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Of mice and men: converging on a common molecular understanding of osteoarthritis

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Despite an increasing burden of osteoarthritis in developed societies, target discovery has been slow and there are currently no approved disease-modifying osteoarthritis drugs. This lack of progress is due in part to a series of misconceptions over the years: that osteoarthritis is an inevitable consequence of ageing, that damaged articular cartilage cannot heal itself, and that osteoarthritis is driven by synovial inflammation similar to that seen in rheumatoid arthritis. Molecular interrogation of disease through ex-vivo tissue analysis, in-vitro studies, and preclinical models have radically reshaped the knowledge landscape. Inflammation in osteoarthritis appears to be distinct from that seen in rheumatoid arthritis. Recent randomised controlled trials, using treatments repurposed from rheumatoid arthritis, have largely been unsuccessful. Genome-wide studies point to defects in repair pathways, which accords well with recent promise using growth factor therapies or Wnt pathway antagonism. Nerve growth factor has emerged as a robust target in osteoarthritis pain in phase 2–3 trials. These studies, both positive and negative, align well with those in preclinical surgical models of osteoarthritis, indicating that pathogenic mechanisms identified in mice can lead researchers to valid human targets. Several novel candidate pathways are emerging from preclinical studies that offer hope of future translational impact. Enhancing trust between industry, basic, and clinical scientists will optimise our collective chance of success.

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Introduction

The global impact of osteoarthritis, the most common form of joint disease in developed societies, is predicted to rise steadily as obesity and longevity increase.¹ Osteoarthritis is a substantial societal burden, associated with increased mortality and frequently complicated by multimorbidity and polypharmacy.^{2–4} The recent acceptance of osteoarthritis as a serious disease has helped to drive the therapeutic agenda forward, to garner support from academia and industry, and to influence health-care prioritisation.⁵ The market for symptomatic and disease-modifying treatments is huge, and yet relatively little progress has been made thus far in bringing new treatments to patients.

Osteoarthritis research can be broadly divided into clinical and basic categories. Clinical research includes pathology, epidemiology, and interventional studies in humans, whereas basic research encompasses the study of molecular pathogenesis through in-vitro systems, preclinical models, and large-scale omics (ie, genomics, transcriptomics, proteomics, and metabolomics) studies. Osteoarthritis is a mechanically driven disease. This notion is compellingly described in the epidemiological literature⁶ and confirmed in basic science studies, which have shown the highly mechanosensitive nature of joint tissues,^{7–12} the activation of inflammatory signalling by mechanical injury,^{12,13} the dependence on mechanics in preclinical osteoarthritis,^{14,15} and the involvement of mechanosensing mechanisms in in-vivo pathogenesis.^{16,17} Several other important causal factors—such as obesity, age, and genetics—affect the ability of joint tissues to withstand mechanical stress over a lifetime and affect the ability to repair damaged tissues. These factors might also increase the risk of osteoarthritis in ways that are independent of mechanics. For example, osteoarthritis in non-weightbearing joints is increased in obese individuals,¹⁸

possibly due to low-grade systemic inflammation,^{19,20} which might be linked to the gut microbiome.²¹

Various impediments are recognised in osteoarthritis drug development. Osteoarthritis is an insidious and heterogeneous disease. These qualities inevitably mean that clinical trials are often prohibitively expensive, and raise the possibility that one target might not work for all. Molecular pathogenesis also has its challenges. Molecular tools have needed to be refined to work in paucicellular, matrix-rich tissues, such as articular cartilage. Low access to human tissue at early stages of disease has necessitated a reliance on preclinical models, which has also required substantial refinement, largely involving moving away from disease models involving chemical induction methods (eg, monosodium iodoacetate, papain, and collagenase injection) in favour of those induced by surgical destabilisation of the joint.²² In the past 15 years, target discovery in osteoarthritis has increased substantially, particularly through large, agnostic omic studies using end-stage human disease tissue and through molecular validation facilitated by preclinical mouse models and clinical trials. There has also been considerable research into methodological tools for improving clinical outcome measures and osteoarthritis trial design.²³ In this Review, recent successes and failures in osteoarthritis clinical trials are considered in parallel with preclinical advances. Together, these different types of research are helping to unravel the complexities of osteoarthritis pathogenesis and to provide future targeting strategies with a higher chance of translational success.

Targeting inflammation in osteoarthritis

Support for the involvement of inflammation in osteoarthritis comes from clinical observation (joint line tenderness, synovial thickening, and episodic joint effusion) and radiographic evidence of synovial hypertrophy and bone

marrow oedema (by MRI and ultrasound) that are associated with clinical outcome.^{24–26} Additionally, various inflammatory molecules—including cytokines, chemokines, and metalloproteinases—have been measured in osteoarthritis cartilage and synovium.^{27,28}

Clinicians distinguish between inflammatory arthritis and osteoarthritis through a relative paucity of leucocytes in osteoarthritis synovial fluid, which are predominantly monocytes (in osteoarthritis) rather than neutrophils (in rheumatoid arthritis). Patients with osteoarthritis typically complain of less than 30 min early morning stiffness and show a modest systemic inflammatory response.²⁹ These features are used clinically to aid the diagnosis of osteoarthritis. Whether low-grade inflammation contributes to osteoarthritis pathogenesis, both in terms of pain and structural disease, has been subject to heated debate over the years. Several randomised controlled trials that address different aspects of inflammation have been recently conducted. All the tested drugs derive from experience in rheumatoid arthritis where there is proven efficacy for such therapies.

