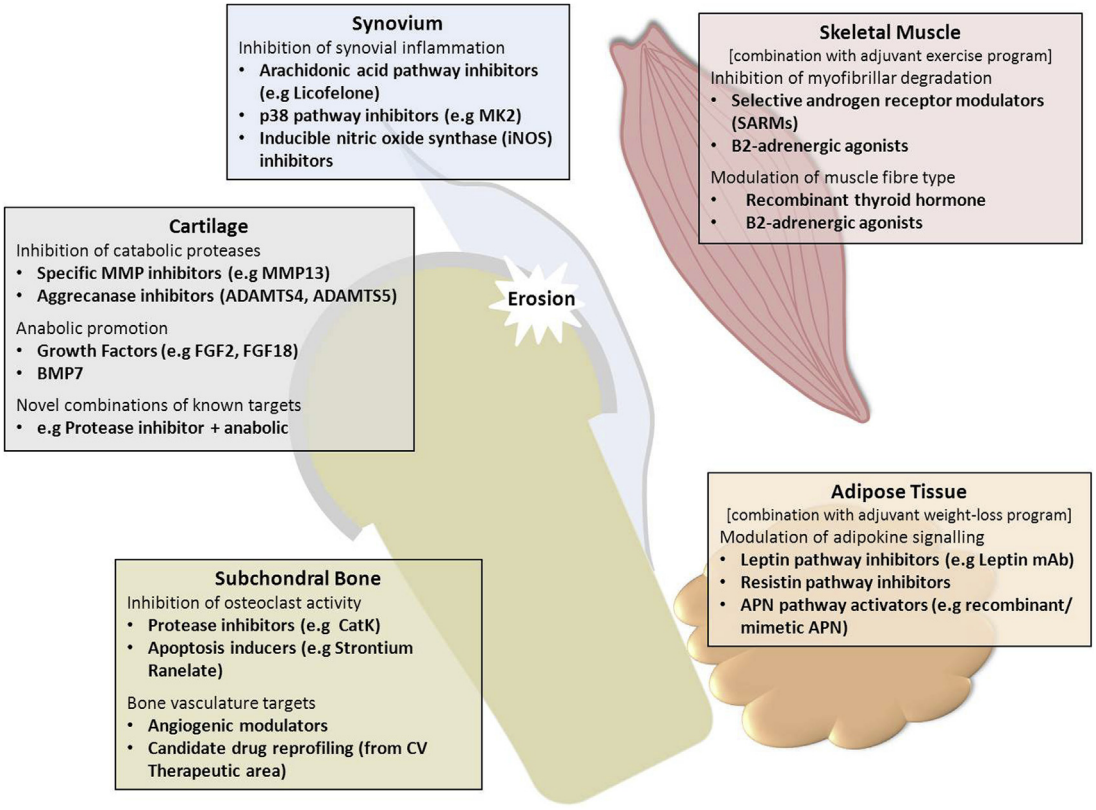

Fig. 1. Representation of the multiple biological effect areas within the OA joint and key pathways to exploit for the development of pharmacological DMOADs. OA is widely recognised as a disease of the whole joint (encompassing cartilage, subchondral bone, synovium, skeletal muscle and adipose tissue), offering new opportunities to identify new drug targets, new drug combinations and re-profiling old drugs from other therapeutic areas.

Table I
Pharmacological targets and approaches for OA disease modification. For each clinical trial cited, the quality of evidence is included in superscript; 1 refers to a randomised controlled trial

Biological effect area	Therapeutic target	Mode of action	Preclinical strength of hypothesis		Clinical data (quality of evidence in superscript)
			In vitro	*In vivo*	
Cartilage Matrix	MMPs (pan) MMP-13	Inhibition of MMP proteases to prevent Type II Collagen degradation.	Efficacy demonstrated in bovine and human cartilage explants using small molecule pan-MMP inhibitors and a selective MMP-13 inhibitor[12].	Efficacy demonstrated in rodent and canine models of OA[12,19].	Terminated in Phase I/II due to musculoskeletal toxicity. **NCT00041756**[1]
	ADAMTS-4 ADAMTS-5	Inhibition of aggrenases to prevent proteoglycan degradation.	Inhibition of ADAMTS-4 and 5 attenuated the degradation of aggrecan in cytokine stimulated normal cartilage explants and un-stimulated OA explants[130]. ADAMTS-4/ADAMTS-5 inhibitors show efficacy in reducing CTXII release from human cartilage explants stimulation with interleukin-1, onocstatin-M and plasminogen[131].	ADAMTS-5 knockout mouse is protected from aggrecan loss following surgically induced joint instability[20]. ADAMTS-4/ADAMTS-5 inhibitor reduces the production of aggrecanase specific neo-epitope in the Dunkin Hartley guinea pig[131].	AGG-523 (ADAMTS4/5 inhibitor) – poor pharmacokinetics identified in Phase I study. **NCT00427687**[1] **NCT00454298**[1]
	Fibroblast Growth Factors FGF-18	Induction of type II Col and proteoglycan synthesis.	rFGF and rFGF18 induce type II collagen and proteoglycan synthesis in cartilage[23].	rFGF18 promotes cartilage repair in the rodent meniscal tear model of OA[24].	Candidate drugs currently in Phase I/II studies. **NCT01066871**[1] **NCT01689337**[1] **NCT01919164**[1]
	BMP-7/OP-1	Induction of type II Col and proteoglycan synthesis.	rOP-1 induces synthesis of collagen and proteoglycan in cartilage[26].	rOP-1 promotes cartilage repair and reduces pain[27,28].	Candidate drugs currently in Phase I studies. **NCT00456157**[1] **NCT01133613**[1] **NCT01111045**[1]
Bone	Cathepsin K	Reduction in osteoclast resorption efficiency.	Inhibition of cathepsin K shown to reduce osteoclast resorption efficiency whilst maintaining other cellular functions in murine and human osteoclasts[49].	CatK deletion increases bone mass[48]. Pharmacological inhibition of CatK shown to protect subchondral bone integrity, reduce the incidence osteophytosis, reduce cartilage degeneration and improve joint pain[46,52,53].	
	Bisphosphonates	Induction of osteoclast apoptosis.	Induction of marked osteoclast apoptosis confirmed in murine osteoclast cell culture[132].	Tiludronate demonstrated a positive effect on gait disability and joint symptoms in a canine model of OA[133].	Several studies have shown that bisphosphonate administration has positive effects on joint pain in various osteoarthritic sites – reviewed by[40]. Lack of DMOAD efficacy reported in Phase II study Laslett *et al.*, 2013
	Calcitonin	Inhibits osteoclast bone resorption activity.	Calcitonin inhibits osteoclast bone resorption in vitro[134].	Reduction of cartilage loss and subchondral bone damage following calcitonin administration in a murine model of traumatic OA[42].	Terminated in Phase III due to reported toxicity. **NCT00376311**[1] **NCT00704847**[1]
	Strontium	Inhibits osteoclast bone resorption activity.	Strontium inhibits bone resorption[43] and stimulates bone formation[44].	Reduces progression in a canine model of OA[45].	Evidence of slowed JSN in knee OA. **ISRCTN41323372**[1]
Inflammation	COX-2	Inhibition of arachidonic acid pathway.	COX-2 inhibition reversed cartilage matrix degradation in human articular cartilage cultures stimulated with peripheral blood mononuclear cells, IL-1β and TNF-α[135].	COX-2 inhibition reduced histological changes and suppressed chondrocyte apoptosis in a rodent instability model of OA[136].	Terminated due to cardiovascular toxicity.
	TNF-α	mAb to block TNF-α inflammatory signalling.	Infliximab and Etanercept suppress TNF-α induced NO production in human cartilage explants from OA patients[137].	Anti-TNF-α administration significantly reduced developing joint pathology in a murine model of collagen-induced arthritis (CIA) however had little effect on established CIA[138]. Reduction in Mankin score noted in meniscectomised rabbits following administration of Infliximab[139].	Lack of DMOAD efficacy reported in Phase II study of patients with hand OA. **NCT00597623**[1]
	IL-1β	Block IL-1β inflammatory signalling.		Reduction in inflammatory mediators (including TNF-α and MMP-13) following blockade of IL-1β by gene knockdown in the Dunkin Hartley strain guinea pig[140]. Pralnacasan reduced joint damage in two murine models of	Terminated in Phase II due to reported liver toxicity in a 9-month animal study. (Pralnacasan).