Corticosteroids

Intra-articular corticosteroids are widely used in clinical practice in osteoarthritis, although few historical studies have applied stringent placebo-controlled, randomised, and double-blind assessments. In hand osteoarthritis, a randomised controlled trial³⁰ of intra-articular triamcinolone hexacetomide (a long-acting steroid preparation) plus lidocaine (a local anaesthetic) showed clinical improvement up to 12 weeks following injection of the drug compared with lidocaine alone. This result met the primary outcome of the study, albeit in only two of eight co-primary endpoints.³⁰ For both groups, the injected joint was splinted for 48 h immediately after treatment. A phase 2b trial³¹ of an extended-release intra-articular steroid showed greater efficacy than placebo in pain outcomes for knee osteoarthritis at several time points, even though the primary endpoint (pain at 12 weeks) was not met. Combined phase 2–3 studies of this preparation have showed an acceptable safety profile and a reduction in use of rescue pain medication (paracetamol or acetaminophen).³² In 2017, this preparation received approval by the US Food and Drug Administration (FDA) for clinical use under the trade name Zilretta.

Oral prednisolone has also been tested in hand osteoarthritis. The first study by Wenham and colleagues,³³ in which 70 patients were randomly assigned to receive 5 mg of prednisolone or placebo daily, found no statistically significant improvement in pain at 4 or 12 weeks. However, a 2019 study,³⁴ in which patients were randomly assigned to receive 10 mg of prednisolone or placebo daily for 6 weeks, showed significant improvement in patient-reported pain and function at the primary endpoint of 6 weeks. Symptoms returned rapidly after withdrawal of the drug. The study found a reduction in synovial thickness, but no improvement in synovitis by MRI or

power doppler assessment, making the primary target tissue of the drug unclear.³⁴

Few studies have attempted to examine the long-term effects of corticosteroids on joints. In a randomised controlled trial by McAlindon and colleagues,³⁵ 140 patients with knee osteoarthritis were randomly assigned to receive intra-articular injections of triamcinolone or saline once every 3 months for 2 years. Clinical outcomes were assessed every 3 months, and cartilage damage was measured by MRI at 2 years. No clinical benefit was seen for any of the outcome measures compared with placebo, although it is possible that the periodicity of follow-up caused transient responses to be missed (ie, if responses returned to baseline by 3 months). Importantly, this study showed a small but statistically significant increase in cartilage volume loss, raising concerns about the effect of repeated and long-term corticosteroid use on joint health.³⁵ Similar findings were also shown using data derived from the Osteoarthritis Initiative.³⁶ A cautious approach to intra-articular steroid is indicated by a “conditional type 1B recommendation” for this treatment in the 2019 guidelines from the Osteoarthritis Research Society International for non-surgical treatment of hip and knee osteoarthritis.³⁷

Disease-modifying anti-rheumatic drugs

Both hydroxychloroquine and methotrexate are used in patients with rheumatoid arthritis and, less commonly, on an individual-patient basis in osteoarthritis. Two randomised controlled trials using oral hydroxychloroquine in hand osteoarthritis have been published, neither of which met the primary study endpoint of reduction in pain.^{38,39} Additionally, no clinical response was seen in a predefined substudy in which patients were stratified by the presence or absence of power doppler signal, which is indicative of a more inflammatory phenotype.³⁸ The PROMOTE study⁴⁰ has reported by abstract⁴¹ a small difference in pain in those with knee osteoarthritis taking methotrexate, although the effect size was not deemed clinically meaningful. A small randomised controlled trial⁴² of 64 patients with hand osteoarthritis taking 10 mg of methotrexate failed to show a beneficial effect on pain, the primary outcome, although some changes to the evolution of joint remodelling were suggested in the reported abstract. A meta-analysis⁴³ has concluded no efficacy of conventional synthetic disease-modifying anti-rheumatic drugs across all joint osteoarthritis.

Anticytokine therapies

An absence of efficacy was also evident in four randomised controlled trials in hand osteoarthritis that targeted either tumour necrosis factor or interleukin (IL)-1^{44–47} and two trials in knee osteoarthritis targeting IL-1.^{48,49} one of which used an intra-articular approach. Despite promise from various small open-label studies, none of the randomised controlled trials met their primary study endpoints, suggesting that classical cytokine-driven inflammation is