(*continued on next page*)

Table I (*continued*)

Biological effect area	Therapeutic target	Mode of action	Preclinical strength of hypothesis		Clinical data (quality of evidence in superscript)
			In vitro	*In vivo*	
				knee OA[141]. Anti- IL-1β administration significantly reduced developing and established joint pathology in a murine model of collagen-induced arthritis (CIA) however combined anti- IL-1α/β provided further protection[138].	
	IL-1 receptor	IL-1 receptor antagonists.	Human recombinant IL-1 receptor suppressed proteoglycan degradation, glycosaminoglycan inhibition and matrix metalloproteinase production in cartilage cultures[142].	Reduced lesion severity in a canine model of OA in response to autologous IL1Ra administration[143]. Reduction in inflammatory mediators (including TNF-α and MMP-13) following adenoviral vector driven expression of IL1- receptor in the Dunkin Hartley strain guinea pig[140]. Reduced cartilage loss in rodent MIA model of knee OA[77].	Lack of DMOAD efficacy reported in an RCT conducted in a population with confirm knee OA. **NCT00110942**[1]
	p38 MAPK	Inhibition of p38 MAPK inflammatory signalling.	p38 inhibitors efficacious in reducing MMP production in bovine cartilage[76].		
	MAPKAPK2 (MK2)	Inhibition of MK2 to inhibit p38 pathway inflammatory signalling.	MK2 siRNA efficacious in inhibiting MMP production and TNFα in cartilage.		
	Nitric oxide synthase	iNOS inhibitor to inhibit inflammation.	NO is induced by IL-1, a cardinal OA cytokine, via the inducible NO synthase pathway (iNOS) in human chondrocytes[68]. Chondrocyte death reduced in canine cartilage explants following iNOS inhibition[144].	Reduced progression and pain in the murine monosodium iodoacetate-induced model of osteoarthritic pain[72]. Reduced progression in the canine model of OA[73,74].	Failure to slow JSN in a cohort of obese female OA patients **NCT00565812**[1]

disease models, the development of MMP inhibitors has been limited by their tendency to elicit various undesirable musculoskeletal pathologies in both preclinical models and in the clinic, at efficacious blood concentrations[9,16–18].

Selectivity profiling initially suggested that the inhibition of interstitial collagenase (MMP-1) and matrilysin (MMP-7) were responsible for the musculoskeletal symptoms associated with broad-spectrum MMP inhibitors[16]. Recent *in vitro* studies have concentrated on the development of inhibitors which specifically target MMP-13, a key MMP expressed in human OA cartilage[9], whilst maintaining selectivity against other MMPs. Furthermore, inhibitors such as ALS 1-0635[12] and PF-152[19] have demonstrated chondroprotective effects in rodent and canine preclinical studies with no reported evidence of musculoskeletal pathology. However, a human clinical trial involving knee OA patients receiving the MMP inhibitor PG-116800 (PG-530742) which has low affinity for both MMP-1 and MMP-7[16] (NCT00041756) was unfortunately terminated due to musculoskeletal toxicity. Although these highly specific MMP inhibitors may offer significant therapeutic potential, no such molecules have yet been approved for use in the clinic and concerns remain that the muscle toxicity may be due to the molecule class. As such no further clinical trials are currently underway investigating MMP inhibitors in OA.

With concerns regarding MMP inhibitor safety profiles, an alternative approach is to develop inhibitors which target the aggrecanases, members of the ADAMTS family which are the major enzymes responsible for aggrecan cleavage during early cartilage remodelling. *In vitro* studies using functional antibodies or siRNA have implicated aggrecanase 1 (ADAMTS-4) and aggrecanase 2 (ADAMTS-5) as the key aggrecanases in mediating aggrecan cleavage in pig and bovine articular cartilage.

Currently, the relative contribution of ADAMTS-4 and ADAMTS-5 proteinases to aggrecan loss and early cartilage erosion in OA has not been fully established. Studies using an ADAMTS-5 knockout showed that mice deficient in ADAMTS-5 (but not ADAMTS-4) were protected from early aggrecan loss and cartilage erosion in both inflammatory and surgical preclinical models of OA[20,21] however it is not yet known whether these findings will translate to human OA. Developing pharmacological aggrecanase inhibitors into the clinic has proven difficult due to poor pharmacokinetic (PK) properties with this class of inhibitor resulting in poor systemic exposure unless potency is compromised. As such, only one aggrecanase inhibitor has been trialled in the clinic, AGG-523, an ADAMTS4/5 dual inhibitor which was investigated in two Phase I studies in patients with mild to moderate (clinical trial NCT00427687) and severe (clinical trial NCT00454298) knee OA. Exploring the potential synergistic efficacy of combining an aggrecanase inhibitor with a selective MMP inhibitor, or indeed a pro-anabolic drug may be one way forward in achieving an efficacious therapeutic drug with suitable PK properties.

Targeting anabolic pathways to promote cartilage repair is an alternative strategy for preventing cartilage degeneration. Members of the fibroblast growth factors (FGF) family of growth factors, FGF-2 and FGF-18, have been implicated in the regulation of articular cartilage homeostasis and repair[22]. *In vitro* and *in vivo* studies have demonstrated the cartilage anabolic effects of recombinant FGF in inducing type II collagen formation and promoting proteoglycan synthesis[23], whilst FGF-18 administration has been shown to induce cartilage repair in rodent preclinical models of OA[24]. Recombinant FGF-18 is currently the focus of several clinical trials including studies investigating its efficacy in stimulating cartilage repair following injury and micro-fracture surgery, and its effect on slowing disease progression in a cohort of knee OA patients (clinical trial identity numbers NCT01066871, NCT01689337, NCT01919164 respectively). Currently, it remains to

be seen whether the anabolic effects on cartilage seen in preclinical models are replicated in the clinic.

Bone morphogenetic protein-7 (BMP-7, osteogenic Protein-1) is another growth factor that has been investigated as a potential therapeutic target to promote OA articular cartilage repair. BMP-7 levels are lower in OA diseased cartilage compared to normal cartilage[25] and *in vitro* and *ex-vivo* studies have demonstrated the pro-anabolic effect of BMP-7 on cartilage of stimulating the synthesis of matrix components and increasing collagen and proteoglycan synthesis[26]. Preclinical data suggests that the administration of recombinant human BMP-7 has reparative effects on cartilage and improves symptoms of joint pain[27,28]. Three clinical trials have investigated the administration of BMP-7 in patients with knee OA to date. A small phase 1 safety and tolerability study of BMP-7 in ~30 patients with knee OA reported a ~20% improvement in pain in the absence of any dose limiting toxicity (NCT01111045)[27]. Results are currently awaited from two further dose finding and dose escalation studies (NCT00456157, NCT01133613).

Targeting bone remodelling

Recent evidence from animal models and from clinical studies suggest that pathological remodelling of the subchondral bone in OA[29–33] may actually precede and mediate cartilage degeneration[33–39]. It is therefore questionable whether any therapeutic targeting a single target involved in cartilage matrix homeostasis is likely to elicit effective disease-modifying efficacy in human OA disease. Thus it is critical to also consider the opportunities for identifying and developing therapeutics that mediate bone remodelling, as well as attempting to better understand the cross-talk between OA cartilage and bone tissues since this may present an attractive therapeutic approach.

OA subchondral bone is characterised as “sclerotic”, being hypomineralised with a thickened and irregular trabecular structure suggestive of abnormal bone remodelling and altered osteoblast-osteoclast coupling. The phenotype is distinct from an osteoporotic phenotype since there is often no reduction in bone volume. However, despite this difference, many clinical studies in patients with OA have been conducted using anti-resorptive bisphosphonates, which are first-line treatments for osteoporosis. Although in some studies bisphosphonates have shown improvements in pain scores[40], they have not as yet shown any disease-modifying efficacy in patients with OA[41]. Preclinical efficacy with calcitonin[42], which binds to the calcitonin receptor on osteoclasts and inhibits bone resorption led to its investigation in phase II (NCT00376311) and III clinical trials (NCT00704847). However, recent indication of an elevated risk of prostatic cancer has led to these clinical studies being terminated.