Target tested	Study details	Cartilage modifying?	Symptom modifying?	
Complement				
Wang et al ⁶²	C5 and Cd59a	Knockout data confirmed by pharmacological approach	Yes	Not examined
Chemokines				
Miotla Zarebska et al, ⁶³ Miller et al, ⁶⁴ Raghu et al, ⁶⁵ Longobardi, ⁶⁶ and Appleton et al ⁶⁷	<i>Ccl2</i> or <i>Ccr2</i>	Constitutive gene deletion inconsistent across different studies but appearing to show structure modification at later time points; pharmacological studies point towards a key treatment window	Inconsistent	Yes
Takebe et al, ⁶⁸ and Raghu et al ⁶⁵	<i>Ccr5</i> or <i>Ccl5</i>	Inconsistent cartilage degradation scores; neither study showed a difference in synovitis scores after gene deletion	Inconsistent	Not examined
Sambamurthy et al ⁶⁹	<i>Ccr7</i>	Modest structural role, knockout mice have reduced pain behaviour	Yes	Yes
Sherwood et al ⁷⁰	<i>Cxcr2</i>	Structural increase at 8 weeks in knockout mice (ie, protective)	Yes	Not examined
Qin et al ⁷¹	<i>Cxcr4</i>	Inhibition in bone abrogates surgically induced osteoarthritis	Yes	Not examined
Mechanoflammation				
Choi et al ⁷²	<i>IkB-zeta</i> subunit of <i>Nf-κB</i>	Over-expression worsens disease; conditional detection leads to decreased disease (both on <i>Col2</i> promoter)	Yes	Not examined
Kobayashi et al ⁷³	<i>RelA</i> (p65) <i>Nf-κB</i> transcription factor	Dual action of <i>RelA</i> in disease: heterozygotes protected; homozygotes showed increased disease through prevention of anti-apoptotic mechanisms induced by <i>Pik3r1</i> (a Gwas hit for cartilage thickness)	Yes	Not examined
Culley et al ⁷⁴	<i>Ikka</i>	Conditional knockout (aggrecan Cre) disease protection associated with increased apoptosis	Yes	Not examined
Ismail et al ⁷⁵	<i>Jnk2</i>	Chondroprotection observed at 4 weeks, 8 weeks, and 12 weeks after surgery	Yes	Not examined
Mast-cell activation				
Wang et al ⁷⁶	<i>c-Kit</i> and <i>Mcl1</i>	Deletion produces functional deletion of <i>c-Kit</i> -dependent and <i>c-Kit</i> -independent mast cells; chondroprotection also observed with <i>Apc366</i> , a tryptase inhibitor	Yes	Not examined
Wang et al ⁷⁶	<i>Igh7</i> and <i>Fcer1</i>	Both genes target IgE-mediated activation of mast cells, indicating that IgE-induced mast-cell activation drives osteoarthritis pathology	Yes	Not examined

Table 1: Putative innate immune targets showing disease modification in preclinical studies

at the root of neither pain nor structural damage in osteoarthritis. These results are in accordance with preclinical data in which gene deletion of IL-1 β ,⁵⁰ the IL-1-converting enzyme, IL-1R (Vincent, unpublished data), tumour necrosis factor,⁵¹ or inflammasome pathway components (which lead to processing of IL-1-family cytokines)⁵² does not confer protection from osteoarthritis after surgical joint destabilisation. Despite a strong rationale based on in-vitro studies, evidence to support a direct pathogenic role for IL-1 in osteoarthritis pathogenesis appears, in retrospect, to have been weak.⁵³

Other putative inflammatory targets from preclinical models

These studies force us to conclude that classical inflammation, of the type that is pathogenic in rheumatoid arthritis, does not drive osteoarthritis. One exception to this notion might be IL-6. Although the osteoarthritis phenotype has been inconsistently reported in IL-6 knockout mice,^{54,55} therapeutic studies suggest that neutralisation of IL-6 modifies disease in murine osteoarthritis.⁵⁶ A clinical trial using tocilizumab, an IL-6-receptor-neutralising antibody, in hand osteoarthritis completed in 2019 but has not yet been reported (registered with ClinicalTrials.gov, NCT02477059).

Targeting the proteases that degrade the articular cartilage extracellular matrix has long been regarded as an

attractive approach to disease modification in osteoarthritis. A disintegrin and metalloproteinase with thrombospondin motif (Adamts)-5 was identified as the principal aggrecan-degrading enzyme in mice,⁵⁷ and in humans ADAMTS-5 also mediates proteolytic activity in osteoarthritis chondrocytes⁵⁸ (possibly also involving ADAMTS-4).⁵⁹ Aggrecanase inhibition is being re-explored, after companies had abandoned earlier studies at the preclinical phase because of adverse cardiovascular events, using an anti-Adamts-5 monoclonal antibody.⁶⁰ A good safety profile and evidence of target engagement with a small molecule inhibitor⁶¹ is now being followed by phase 2 studies in knee osteoarthritis, with structural disease as the primary outcome (registered with ClinicalTrials.gov, NCT03595618).

Activation of other components of the innate immune system might have more important pathogenic roles in disease, and some of these components have been examined in preclinical osteoarthritis (table 1). Several chemokine family members have been explored after joint destabilisation, with some having disease-modifying effects in murine osteoarthritis (table 1). These proteins are expressed by chondrocytes and have chondroprotective and disease-causing roles, not always correlating with cell infiltration of the joint. They therefore probably act in both canonical and non-canonical ways.⁶⁸⁻⁷⁰ C-C motif chemokine 2 (*Ccl2*) and its receptor, C-C chemokine receptor type 2 (*Ccr2*), are the best validated of these targets.

Constitutive deletion of *Ccl2* or *Ccr2* delays and suppresses pain severity in preclinical osteoarthritis but has little effect on cartilage damage when induced in animals that are 10 weeks old.^{63,64} However, a reduction in structural disease has been seen when older (aged 20 weeks) *Ccr2* knockout mice are subjected to joint destabilisation,⁶⁵ and when pharmacological *Ccr2* inhibition is delivered.⁶⁷ In another study,⁶⁶ structure modification was observed when a *Ccr2* antagonist was given either between 1–4 or 4–8 weeks after joint destabilisation, but not when given between 8–12 or 1–8 weeks after. A reduction in pain behaviour was observed over short (3 week) and long (12 week) periods of treatment at all stages of disease. Blocking transforming growth factor α (*Tgfa*) signalling, a strong inducer of *Ccl2* in the rodent osteoarthritis joint, also reduced structural disease after joint destabilisation in the rat.⁶⁷ *TGFA* is of particular interest because it has been identified as a candidate gene for determining cartilage thickness and osteoarthritis risk in humans.^{77,78} These results point towards a role for *Ccl2* and *Ccr2* in murine osteoarthritis pain and a possible role in structural progression.

Two mRNA studies of human synovium have been done in individuals stratified by having painful or non-painful osteoarthritis.^{27,79} One of these studies²⁷ identified *CCL2* as being significantly up-regulated in painful disease. *CCR2* antagonism in osteoarthritis pain has been explored clinically (registered with ClinicalTrials.gov, NCT00689273), although the results of the study do not appear to have been reported. A clinical study examining *TGFA* blockade is currently recruiting (registered with ClinicalTrials.gov, NCT04456686). All current osteoarthritis disease-modifying drug trials are summarised in table 2.

Other types of innate immune activation might be important in osteoarthritis pathogenesis but have as yet only been explored as targets in preclinical models (table 1). Components of the common terminal pathway of complement activation are strongly up-regulated in the synovial fluid of individuals with osteoarthritis,⁸⁰ with evidence of the formation of membrane attack complex within human osteoarthritis cartilage.⁶² Deletion of *C5* (an upstream activator of the common pathway) in mice led to reduced disease severity after joint destabilisation, whereas deletion of an inhibitor of terminal activation (*Cd59a*) led to increased disease severity.⁶² The same research group also identified mast-cell activity as a pathogenic mediator in murine osteoarthritis.⁷⁶ Mast-cell activation has previously been described in the osteoarthritis joint,⁸¹ and is associated with structural disease.²⁵

Inflammasome activation is purported to have a role in osteoarthritis, especially when disease is complicated by a crystal arthropathy. However, studies in mice in which components of the inflammasome pathway (activated by crystals) were genetically deleted failed to show a role for inflammasome in surgically induced osteoarthritis.^{82,83} Several groups have examined the role of alarmins in osteoarthritis, through deletion of Toll-like receptors, S100 proteins, or advanced glycosylation end productspecific

receptors. Collectively, these studies do not support a role for these molecules in surgically induced murine osteoarthritis.^{82,84} Many preclinical studies in this area of research remain unpublished, and this reporting bias has been unhelpful for research over the years.⁸⁵

My own work, and work arising from the Centre of Osteoarthritis Pathogenesis at the Kennedy Institute of Rheumatology (Oxford, UK) has highlighted an important role for what has been termed mechanoflamination,⁸⁶ showing that mechanical injury directly drives inflammatory signalling and inflammatory genes in joint tissues, including the articular cartilage and synovium.^{87,88} Joint immobilisation after destabilisation surgery attenuates the induction of pathogenic proteases and prevents osteoarthritis development.¹⁴ Mechanoflamination drives *TGF β* -activated kinase (TAK1) and downstream activation of the inflammatory mitogen-activated protein kinases (JNK and p38) and nuclear factor κ B (NF- κ B).¹² NF- κ B signalling pathway has long been considered an important inducer of inflammatory gene regulation in osteoarthritis. It is a complex pathway with canonical and non-canonical pathways that mediate anti-apoptotic and pro-inflammatory functions. This characterisation has been confirmed in vivo in a dose-dependent manner, in which heterozygous deletion of *RelA* (p65), a transcription factor activated upon canonical NF- κ B activation, resulted in chondroprotection, whereas homozygous deletion led to accelerated disease through the suppression of apoptosis.⁷³ Accelerated disease resulting from homozygous deletion of p65 was mediated through decreased expression of the anti-apoptotic gene *Pik3r1*, itself a candidate gene arising from a genome-wide association study for cartilage thickness.⁸⁹ Deletion of *Ikka* (which inhibits κ B-kinase- α , an upstream NF- κ B pathway activator) leads to disease protection and anti-apoptotic effects in vivo.⁷⁴ Although NF- κ B might be important in transcriptional regulation of proteases in osteoarthritis, JNK activation controls the bioavailability of aggrecanase activity in vitro⁸⁸ and in vivo,⁷⁵ by a mechanism that appears to involve re-uptake of aggrecanases by the cell surface scavenger receptor, low-density lipoprotein receptor-related protein.^{90,91} Targeting protease activity through metal cation symporter Zip8, a zinc transporter, has also been shown in murine osteoarthritis.⁹² Zip8 is regulated by the hypoxia transcription factor Hif2 α ,⁹³ which has also been shown to be disease-modifying in preclinical osteoarthritis models.⁹⁴

Promoting anabolism and repair in osteoarthritis

The inability of articular cartilage to repair is famously attributed to William Hunter who stated in 1743 that "...ulcerated Cartilage is universally allowed to be a very troublesome disease...and when destroyed, it is never recovered".⁹⁵ The essence of this statement has been reiterated in textbooks for decades, but recent years have seen a paradigm shift. Improved MRI imaging indicates that asymptomatic focal defects in the joint surface are much more common than previously suggested, and prospective studies conclude that around 30% of focal