More promising is the recently disclosed clinical trial data on strontium ranelate, which is currently indicated for the treatment of osteoporosis in post-menopausal women. Previous *in vitro* studies have shown that strontium inhibits bone resorption and stimulates bone formation[43,44]. *In vivo* studies conducted in a canine model have also shown that strontium ranelate reduces OA progression[45]. Most significantly, a recent phase III study (ISRCTN41323372) conducted in a population ($n = 1371$) with knee OA (Kellgren and Lawrence grade 2–3, and joint space width 2.5–5 mm) reported that strontium administration (1 g/day) was associated with smaller degradations in joint space width than placebo and that fewer patients in the treated group exhibited radiological progression. Furthermore, reductions in indicators of knee pain and improvements in physical function were noted following the administration of 2 g/day strontium[4].

An alternative strategy is to target osteoclast proteolytic activity by developing small molecule inhibitors to Cathepsin K (CatK). CatK is a lysosomal protease which is highly expressed in actively resorbing osteoclasts where it mediates the degradation of matrix proteins[46] and its expression has been confirmed in the synovium of OA patients[47]. Targeted deletion of CatK leads to an increased bone mass phenotype[48], suggesting a role in bone remodelling and homeostasis. The pharmacologic inhibition of CatK using molecules such as L-006235 and Odanacatib, has been shown to reduce osteoclastic bone resorption both *in vitro*[49] and *in vivo*[50] whilst allowing bone formation to continue[51]. Furthermore, CatK inhibition has been shown to protect subchondral bone integrity, reduce the incidence osteophytosis[46], reduce cartilage degeneration and improve joint pain in various preclinical animal models of OA[46,52,53]. Despite the availability of candidate pharmacologic agents and encouraging preclinical findings, to date no studies have assessed the efficacy of CatK inhibition in modulating the course of human OA. However, several clinical trials are underway to investigate the utility of CatK inhibitors in other medical conditions, such as osteoporosis and cancer.

A potential new avenue for targeting bone remodelling in OA could be to target the bone vasculature. Importantly, knee and hip OA are both associated with vascular-related co-morbidities[54–56], and there is now growing evidence that vascular dysfunction may also play a role in mediating subchondral bone remodelling in OA. The subchondral bone in both hip and knee OA exhibits evidence of vascular dysfunction, with vascular occlusion and reduced venous outflow[57,58], which may result in local hypoxia[59]. Furthermore, bone ischemia has been linked to bone marrow lesions (BMLs), which are one of the morphological hallmarks of OA bone and are strong predictors of progressive cartilage degeneration and pain.

Recent analysis of BMLs from patients with knee OA showed that these lesions consisted of highly under-mineralised sclerotic bone with histopathology features of secondary modelling of vessels, evidence of fibrosis and multiple thrombus inclusions, consistent with a localised oxygen deficit[60]. We recently found that osteoblasts isolated from subchondral bone exhibited a hypomineralised OA bone phenotype when cultured under hypoxic conditions (unpublished). Therapeutics that are capable of targeting local hypoxia (i.e., angiogenic modulators) in the OA bone microenvironment could therefore be a potential strategy to prevent pathological bone remodelling opening the opportunity for the re-profiling of candidate drugs from the cardiovascular therapeutic area.

Targeting inflammation

Inflammation is now recognized as an important pathological driver in OA, even where there is the involvement of mechanical factors in OA development such as in meniscal injury or anterior cruciate ligament tear. MRI, immunohistochemical studies and ultrasonography have all demonstrated synovitis in early OA with increased cellular infiltrate of macrophages and T cells[61]. Furthermore, elevated levels of several pro-inflammatory cytokines including IL-1β, TNFα, IL-6, IL-8 have been detected in the synovial fluid and serum of patients with OA compared to healthy individuals. Importantly, the effect on *ex-vivo* cartilage and bone tissue of stimulation with cytokines such as TNFα and IL-1β mimic the structural changes observed within the OA joint[62] strongly suggesting that an anti-inflammatory therapeutic could positively affect cartilage integrity and bone remodelling.

Despite their success in treating rheumatoid arthritis (RA), monoclonal antibodies targeting TNFα have disappointed in clinical studies in OA patients, showing only limited effectiveness in painful OA but no disease modification (NCT00597623). IL-1β antagonists have also been trialled, but pralnacasan was halted in phase II due to the emergence of liver toxicity data (Wieland HA 2005), whilst

clinical studies on IL-1 receptor antagonists did not meet primary endpoints (NCT00110942)[63]. Given the multitude of cytokines reported to be elevated in OA joints it would appear likely that targeting of multiple cytokines would be required to achieve efficacy. However, targeting of multiple cytokines would also be expected to increase the risk of infection and thus such an approach is currently deemed unsuitable for chronic administration.

Another approach to targeting inflammation in OA is to target the arachidonic acid pathway. As previously noted, NSAIDs failed in the clinical due to adverse side effects. Cycoloxygenase-1 (COX-1) inhibitors such as Aspirin resulted in gastrointestinal adverse events, whilst COX-2 inhibitors were associated with severe cardiovascular side effects. The cardiovascular side effects of COX inhibition have since been attributed to the effect of COX-2 inhibition on the balance of prostacyclin and thromboxane A (TxA) with an increase in the relative levels of TxA favouring prothrombotic events. An alternative strategy is therefore to target both arms of the arachidonic acid pathway so as not to disrupt the prostacyclin/thromboxane balance and avoid the cardiovascular side effects. Licofelone is a COX and lipoxygenase (LOX) inhibitor with no reported gastrointestinal or cardiovascular side effects at efficacious concentrations[64]. Preclinical studies have shown that licofelone administration prevents the morphological and biochemical changes characteristic of early experimental OA[65], and suggest that this is mediated by a reduction in MMP-13 and Cathepsin K synthesis. Furthermore, licofelone has been shown to significantly reduce cartilage volume loss (vs patients taking a standard NSAID alone) in a recent human clinical trial of knee OA patients[66].

Nitric oxide (NO) plays an important role in inflammatory processes and is considered to be one of the key mediators of cartilage destruction in OA[67]. NO is induced by IL-1, a cardinal OA cytokine, *via* the inducible NO synthase pathway (iNOS)[68] and is elevated in both experimental[69] and human OA[70], In this regard, NO mediates many of the pathogenic effects of IL-1 through the activation of MMPs, the inhibition of proteoglycan and collagen synthesis and the enhancement of inflammation[71]. The iNOS pathway has been considered an attractive target for disease-modifying drugs and is currently the subject of several preclinical studies. The pharmacologic inhibition of iNOS has been shown to reduce progression and pain in the murine monosodium iodoacetate (MIA)-induced model of osteoarthritic pain[72], and reduce disease progression in a canine model of experimental OA[73,74]. However, a recent clinical trial investigating the safety and efficacy of SD-6010, a novel iNOS inhibitor on slowing OA progression in a cohort of overweight and obese patients with knee OA (clinical trial NCT00565812) has shown that whilst well tolerated, iNOS inhibition failed to slow the rate of JSN vs a placebo treatment over a course of 96 weeks[75]. Noteworthy is that this study population consisted predominantly of obese female OA patients (>75%). Given that OA is a heterogeneous condition, it is unclear whether the lack of beneficial effect noted was specific to the patient subgroup studied.

In addition to the study by le Graverand *et al.* (2013), More *et al.* also investigated iNOS inhibition as a potential route for therapy in OA patients[72]. S-methylisothiourea (SMT) was found to be particularly effective in reducing NO. Using a MIA-induced model of OA in rats, 30 mg/kg SMT was found to reduce NO production in synovial fluid. This was complemented by histopathological evidence suggesting a reduction in disease progression through measures of intact cartilage. Translatability into human subjects is a vital next step for this work but early evidence is encouraging. Furthermore, in light of the availability of well tolerated inhibitors and positive preclinical data, it is plausible that iNOS inhibition may prove a useful addition to combination therapies designed to target multiple hallmarks of the disease. In this regard, further studies of iNOS inhibition in other OA patient cohorts could be fruitful.