	Study type and number of participants	Drug	Target or drug type	Route	Trial status	Primary outcome	Secondary outcomes
NCT04456686	Phase 2 randomised controlled trial; 125 participants	LY3016859	Transforming growth factor α and epiregulin	Intravenous	Recruiting	Pain (numeric rating scale)	Function
NCT04447898	Phase 1 randomised controlled trial; 24 participants	PPV-06 vaccination	Interleukin-6	Subcutaneous	Not yet recruiting	Safety	Not given
NCT04385303	Phase 3 randomised controlled trial; 726 participants	Lorecivivint (SM04690)	Wnt pathway	Intra-articular	Recruiting	Pain (numeric rating scale)	Function
NCT03928184	Phase 3 randomised controlled trial; 725 participants	Lorecivivint (SM04690)	Wnt pathway	Intra-articular	Recruiting	Pain (numeric rating scale)	Function; structure
NCT04318041	Phase 3 randomised controlled trial; 128 participants	Diacerin	Unknown or anti-inflammatory	Oral	Not yet recruiting	Structure (MRI)	Function
NCT04303026	Phase 3 randomised controlled trial; 70 participants	Zoledronic acid	Osteoclast activity	Intravenous	Recruiting	Pain (Visual analogue scale)	Function; structure
NCT04231318	Phase 3 randomised controlled trial; 231 participants	Cingal	Triamcinolone plus hyaluronate	Intra-articular	Not yet recruiting	Pain (WOMAC)	Not given
NCT04224584	Phase 2 crossover controlled trial; 40 participants	Duloxetine	CNS reuptake inhibitor	Oral	Recruiting	Pressure pain threshold	Not given
NCT04117893	Phase 4 randomised open-label trial; 150 participants	Duloxetine plus hyaluronic acid plus triamcinolone	CNS reuptake inhibitor plus corticosteroid plus hyaluronan	Oral and intra-articular	Not yet recruiting	Pain (average pain scores)	Function
NCT04261049	Open-label trial; 35 participants	Zilretta	Corticosteroid (slow release)	Intra-articular	Not yet recruiting	Muscle strength; function and gait	Not given
NCT04123561	Phase 3 randomised controlled trial; 500 participants	TLC599	Corticosteroid (slow release)	Intra-articular	Recruiting	Pain (WOMAC)	Function
NCT04120402	Phase 2 randomised controlled trial; 238 participants	EP-104IAR	Corticosteroid (slow release)	Intra-articular	Not yet recruiting	Pain (WOMAC)	Function
NCT04097379	Phase 2 randomised controlled trial; 40 participants	LRX712	Not disclosed; pro-regenerative	Intra-articular	Not yet recruiting	Structure (sodium cartilage content by MRI)	Pharmacokinetics
NCT03913442	Phase 4 randomised controlled trial; 120 participants	Colchicine	Anti-inflammatory; precise mechanism disputed	Oral	Recruiting	Pain (visual analogue scale)	Function
NCT03815448	Randomised controlled trial; 200 participants	Methotrexate	Immunosuppressant (folate antagonist)	Oral	Recruiting	Synovitis (MRI); pain (visual analogue scale)	Function
NCT01927484	Randomised controlled trial; 120 participants	Methotrexate	Immunosuppressant (folate antagonist)	Oral	Not yet recruiting*	Pain (visual analogue scale)	Function
NCT02905799	Phase 3 randomised controlled trial; 164 participants	Resveratrol	Anti-ageing or anti-inflammatory (multiple proposed mechanisms of action)	Oral	Recruiting	Pain (numeric rating scale)	Function
NCT04119687	Phase 1 open-label trial; 24 participants	FX201	Interleukin-1 receptor antagonist gene therapy	Intra-articular	Recruiting	Safety	Biodistribution
NCT02790723	Phase 1 open label; 9 participants	Sc-rAAV2.5IL-1Ra	Interleukin-1 receptor antagonist gene therapy	Intra-articular	Recruiting	Safety	Not given
NCT02471118	Phase 2 crossover randomised controlled trial; 100 participants	Adalimumab	Anti-tumour necrosis factor	Subcutaneous	Recruiting	OARSI/OMERACT response	Pain; function
NCT03595618	Phase 2 randomised controlled trial; 928 participants	GLPG1972	ADAMTS-5 inhibitor	Oral	Not yet recruiting	Structure (cartilage thickness by MRI)	Other structure; function and pain

Data taken from Clinicaltrials.gov on July 24, 2020. *Trial terminated due to COVID-19.