Inhibitors of p38 MAPK are efficacious in reducing MMP production in bovine cartilage explants[76]. Furthermore, p38 MAPK inhibition has been shown to reduce cartilage degradation in murine preclinical models of OA[77]. Despite these positive findings, p38 inhibitors cannot be given systemically since p38 MAPK has both pro-inflammatory and anti-inflammatory functions dependent on the cell type. An alternative strategy is therefore to develop therapeutics that target molecules downstream in the p38 MAPK pathway thus providing a more selective targeting approach. In preclinical *ex-vivo* OA models we have previously demonstrated that inhibition of MAPKAPK2 (MK2) is as effective as p38 inhibition at reducing the cytokine-mediated release of MMPs and PGE2 in human OA cartilage tissue[62]. Therefore small molecule inhibitors developed against MK2 or other downstream MAPKAP kinases might enable an oral anti-inflammatory approach in OA.

Targeting dysfunctional skeletal muscle

Patients with knee OA exhibiting significant muscle weakness[78–80] is one of the most frequent and earliest reported symptoms of OA. Furthermore, muscle weakness is reported in patients with either painful or non-painful OA, suggesting that muscle weakness may precede the onset of disease and be directly involved in its pathogenesis[81,82]. Histochemical studies have shown specific atrophy of type II muscle fibres in the quadriceps muscles of patients with knee OA[83] and in the hip muscles of patients with hip OA[84].

Although it is unclear whether a strong quadriceps muscle can be a protective factor in the initiation of knee OA[85,86], there is extensive clinical evidence to suggest that strengthening lower limbs through exercise may improve OA symptoms[87–92] in patients with established OA. Furthermore, the benefits of exercise and diet-induced weight loss have been investigated in overweight and obese OA patients with beneficial effects on various disease parameters[93]. However, improving skeletal muscle strength and functional performance through intensive exercise regimes is often inappropriate for the many OA patients who are elderly, overweight, co-morbid and may be frail. Therefore, the development of pharmacological agents, that, either alone or in combination with adjuvant exercise programs, are capable of mimicking intensive exercise regimes by improving muscle function in knee OA patients could provide a plausible route through which to modify the disease course of OA during both initiation and late-stage progression.

Several pharmacologic agents have been shown to increase skeletal muscle mass, including androgens such as Testosterone[94]. Therefore, selective androgen receptor modulators (SARMs) that are selectively anabolic hold promise as anabolic therapeutics. In addition to increasing muscle mass, various agents have been shown to modulate skeletal muscle fibre type composition. For example, β2-adrenergic agonists such as clenbuterol increase muscle mass, decrease adiposity[95] and induce a slow to fast fibre type transitions[96], whilst thyroid hormone administration induces slow to fast fibre type transitions with associated increases in contractile activity[97]. Although several pharmacological agents elicit well described effects on skeletal muscle, their utility in OA disease is hampered at present by our lack of understanding of the precise spectrum of changes taking place within the muscle fibres in response to OA development and the lack of an appropriate musculoskeletal animal model of OA for preclinical studies. Indeed, a previous study investigating the use of a muscle modulating agent prior to the induction of experimental surgically induced OA failed to modulate the disease course in the rodent. However, the authors acknowledged that the rapid rate of OA development in the preclinical model utilised may have masked any potential benefits[98].

Such studies highlight the need to clarify the key molecular changes taking place in OA skeletal muscle in order to identify the most suitable muscle targets for modulation (muscle mass *per se*, fibre type, contractility, metabolic potential or a combination) and develop better translational preclinical models.

Targeting adipose tissue

Recent data reveals that many knee and hip joint replacements are attributable to patients being overweight or obese[99]. Specifically, central adiposity is a risk factor for hip and knee OA, suggesting the importance of body composition and fat distribution. Crucially, obesity is associated with OA in both weight-bearing and non-weight-bearing joints such as the hands[100,101] suggesting that it is not simply due to increased load on the joint.

The adipose-secreted cytokines (adipokines), which are known mediators of metabolic homeostasis[102–105], provide a mechanistic link between metabolism and joint remodelling and erosion. The adipokines leptin, adiponectin (APN) and resistin have all been detected within the synovial fluid of OA patients[106,107] and elevated serum levels of adipokines have been found in knee OA patients associated with synovial inflammation[108]. Furthermore, data from *in vitro* studies suggests that adipokines can mediate pathological cartilage and bone remodelling. For example, it has been shown that leptin can potentiate the action of pro-inflammatory cytokines in human primary chondrocytes[109] and stimulate osteoblast activity and proliferation[110], whilst APN has been shown to modulate the expression of both pro-inflammatory cytokines and cartilage proteases including MMP-3, MMP-9, MMP-13 and TIMP-1[111–113].

Studies have shown that serum leptin levels correlate positively to bone mineral density[114–116] and we have shown in females with knee OA that serum leptin and its soluble receptor (Ob-R) are associated with biomarkers of bone and cartilage remodelling as well as cartilage volume loss over a 2 year period[117]. Data on APN supports a protective function in OA[111] since an inverse correlation between serum and synovial fluid levels of APN and disease severity has previously been reported in patients with knee OA[118], and it has been shown that patients with high APN levels had a decreased risk for hand OA progression[118,119].

Antagonism of the leptin axis may provide a novel therapeutic pathway which has as yet been largely unexplored. In 2006[120], identified a monoclonal leptin receptor antagonist antibody, 9F8, which was shown to reduce leptin-induced TNFα production from human monocytes as well as activation and proliferation of T cells following CD3 stimulation[120]. However, there is a lack of published material exploring the potential benefits of 9F8 as a therapeutic, although many recent meeting reports do exist. However, the identification of 9F8 monoclonal antibody (mAb) and its interactions with the leptin receptor have helped to enable a greater understanding of the structural conformation of the leptin receptor thus opening up further possibilities for identifying novel leptin receptor inhibitors[121].

New therapeutic applications for old drugs, termed "drug reprofiling", are becoming increasingly more common. The therapeutic antibody, Infliximab, is an anti-TNFα therapy used predominantly in rheumatoid arthritis patients[122]. In 2007, it was discovered that infliximab is also able to attenuate resistin in inflammatory bowel disease (IBD) patients[123]. Although leptin and APN levels remained unchanged in their patient cohort, the reduction of resistin and subsequent amelioration of IBD symptoms, suggest that resistin could have a central role to play in pathological inflammation. Indeed, Guler-Yuksel *et al.* found circumstantial evidence in RA patients with secondary hand OA who were receiving infliximab treatment that the symptoms of their hand OA were reduced[124]. More work is required, however, to determine the mechanism by which this secondary OA in RA patients is being reduced by Infliximab.

APN is considered in many disease states to be a "good" adipokine, being negatively associated with metabolic syndrome and also anti-inflammatory action. For example, APN has been shown to downregulate TNFα and IL-1β and to upregulate IL-10 and IL-1RA[111–113]. Therefore, unlike leptin and resistin, blocking of APN may not be beneficial in combating inflammatory disease. Instead topical applications of recombinant APN may be beneficial in attenuating the inflammatory environment, since it was recently shown that topical applications of APN in dry eye disease in mice reduced the inflammatory component of the disease[125]. However, at present, no clinical trials are in progress to assess the potential benefits of APN therapy in OA disease.

Therapeutic targeting of leptin and/or APN in OA patients, particularly those patients who are overweight or obese, could have great potential in ameliorating disease progression and severity through modulating the inflammatory environment created by pathological adiposity. Preclinical work in this area has shown promising results as discussed above, but further investigation into the molecular signalling pathways mediated by adipokines in OA diseased joint tissue and how this differs across different patient cohorts is required. Indeed, Infliximab is now being used clinically to treat OA patients (and RA patients with secondary OA), but therapeutic modulation of adipokines or indeed therapeutic modulation of targets within adipokine-mediated signalling pathways are still some way away from being realised for the treatment of OA. However, it is envisaged that the development of such agents, could complement adjuvant weight-loss programs in OA patient cohorts who are overweight or obese.

Potential for the development of personalised pharmacological medicines in OA

Current OA patient stratification is limited and predominantly based on clinical factors such as the mechanism of disease onset (primary or secondary OA), the involved joint, the degree of inflammation, the rate of disease progression and the disease stage (early or late OA). This clinical stratification, combined with a limited choice of available therapeutics, does very little to assist the clinician in selecting the best treatment option. For the management of patients with knee or hip OA, the OARSI recommendations[126] include a combination of pharmacological and non-pharmacological treatments. For example, patients are encouraged to undertake muscle strengthening/range of motion exercises, whilst those who are overweight are encouraged to lose weight. NSAIDs (either alone or in combination with a gastroprotective agent for those with GI risk) are recommended for patients with symptomatic painful OA. For those patients with moderate-severe pain, intra-articular injections of corticosteroids are recommended, particularly for those who have not responded to NSAIDs or whose joints exhibit synovial inflammation.

In considering the development of a personalised DMOADs, it is critical to recognise that OA is a highly heterogeneous condition with potentially varying root causes across different patient groups[127], and that this heterogeneity should guide the selection of patients and their disease stage for a particular disease-modifying therapeutic (Table II). For example, the degree of synovitis observed in the joints of patients with OA is highly variable, suggesting that some, but not all patients would benefit from an anti-inflammatory therapeutic. Similarly, it is also recognised that some patients' OA is characterised as exhibiting a greater involvement of bone remodelling than others. Therefore patients who exhibit this "bony" OA phenotype may be more suitable to being treated with therapeutics that directly target bone remodelling. In addition, the metabolic

Table II
Biological effect area DMOADs aligned to disease stage

		Kellgren–Lawrence grade			
		KL1	KL2	KL3	KL4
Biological effect area	Cartilage			Cartilage repair therapeutics, combinations of anti-catabolics and pro-anabolics.	Cartilage repair therapeutics, combinations of anti-catabolics and pro-anabolics.
	Bone		Therapeutics targeting bone remodelling, particularly to individuals with "bony OA" pathology.	Therapeutics targeting bone remodelling, particular to individuals with "bony OA" pathology.	
	Inflammation	Anti-inflammatory therapeutics in "at-risk" populations with pathological inflammatory biomarkers and/or synovitis to slow/prevent cartilage destruction. Combinations with NSAIDs for those with painful OA	Anti-inflammatory therapeutics in "at-risk" populations with pathological inflammatory biomarkers and/or synovitis to slow/prevent cartilage destruction. Combinations with NSAIDs for those with painful OA		
	Muscle	Muscle anabolic therapeutics in combinations with exercise programs in "at-risk" individuals with weak muscles/biomarkers of muscle atrophy.	Muscle anabolic therapeutics in combinations with exercise programs in "at-risk" individuals with weak muscles/biomarkers of muscle atrophy.		
	Adipose	Targeting of adipokine-mediated pathways in combination with weight loss in "at-risk" individuals with pathological adipokine profiles and high BMI/WHR	Targeting of adipokine-mediated pathways in combination with weight loss in "at-risk" individuals with pathological adipokine profiles and high BMI/WHR		

risk of OA may depend on the particular patient cohort. Central adiposity (waist : hip ratio) has previously been shown to be more strongly associated with OA in women than in men[119], and we recently found that females but not males with knee OA had significantly higher BMI than controls and exhibited a higher proportion of generalised OA (nodal hand OA), indicative of a more systemic condition. By contrast, in the males there was no difference in BMI between OA and controls, and no difference in the incidence of generalised OA. However, there was a greater association of occupational risk in males with knee OA compared to males without knee OA. These data, suggest that there are different route causes of OA, each likely requiring a different therapeutic approach.

It is also likely to be necessary to stratify OA patients not solely on clinical measures but also biochemical, genetic and epigenetic profiles. By far the best example of this is the field of oncology which has seen the recent approval of several therapeutics with companion biomarker assays, which prospectively help to predict likely response or adverse effects[128]. This shift towards personalised medicine has been further exemplified by the release of the US Food and Drug Administration (FDA) "Table of Pharmacogenomic Biomarkers in Drug Labels" which serves as a repository of therapeutic agents that have associated pharmacogenomic requirements.

Stratification biomarkers are categorised by their molecule class and include genetic and expression biomarkers of nucleic acid origin, those derived from protein, and those representing changes in metabolite concentration[129]. Currently available genomic information in patients with OA has not enabled the stratification of patients into subsets. However, the recent advent of next generation sequencing technologies is now rapidly accelerating the field of nucleic acid based biomarker discovery significantly. Although several competing sequencing technologies are currently available which tend to vary only in their acquisition methods and depth of coverage, they all offer the ability to sequence large quantities of nucleic material rapidly and cost effectively. For example, such technologies are suitable for the global detection of structural (single nucleotide polymorphisms, translocations) and methylation changes in DNA, and the detection of expression changes in various RNA molecule classes (mRNA, microRNA, piRNA, lincRNA).

This in depth analysis of both genomic and transcriptomic data will provide new insights into OA patient molecular phenotype and identify new disease subsets which should be informative in identifying and developing personalised DMOAD therapeutics. Furthermore, a paradigm shift towards "personalised medicine", where OA patients are stratified based upon molecular biomarkers integrated with clinical pathological assessments, has the potential to also reduce candidate drug attrition during clinical development due to potentially efficacious drugs being masked when tested on heterogeneous population studies. This approach should therefore accelerate the development of new personalised DMOADs for specific OA populations.

Summary and conclusions

The recognition that OA is not simply a wear and tear disease of the cartilage but is a multi-faceted disease involving the whole joint offers new opportunities to identify and develop novel disease-modifying therapeutics and also to consider the re-profiling of candidate drugs from different therapeutic areas. However, this complexity also means it is likely that a single therapeutic agent targeting a single target within a single tissue type may not be sufficient to achieve effective disease modification. As in the oncology therapeutic area we will likely need to consider combinations of drugs targeting different hallmarks of OA biology. Furthermore, given the heterogeneity of OA it is hoped that the

recent emergence of improved next generation sequencing technologies will provide novel molecular phenotyping of OA patients, which when combined with MRI and pathological assessment will enable improved patient stratification, thus leading to the design and development of personalised OA therapeutics.

Author contributions

All authors were involved in drafting the article, and all authors approved the final version.

Competing interests

The authors declare no competing interests.