Table 2: Registered active drug trials in osteoarthritis

cartilage defects spontaneously regress over time.⁹⁶ Regression of osteoarthritis, as measured by Kellgren and Lawrence x-ray score during a 14-year period, has been documented in the Chingford Women's cohort,⁹⁷ and preclinical studies show evidence of intrinsic repair of focal cartilage defects in a mouse strain (genetic) and age-dependent manner.^{98,99}

Load-altering procedures

The best clinical evidence of intrinsic cartilage repair in individuals with osteoarthritis comes from open-label studies of joint distraction. The largest study to date involved 20 patients. Applying a distraction frame for 6 weeks across the osteoarthritis knee joint resulted in an impressive clinical response (reduced pain and improved function assessed by the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) and regrowth of tissue that resembled articular cartilage by MRI at 1 year and 2 years.^{100,101} Extended follow-up of this cohort showed that trial participants were less likely than a disease-matched osteoarthritis population to undergo joint replacement surgery.¹⁰² Similar, albeit smaller, studies have been done by other groups.¹⁰³ The procedure results in a reduction of compressive load through the joint and complete prevention of surface shear stress (ie, no joint flexion). These concepts fit well with observations in mice, in which immobilising the knee joint in a fully extended position prevents protease regulation and protects the mouse from osteoarthritis after joint destabilisation. Maintaining some compressive force is likely to be more effective than complete joint immobilisation because it promotes the release of matrix-bound chondroprotective growth factors, such as fibroblast growth factor (FGF) 2.^{14,16} When the synovial fluid levels of candidate molecules were examined over the course of joint distraction, out of ten analytes examined, only two, FGF2 and TGF β (both pro-regenerative growth factors), predicted a good clinical response.¹⁰⁴

High tibial osteotomy, whereby a wedge of bone is removed from the top of the tibia (usually) to correct valgus–varus joint malalignment, is also associated with clinical improvement.¹⁰⁵ Moreover, when studies have examined the cartilage macroscopically through arthroscopy, histologically, or by MRI, evidence of cartilage regeneration is observed in the now off-loaded part of the joint.^{106–108}

Intra-articular FGF18

Sprifermin is a truncated form of FGF18. The FGFs form a large family of pleiotropic growth factors implicated in a range of physiological and pathological processes, including embryonic development, tissue repair, and cancer.¹⁰⁹ Whereas FGF2 is promiscuous, binding to all four FGF receptors (FGFRs), FGF18 is thought to be more selective for FGFR3, which is the chondroprotective FGFR in murine osteoarthritis studies.^{110–112} Of note, polymorphic

variants in FGFR3 have been identified in two genome-wide association studies: a population study⁷⁷ associating a polymorphic variant with articular cartilage thickness, and another study¹¹³ that identified it as an at-risk allele in osteoarthritis. The latter study also identified FGF18 as a candidate gene associated with osteoarthritis risk.¹¹³

In 2014, a proof-of-concept study¹¹⁴ was reported in which 192 individuals with osteoarthritis were randomly assigned to receive three doses of intra-articular sprifermin (recombinant truncated form of FGF18) or placebo, with follow-up at 6 months and 12 months. The study failed to meet its primary endpoint (a difference in articular cartilage thickness in the central medial femoro-tibial compartment), but it did show delayed loss of cartilage overall and thickening in the lateral compartment.¹¹⁴ In 2019, the FORWARD trial,¹¹⁵ in which 549 participants received intra-articular sprifermin every 6 months or 12 months, or placebo, reported a significant increase in total femoro-tibial cartilage volume compared with placebo at 2-year follow-up, albeit without significant clinical improvement. In a recent post-hoc analysis¹¹⁶ of the original trial data (thus far reported in abstract form), sprifermin treatment showed a statistically significant clinical and structural improvement over among a subgroup of 161 patients who were defined as being at high risk of progression. Although these studies do not specifically show reversal of cartilage damage (ie, true repair), they do show that damage can be arrested and therefore indicate a structure-modifying osteoarthritis drug. Whether these drugs turn out to be true disease-modifying osteoarthritis drugs is not yet clear. The apparent discordance between structure and symptoms in osteoarthritis is discussed later in this Review.

Intra-articular Wnt inhibitor

Wnts are a complex family of cellular signalling molecules that direct a broad range of cellular responses, particularly regarding bone development. Wnts are activated upon mechanical stress of articular cartilage^{117,118} and are thought to drive the dedifferentiated chondrocyte phenotype, bone remodelling, and induction of catabolic enzymes seen in osteoarthritis.^{119–121} Canonical Wnt signalling involves stabilisation of the signalling molecule beta-catenin within the cell. Interfering with beta-catenin has shown conflicting outcomes in experimental osteoarthritis, indicating that this molecule is not readily amenable to therapeutic translation.¹²² Interfering with natural inhibitors of Wnt signalling in mice, such as *Dkk1* and *Dot1l*, reveals the disease-modifying potential of this pathway.^{123–126} SM04690 is a synthetic Wnt inhibitor with an undisclosed (unknown) primary mechanism of action that has shown success in murine models of osteoarthritis.^{127,128} A phase 1 study of a single intra-articular dose of SM04690 in 61 participants with moderate osteoarthritis showed acceptable safety, with exploratory clinical endpoints that showed a positive trend towards improvement in pain and joint space narrowing.¹²⁹ A phase 2 study of 455 individuals with

unilateral knee osteoarthritis, although not reaching its primary endpoint (improvement of WOMAC pain at week 13), showed improvement in pain and an increase in joint space indicative of disease modification, which was especially evident in people with unilateral disease.¹³⁰ In May 2019, the phase 3 studies were launched (registered on ClinicalTrials.gov, NCT04385303).

Other putative anabolic targets from preclinical studies

Recent studies in murine osteoarthritis identify the transcriptional coactivator Yap and WW domain-containing transcription regulator protein 1 (Taz) pathway as a strong chondroprotective mechanism. Yap and Taz are both transcription factors that are activated by Hippo signalling, a highly conserved pathway thought to be involved in cellular mechanotransduction.¹³¹ Genetic and pharmacological enhancement of this pathway protects joints from osteoarthritis after joint destabilisation,¹³² which might in part be due to it controlling the generation of chondroprogenitor cells arising from the synovium.¹³³ The Yap–Taz pathway also reciprocally controls Tak1¹³² (strongly induced by cartilage injury), and this might be an important mechanism by which inflammation suppresses repair (figure 1).

Targeting nerve growth factor to treat osteoarthritis pain

Nerve growth factor (NGF) has long been known to sensitise pain fibres and, in doing so, enhance the firing rate of nociceptors in response to mechanical and thermal stimuli. NGF is also known to be a neurotrophic factor, directing the growth of new nerves.¹³⁴ The use of anti-NGF neutralising antibodies to inhibit osteoarthritis pain has been heralded as a huge breakthrough for osteoarthritis patients who have struggled for years with inadequate pain relief. Several biological drugs targeting NGF, all delivered systemically (intravenously or subcutaneously), have been tested in phase 2 studies, with a meta-analysis showing efficacy across the different studies.¹³⁵ Two companies have now published phase 2–3 studies using NGF neutralising antibodies,^{136–138} with fasinumab and tanezumab showing efficacy over placebo. Concerns over patients developing rapidly progressive osteoarthritis in index and non-index joints (ranging from 2 to 10% according to dose and study) forced the FDA to introduce mitigation strategies, which included reducing highest doses and prohibiting the use of concomitant non-steroidal anti-inflammatory drugs. The community now awaits a decision from the FDA on whether this class of drug, which was designated as fast track in 2017, will be approved for patient use.

Other strategies to target NGF signalling have also been tested. In 2019, two randomised controlled trials targeting high affinity nerve growth factor receptor (TrkA), the receptor through which NGF signals, were published.^{139,140} In one study,¹³⁹ 215 participants were randomly assigned to receive twice daily oral dosing with ASP7962, placebo or naproxen for 4 weeks. The study failed to meet its primary

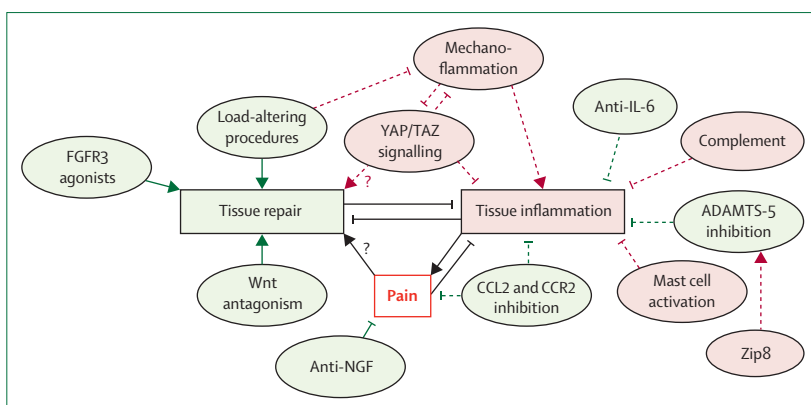


Figure 1: Emerging therapeutic targets in osteoarthritis

Pathological targets largely cluster into those promoting repair, those neutralising pain, and those suppressing tissue inflammation (leading in turn to degradation). A reciprocal relationship exists between inflammatory and repair pathways in the osteoarthritis joint, both of which affect pain. Green circles indicate targets that show efficacy in mouse experiments and for which therapeutic strategies are being tested in clinical trials, and red circles indicate putative pathways identified in mice that have not yet been tested in clinical studies. Solid lines represent those with proven efficacy in human studies, and dashed lines indicate where clinical study outcomes are not yet known. Arrows indicate promotion, and flat line-ends represent suppression. Question marks indicate where connection is speculative. Load-altering procedures include surgical joint distraction and wedge osteotomy to correct joint malalignment, which probably suppress mechanoflammation. Peripheral pain arises from joint pathology and might suppress tissue inflammation and enable tissue repair by preventing mechanical overload of the joint. Zip8 is a zinc transporter that controls protease regulation in chondrocytes. FGFR=fibroblast growth factor receptor. IL=interleukin. YAP=transcriptional coactivator Yap. TAZ=WW domain-containing transcription regulator protein 1. ADAMTS=a disintegrin and metalloproteinase with thrombospondin motif. CCL=C-C motif chemokine. CCR=C-C chemokine receptor. Zip8=metal cation symporter Zip8. NGF=nerve growth factor.

endpoint (WOMAC pain subscore).¹³⁹ A second study¹⁴⁰ randomly assigned 104 participants to intraarticular GZ389988A or placebo. This study did show improved pain outcomes of the drug compared with placebo, although the effect size was small and of questionable clinical value.¹⁴⁰ Neither study was accompanied by evidence of target tissue drug bioavailability.