References

1. Peat G, Thomas E, Handy J, Wood L, Dziedzic K, Myers H, *et al*. The Knee Clinical Assessment Study—CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population. BMC Musculoskelet Disord 2004;5:4.
2. Hunter DJ. Pharmacologic therapy for osteoarthritis—the era of disease modification. Nat Rev Rheumatol 2010;7:13–22.
3. Coruzzi G, Venturi N, Spaggiari S. Gastrointestinal safety of novel nonsteroidal antiinflammatory drugs: selective COX-2 inhibitors and beyond. Acta Biomed 2007;78:96–110.
4. Reginster JY, Badurski J, Bellamy N, Bensen W, Chapurlat R, Chevalier X, *et al*. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis 2013;72:179–86.
5. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.
7. Armour AA, Watkins CL. The challenge of targeting EGFR: experience with gefitinib in nonsmall cell lung cancer. Eur Respir Rev 2010;19:186–96.
8. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
9. Mazurek SGN, Li J, Nabozny GH, Reinhart GA, Muthukumarana AC, Harrison PC, *et al*. Functional biomarkers of musculoskeletal syndrome (MSS) for early in vivo screening of selective MMP-13 inhibitors. J Pharmacol Toxicol Methods 2011;64:89–96.
10. Lorenz H, Richter W. Osteoarthritis: cellular and molecular changes in degenerating cartilage. Prog Histochem Cytochem 2006;40:135–63.
11. Tugwood JD, Kelsall J, Coverley LC, Westwood FR, Haque K, Huby RDJ. Fibrodysplasia induced in dog skin by a matrix metalloproteinase (MMP) Inhibitor—A mechanistic analysis. Toxicol Sci 2012;127:236–45.
12. Baragi VM, Becher G, Bendele AM, Biesinger R, Bluhm H, Boer J, *et al*. A new class of potent matrix metalloproteinase 13 inhibitors for potential treatment of osteoarthritis: evidence of histologic and clinical efficacy without musculoskeletal toxicity in rat models. Arthritis Rheum 2009;60:2008–18.
13. Amalinei C, Caruntu ID, Giusca SE, Balan RA. Matrix metalloproteinases involvement in pathologic conditions. Rom J Morphol Embryol 2010;51:215–28.
14. Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. J Cell Sci 2002;115:3719–27.
15. Zucker S, Cao J. Selective matrix metalloproteinase (MMP) inhibitors in cancer therapy: ready for prime time? Cancer Biol Ther 2009;8:2371–3.
16. Krzeski P, Buckland-Wright C, Balint G, Cline G, Stoner K, Lyon R, *et al*. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. Arthritis Res Ther 2007;9:R109.
17. Renkiewicz R, Qiu L, Lesch C, Sun X, Devalaraja R, Cody T, *et al*. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. Arthritis Rheum 2003;48:1742–9.
18. Westwood R, Scott RC, Somers RL, Coulson M, Maciewicz RA. Characterization of fibrodysplasia in the dog following inhibition of metalloproteinases. Toxicol Pathol 2009;37:860–72.
19. Settle S, Vickery L, Nemirovskiy O, Vidmar T, Bendele A, Messing D, *et al*. Cartilage degradation biomarkers predict efficacy of a novel, highly selective matrix metalloproteinase 13 inhibitor in a dog model of osteoarthritis: confirmation by multivariate analysis that modulation of type II collagen and aggrecan degradation peptides parallels pathologic changes. Arthritis Rheum 2010;62:3006–15.
20. Glasson SS, Askew R, Sheppard B, Carito B, Blanchet T, Ma H-L, *et al*. Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis. Nature 2005;434:644–8.
21. Stanton H, Rogerson FM, East CJ, Golub SB, Lawlor KE, Meeker CT, *et al*. ADAMTS5 is the major aggrecanase in mouse cartilage in vivo and in vitro. Nature 2005;434:648–52.
22. Ellman MB, An HS, Muddasani P, Im H-J. Biological impact of the fibroblast growth factor family on articular cartilage and intervertebral disc homeostasis. Gene 2008;420:82–9.
23. Ellsworth JL, Berry J, Bukowski T, Claus J, Feldhaus A, Holderman S, *et al*. Fibroblast growth factor-18 is a trophic factor for mature chondrocytes and their progenitors. Osteoarthritis Cartilage 2002;10:308–20.
24. Moore EE, Bendele AM, Thompson DL, Littau A, Waggie KS, Reardon B, *et al*. Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. Osteoarthritis Cartilage 2005;13:623–31.
25. Merrihew C, Kumar B, Heretis K, Rueger DC, Kuettner KE, Chubinskaya S. Alterations in endogenous osteogenic protein-1 with degeneration of human articular cartilage. J Orthop Res 2003;21:899–907.
26. Chubinskaya S, Kuettner KE. Regulation of osteogenic proteins by chondrocytes. Int J Biochem Cell Biol 2003;35:1323–40.
27. Hunter DJ, Pike MC, Jonas BL, Kissin E, Krop J, McAlindon T. Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. BMC Musculoskelet Disord 2010;11:232.
28. Badlani N, Oshima Y, Healey R, Coutts R, Amiel D. Use of bone morphogenic protein-7 as a treatment for osteoarthritis. Clin Orthop Relat Res 2009;467:3221–9.
29. Buckland-Wright C. Subchondral bone changes in hand and knee osteoarthritis detected by radiography. Osteoarthritis Cartilage 2004;12(Suppl A):S10–9.
30. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. Nat Rev Rheumatol 2012;8:665–73.
31. Radin EL. Subchondral bone changes and cartilage damage. Equine Vet J 1999;31:94–5.
32. Radin EL, Paul IL, Rose RM. Role of mechanical factors in pathogenesis of primary osteoarthritis. Lancet 1972;1:519–22.
33. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986:34–40.

34. Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis 2006;65:1261–4.
35. Anderson-MacKenzie JM, Quasnichka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. Int J Biochem Cell Biol 2005;37:224–36.
36. Quasnichka HL, Anderson-MacKenzie JM, Bailey AJ. Subchondral bone and ligament changes precede cartilage degradation in guinea pig osteoarthritis. Biorheology 2006;43:389–97.
37. Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong LT. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone 2006;38:234–43.
38. Neogi T. Clinical significance of bone changes in osteoarthritis. Ther Adv Musculoskelet Dis 2012;4:259–67.
39. Williams TG, Holmes AP, Waterton JC, Maciewicz RA, Hutchinson CE, Moots RJ, *et al*. Anatomically corresponded regional analysis of cartilage in asymptomatic and osteoarthritic knees by statistical shape modelling of the bone. IEEE Trans Med Imaging 2010;29:1541–59.
40. Davis AJ, Smith TO, Hing CB, Sofat N. Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review. PLoS ONE 2013;8:e72714.
41. Bingham CO, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, *et al*. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum 2006;54:3494–507.
42. Nielsen RH, Bay-Jensen AC, Byrjalsen I, Karsdal MA. Oral salmon calcitonin reduces cartilage and bone pathology in an osteoarthritis rat model with increased subchondral bone turnover. Osteoarthritis Cartilage 2011;19:466–73.
43. Takahashi N, Sasaki T, Tsouderos Y, Suda TS. 12911-2 inhibits osteoclastic bone resorption in vitro. J Bone Miner Res 2003;18:1082–7.
44. Canalis E, Hott M, Deloffre P, Tsouderos Y, Marie PJ. The divalent strontium salt S12911 enhances bone cell replication and bone formation in vitro. Bone 1996;18:517–23.
45. Pelletier JP, Kapoor M, Fahmi H, Lajeunesse D, Blesius A, Maillet J, *et al*. Strontium ranelate reduces the progression of experimental dog osteoarthritis by inhibiting the expression of key proteases in cartilage and of IL-1beta in the synovium. Ann Rheum Dis 2013;72:250–7.
46. Hayami T, Zhuo Y, Wesolowski GA, Pickarski M, Duong LT. Inhibition of cathepsin K reduces cartilage degeneration in the anterior cruciate ligament transection rabbit and murine models of osteoarthritis. Bone 2012;50:1250–9.
47. Hou WS, Li W, Keyszer G, Weber E, Levy R, Klein MJ, *et al*. Comparison of cathepsins K and S expression within the rheumatoid and osteoarthritic synovium. Arthritis Rheum 2002;46:663–74.
48. Pennypacker B, Shea M, Liu Q, Masarachia P, Saftig P, Rodan S, *et al*. Bone density, strength, and formation in adult cathepsin K (-/-) mice. Bone 2009;44:199–207.
49. Leung P, Pickarski M, Zhuo Y, Masarachia PJ, Duong LT. The effects of the cathepsin K inhibitor odanacatib on osteoclastic bone resorption and vesicular trafficking. Bone 2011;49:623–35.
50. Stoch SA, Zajic S, Stone J, Miller DL, Van Dyck K, Gutierrez MJ, *et al*. Effect of the cathepsin K inhibitor odanacatib on bone resorption biomarkers in healthy postmenopausal women: two double-blind, randomized, placebo-controlled phase I studies. Clin Pharmacol Ther 2009;86:175–82.
51. Duong LT. Therapeutic inhibition of cathepsin K[mdash] reducing bone resorption while maintaining bone formation. BoneKEy Rep 2012:1.
52. McDougall JJ, Schuelert N, Bowyer J. Cathepsin K inhibition reduces CTXII levels and joint pain in the guinea pig model of spontaneous osteoarthritis. Osteoarthritis Cartilage 2010;18:1355–7.
53. Connor JR, LePage C, Swift BA, Yamashita D, Bendele AM, Maul D, *et al*. Protective effects of a cathepsin K inhibitor, SB-553484, in the canine partial medial meniscectomy model of osteoarthritis. Osteoarthritis Cartilage 2009;17:1236–43.
54. Marks R. Comorbid depression and anxiety impact hip osteoarthritis disability. Disabil Health J 2009;2:27–35.
55. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? Ann Rheum Dis 2005;64:1539–41.
56. Weinberger M, Tierney WM, Booher P. Common problems experienced by adults with osteoarthritis. Arthritis Care Res 1989;2:94–100.
57. Arnoldi CC, Lemperg R, Linderholm H. Immediate effect of osteotomy on the intramedullary pressure in the femoral head and neck in patients with degenerative osteoarthritis. Acta Orthop Scand 1971;42:454–5.
58. Arnoldi CC, Linderholm H, Mussbichler H. Venous engorgement and intraosseous hypertension in osteoarthritis of the hip. J Bone Joint Surg Br 1972;54:409–21.
59. Pedersen NW, Kiaer T, Kristensen KD, Starklint H. Intraosseous pressure, oxygenation, and histology in arthrosis and osteonecrosis of the hip. Acta Orthop Scand 1989;60:415–7.
60. Hunter DJ, Gerstenfeld L, Bishop G, Davis AD, Mason ZD, Einhorn TA, *et al*. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. Arthritis Res Ther 2009;11:R11.
61. Kim HA, Cho ML, Choi HY, Yoon CS, Jhun JY, Oh HJ, *et al*. The catabolic pathway mediated by Toll-like receptors in human osteoarthritic chondrocytes. Arthritis Rheum 2006;54:2152–63.
62. Jones SW, Brockbank SM, Clements KM, Le GN, Campbell D, Read SJ, *et al*. Mitogen-activated protein kinase-activated protein kinase 2 (MK2) modulates key biological pathways associated with OA disease pathology. Osteoarthritis Cartilage 2009;17:124–31.
63. Cohen SB, Proudman S, Kivitz AJ, Burch FX, Donohue JP, Burstein D, *et al*. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther 2011;13:R125.
64. Kulkarni SK, Singh VP. Licofelone–a novel analgesic and anti-inflammatory agent. Curr Top Med Chem 2007;7:251–63.
65. Pelletier JP, Boileau C, Brunet J, Boily M, Lajeunesse D, Reboul P, *et al*. The inhibition of subchondral bone resorption in the early phase of experimental dog osteoarthritis by licofelone is associated with a reduction in the synthesis of MMP-13 and cathepsin K. Bone 2004;34:527–38.
66. Raynauld JP, Martel-Pelletier J, Bias P, Laufer S, Haraoui B, Choquette D, *et al*. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. Ann Rheum Dis 2009;68:938–47.
67. Bentz M, Zaouter C, Shi Q, Fahmi H, Moldovan F, Fernandes JC, *et al*. Inhibition of inducible nitric oxide synthase prevents lipid peroxidation in osteoarthritic chondrocytes. J Cell Biochem 2012;113:2256–67.

68. Palmer RM, Hickery MS, Charles IG, Moncada S, Bayliss MT. Induction of nitric oxide synthase in human chondrocytes. Biochem Biophys Res Commun 1993;193:398–405.
69. Hashimoto S, Takahashi K, Amiel D, Coutts RD, Lotz M. Chondrocyte apoptosis and nitric oxide production during experimentally induced osteoarthritis. Arthritis Rheum 1998;41:1266–74.
70. Scher J, Pillinger M, Abramson S. Nitric oxide synthases and osteoarthritis. Curr Rheumatol Rep 2007;9:9–15.
71. Jarvinen K, Vuolteenaho K, Nieminen R, Moilanen T, Knowles RG, Moilanen E. Selective iNOS inhibitor 1400W enhances anti-catabolic IL-10 and reduces destructive MMP-10 in OA cartilage. Survey of the effects of 1400W on inflammatory mediators produced by OA cartilage as detected by protein antibody array. Clin Exp Rheumatol 2008;26:275–82.
72. More AS, Kumari RR, Gupta G, Lingaraju MC, Balaganur V, Pathak NN, *et al*. Effect of iNOS inhibitor S-methylisothiourea in monosodium iodoacetate-induced osteoathritic pain: implication for osteoarthritis therapy. Pharmacol Biochem Behav 2013;103:764–72.
73. Pelletier JP, Jovanovic D, Fernandes JC, Manning P, Connor JR, Currie MG, *et al*. Reduced progression of experimental osteoarthritis in vivo by selective inhibition of inducible nitric oxide synthase. Arthritis Rheum 1998;41:1275–86.
74. Pelletier JP, Jovanovic D, Fernandes JC, Manning P, Connor JR, Currie MG, *et al*. Reduction in the structural changes of experimental osteoarthritis by a nitric oxide inhibitor. Osteoarthritis Cartilage 1999;7:416–8.
75. Hellio le Graverand MP, Clemmer RS, Redifer P, Brunell RM, Hayes CW, Brandt KD, *et al*. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. Ann Rheum Dis 2013;72:187–95.
76. Hui W, Litherland GJ, Jefferson M, Barter MJ, Elias MS, Cawston TE, *et al*. Lithium protects cartilage from cytokine-mediated degradation by reducing collagen-degrading MMP production via inhibition of the P38 mitogen-activated protein kinase pathway. Rheumatology 2010;49(11):2043–53.
77. Brown K, Heitmeyer S, Hookfin E, Hsieh L, Buchalova M, Taiwo Y, *et al*. P38 MAP kinase inhibitors as potential therapeutics for the treatment of joint degeneration and pain associated with osteoarthritis. J Inflamm 2008;5:1–8.
78. Slemenda C, Heilman D, Brandt K, Katz B, Mazzuca S, Braunstein E, *et al*. Reduced quadriceps strength relative to body weight – a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998;41:1951–9.
79. Hall MC, Mockett SP, Doherty M. Relative impact of radiographic osteoarthritis and pain on quadriceps strength, proprioception, static postural sway and lower limb function. Ann Rheum Dis 2006;65:865–70.
80. Omori G, Koga Y, Tanaka M, Nawata A, Watanabe H, Narumi K, *et al*. Quadriceps muscle strength and its relationship to radiographic knee osteoarthritis in Japanese elderly. J Orthop Sci 2013;18:536–42.
81. Hurley M. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999;25:283.
82. Ikeda S, Tsumura H, Torisu T. Age-related quadriceps-dominant muscle atrophy and incident radiographic knee osteoarthritis. J Orthop Sci 2005;10:121–6.
83. Fink B, Egl M, Singer J, Fuerst M, Bubenheim M, Neuen-Jacob E. Morphologic changes. in the vastus medialis muscle in patients with osteoarthritis of the knee. Arthritis Rheum 2007;56:3626–33.
84. Sirca A, Susec-Michieli M. Selective type II fibre muscular atrophy in patients with osteoarthritis of the hip. J Neurol Sci 1980;44:149–59.
85. Thorstensson C, Petersson I, Jacobsson L, Boegard T, Roos E. Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. Ann Rheum Dis 2004;63:402–7.
86. Segal NA, Torner JC, Felson D, Niu J, Sharma L, Lewis CE, *et al*. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. Arthritis Care Res 2009;61:1210–7.
87. Baker K, McAlindon T. Exercise for knee osteoarthritis. Curr Opin Rheumatol 2000;12:456–63.
88. Eyigor S. A comparison of muscle training methods in patients with knee osteoarthritis. Clin Rheumatol 2004;23:109–15.
89. Keefe F, Blumenthal J, Baucom D, Affleck G, Waugh R, Caldwell D, *et al*. Effects of spouse-assisted coping skills training and exercise training in patients with osteoarthritic knee pain: a randomized controlled study. Pain 2004;110:539–49.
90. Jan M, Lin J, Liau J, Lin Y, Lin D. Investigation of clinical effects of high- and low-resistance training for patients with knee osteoarthritis: a randomized control-led trial. Phys Ther 2008;88:427–36.
91. Rosemffet M, Schneeberger E, Citera G, Sgobba M, Laiz C, Schmulevich H, *et al*. Effects of functional electrostimulation on pain, muscular strength, and functional capacity in patients with osteoarthritis of the knee. JCR-J Clin Rheumatol 2004;10:246–9.
92. Wang Y, Wluka AE, Berry PA, Siew T, Teichtahl AJ, Urquhart DM, *et al*. Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis. Arthritis Rheum 2012;64:3917–25.
93. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, *et al*. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263–73.
94. Sinha-Hikim I, Cornford M, Gaytan H, Lee ML, Bhasin S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrinol Metab 2006;91:3024–33.
95. Zhang J, He Q, Liu Q, Guo W, Deng X, Zhang W, *et al*. Differential gene expression profile in pig adipose tissue treated with/without clenbuterol. BMC Genomics 2007;8:433.
96. Zeman RJ, Ludemann R, Easton TG, Etlinger JD. Slow to fast alterations in skeletal muscle fibers caused by clenbuterol, a beta 2-receptor agonist. Am J Physiol 1988;254:E726–32.
97. Larsson L, Li X, Teresi A, Salviati G. Effects of thyroid hormone on fast- and slow-twitch skeletal muscles in young and old rats. J Physiol 1994;481(Pt 1):149–61.
98. Tonge DP, Jones SW, Parr T, Bardsley R, Doherty M, Maciewicz RA. β2-Adrenergic agonist-induced hypertrophy of the quadriceps skeletal muscle does not modulate disease severity in the rodent meniscectomy model of osteoarthritis. Osteoarthritis Cartilage 2009;18:555–62.
99. Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, *et al*. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. Arthritis Res Ther 2009;11:R31.
100. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. J Rheumatol 1996;23:1221–6.

101. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10:161–6.
102. Yang WS, Chuang LM. Human genetics of adiponectin in the metabolic syndrome. J Mol Med (Berl) 2006;84:112–21.
103. Lu JY, Huang KC, Chang LC, Huang YS, Chi YC, Su TC, *et al*. Adiponectin: a biomarker of obesity-induced insulin resistance in adipose tissue and beyond. J Biomed Sci 2008;15:565–76.
104. Dyck DJ, Heigenhauser GJ, Bruce CR. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. Acta Physiol (Oxf) 2006;186:5–16.
105. Hamerman D. Osteoporosis and atherosclerosis: biological linkages and the emergence of dual-purpose therapies. QJM 2005;98:467–84.
106. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, *et al*. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;48:3118–29.
107. Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S, *et al*. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis Cartilage 2006;14:690–5.
108. de Boer TN, Van Spil WE, Huisman AM, Polak AA, Bijlsma JW, Lafeber FP, *et al*. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage 2012;20:846–53.
109. Otero M, Lago R, Gomez R, Lago F, Gomez-Reino JJ, Gualillo O. Leptin: a metabolic hormone that functions like a proinflammatory adipokine. Drug News Perspect 2006;19:21–6.
110. Mutabaruka MS, Aoulad AM, Delalandre A, Lavigne M, Lajeunesse D. Local leptin production in osteoarthritis subchondral osteoblasts may be responsible for their abnormal phenotypic expression. Arthritis Res Ther 2010;12:R20.
111. Chen TH, Chen L, Hsieh MS, Chang CP, Chou DT, Tsai SH. Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta 2006;1762:711–8.
112. Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, *et al*. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008;16:1101–9.
113. Tong KM, Chen CP, Huang KC, Shieh DC, Cheng HC, Tzeng CY, *et al*. Adiponectin increases MMP-3 expression in human chondrocytes through AdipoR1 signaling pathway. J Cell Biochem 2011;112:1431–40.
114. Pasco JA, Henry MJ, Kotowicz MA, Collier GR, Ball MJ, Ugoni AM, *et al*. Serum leptin levels are associated with bone mass in nonobese women. J Clin Endocrinol Metab 2001;86:1884–7.
115. Thomas T, Burguera B, Melton III LJ, Atkinson EJ, O'Fallon WM, Riggs BL, *et al*. Role of serum leptin, insulin, and estrogen levels as potential mediators of the relationship between fat mass and bone mineral density in men versus women. Bone 2001;29:114–20.
116. Yamauchi M, Sugimoto T, Yamaguchi T, Nakaoka D, Kanzawa M, Yano S, *et al*. Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. Clin Endocrinol (Oxf) 2001;55:341–7.
117. Berry PA, Jones SW, Cicuttini FM, Wluka AE, Maciewicz RA. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. Arthritis Rheum 2011;63:700–7.
118. Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res 2010;41:593–8.
119. Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. Osteoarthritis Cartilage 2011;19:37–43.
120. Fazeli M, Zarkesh-Esfahani H, Wu Z, Maamra M, Bidlingmaier M, Pockley AG, *et al*. Identification of a monoclonal antibody against the leptin receptor that acts as an antagonist and blocks human monocyte and T cell activation. J Immunol Methods 2006;312:190–200.
121. Matarese G, De Rosa V. Ob-stopping obesity, metabolic and immune-mediated disorders. Structure 2012;20:385–7.
122. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med 2000;343:1594–602.
123. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Kouroumalis EA. The effect of infliximab on circulating levels of leptin, adiponectin and resistin in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2007;19:789–94.
124. Guler-Yuksel M, Allaart CF, Watt I, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Schaardenburg D, *et al*. Treatment with TNF-alpha inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. Osteoarthritis Cartilage 2010;18:1256–62.
125. Li Z, Woo JM, Chung SW, Kwon MY, Choi JS, Oh HJ, *et al*. Therapeutic effect of topical adiponectin in a mouse model of desiccating stress-induced dry eye. Invest Ophthalmol Vis Sci 2013;54:155–62.
126. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137–62.
127. Driban JB, Sitler MR, Barbe MF, Balasubramanian E. Is osteoarthritis a heterogeneous disease that can be stratified into subsets? Clin Rheumatol 2010;29:123–31.
128. Duffy MJ, Crown J. Companion biomarkers: paving the pathway to personalized treatment for cancer. Clin Chem 2013;59:1447–56.
129. Deyati A, Younesi E, Hofmann-Apitius M, Novac N. Challenges and opportunities for oncology biomarker discovery. Drug Discov Today 2013;18:614–24.
130. Song RH, Tortorella MD, Malfait AM, Alston JT, Yang Z, Arner EC, *et al*. Aggrecan degradation in human articular cartilage explants is mediated by both ADAMTS-4 and ADAMTS-5. Arthritis Rheum 2007;56:575–85.
131. De Savi C, Pape A, Sawyer Y, Milne D, Davies C, Cumming JG, *et al*. Orally active achiral N-hydroxyformamide inhibitors of ADAM-TS4 (aggrecanase-1) and ADAM-TS5 (aggrecanase-2) for the treatment of osteoarthritis. Bioorg Med Chem Lett 2011;21:3301–6.
132. Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, *et al*. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. J Bone Miner Res 1995;10:1478–87.
133. Moreau M, Rialland P, Pelletier J-P, Martel-Pelletier J, Lajeunesse D, Boileau C, *et al*. Tiludronate treatment improves structural changes and symptoms of osteoarthritis in the canine anterior cruciate ligament model. Arthritis Res Ther 2011;13:R98.

134. Lucht U. Effects of calcitonin on osteoclasts in vivo. An ultrastructural and histochemical study. Z Zellforsch Mikrosk Anat 1973;145:75–87.
135. Mastbergen SC, Lafeber FP, Bijlsma JW. Selective COX-2 inhibition prevents proinflammatory cytokine-induced cartilage damage. Rheumatology (Oxford) 2002;41:801–8.
136. Ou Y, Tan C, An H, Jiang D, Quan Z, Tang K, *et al*. Selective COX-2 inhibitor ameliorates osteoarthritis by repressing apoptosis of chondrocyte. Med Sci Monit 2012;18:BR247–252.
137. Vuolteenaho K, Moilanen T, Hamalainen M, Moilanen E. Effects of TNFalpha-antagonists on nitric oxide production in human cartilage. Osteoarthritis Cartilage 2002;10:327–32.
138. Joosten LA, Helsen MM, van de Loo FA, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice: a comparative study using anti-TNFalpha, anti-IL-1alpha/beta and IL-1Ra. Arthritis Rheum 2008;58:S110–22.
139. Zhang Q, Lv H, Chen A, Liu F, Wu X. Efficacy of infliximab in a rabbit model of osteoarthritis. Connect Tissue Res 2012;53:355–8.
140. Santangelo KS, Nuovo GJ, Bertone AL. In vivo reduction or blockade of interleukin-1beta in primary osteoarthritis influences expression of mediators implicated in pathogenesis. Osteoarthritis Cartilage 2012;20:1610–8.
141. Rudolphi K, Gerwin N, Verzijl N, van der Kraan P, van den Berg W. Pralnacasan, an inhibitor of interleukin-1beta converting enzyme, reduces joint damage in two murine models of osteoarthritis. Osteoarthritis Cartilage 2003;11:738–46.
142. Smith RJ, Chin JE, Sam LM, Justen JM. Biologic effects of an interleukin-1 receptor antagonist protein on interleukin-1–stimulated cartilage erosion and chondrocyte responsiveness. Arthritis Rheum 1991;34:78–83.
143. Pelletier JP, Caron JP, Evans C, Robbins PD, Georgescu HI, Jovanovic D, *et al*. In vivo suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. Arthritis Rheum 1997;40:1012–9.
144. Pelletier JP, Fernandes JC, Jovanovic DV, Reboul P, Martel-Pelletier J. Chondrocyte death in experimental osteoarthritis is mediated by MEK 1/2 and p38 pathways: role of cyclooxygenase-2 and inducible nitric oxide synthase. J Rheumatol 2001;28:2509–19.