Anti-NGF clinical trials align well with evidence of NGF-mediated pain-like behaviour in rodent osteoarthritis. Pain-like behaviour can be measured by evoked or non-evoked methods. Like humans, rodents will spontaneously off-load the damaged joint when experiencing pain, and this behaviour can be measured by assessing the amount of weight transmitted through each hind limb. Using this technique, mice have been shown to display two phases of pain behaviour after joint destabilisation: an initial post-operative phase that resolves after 1 week, and a later phase that starts only once there is significant joint damage (10 weeks after destabilisation of the medial meniscus or 8 weeks after partial meniscectomy).^{141–143} Late osteoarthritis pain in rodents is Ngf-dependent^{144,145} and tumour necrosis factor-independent.¹⁴⁵ The driver of NGF-dependent late osteoarthritis pain is unclear, but Ngf mRNA upregulation occurs in the articular cartilage rather than bone or meniscus, and there is very little inflammatory gene regulation in the joint during this time.¹⁴⁶ Although this observation might be surprising in view of broadly held views that osteoarthritis pain originates from inflammatory processes in the synovium or subchondral bone, emerging molecular data from

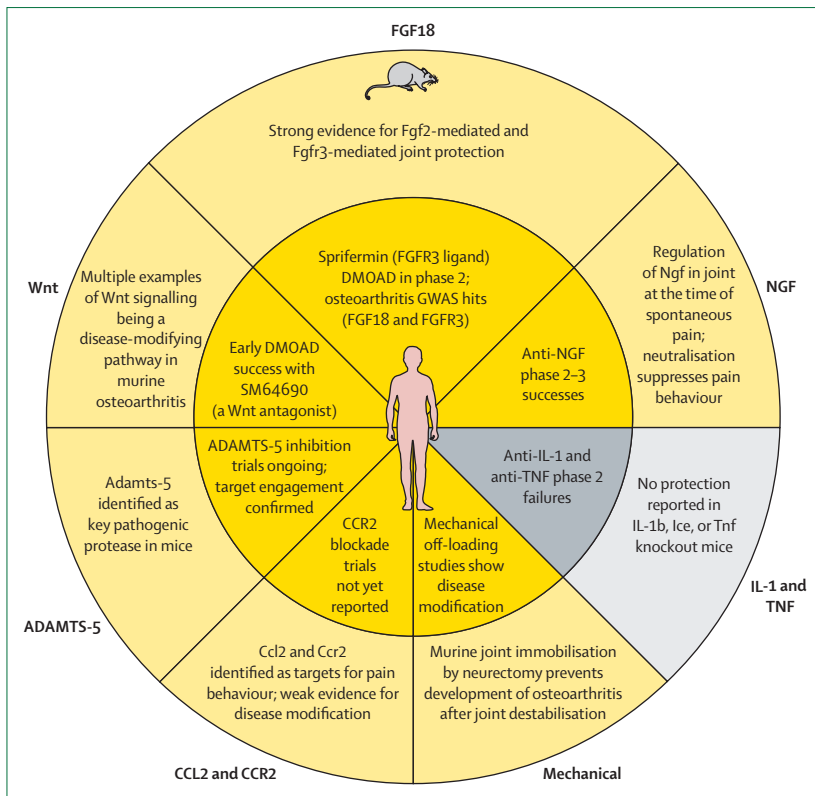


Figure 2: Concordance between tested targets in mouse and human osteoarthritis studies

Several pathways have been or are being tested in human osteoarthritis, having also been tested in murine surgical models. Yellow indicates therapies that show treatment success or target engagement in each study. Grey shows therapies that have failed to modify symptomatic or structural disease. Note that there is 100% concordance between mouse (outer ring) and human (inner ring) studies. FGF=fibroblast growth factor. FGFR=fibroblast growth factor receptor. DMOAD=disease-modifying osteoarthritis drug. GWAS=genome-wide association study. NGF=nerve growth factor. IL=interleukin. TNF=tumour necrosis factor. ICE=capsase-1/interleukin-1 converting enzyme. CCL=C-C motif chemokine. CCR=C-C chemokine receptor. ADAMTS=A disintegrin and metalloproteinase with thrombospondin motif.

human tissue also support the notion that cartilage is the principal source of NGF in the osteoarthritis joint. Using agnostic approaches, NGF was not regulated in the synovium of individuals with painful compared with non-painful osteoarthritis,^{27,79} and it was not found in bone marrow lesions from samples taken at the time of arthroplasty.¹⁴⁷ NGF was found to be regulated in damaged articular cartilage in early microarray studies of osteoarthritis cartilage,¹⁴⁸ and it defines one of seven subsets of chondrocytes identified by single-cell sequencing of human osteoarthritis cartilage.¹⁴⁹ NGF is regulated by direct cartilage injury (mechanoflamination) in a TAK1-dependent manner, and it is tempting to speculate that damage to chondrocytes near the osteochondral junction is an important trigger for the NGF-driven neoinnervation of the articular cartilage that is seen late in both murine and human disease.^{150,151} Neoinnervation of this region also requires a permissive subchondral bone to support axonal extension. This neoinnervation has recently been shown to be dependent upon Netrin-1, secreted by osteoclasts during the course of murine osteoarthritis.¹⁵² An overall

model for the development of pain in osteoarthritis has been proposed.¹⁵³

Conclusions

There are many reasons to be optimistic about new therapeutic developments in osteoarthritis. Although it is true that much of what has been learned in the past few years from clinical studies is what not to use in disease, these negative studies have been highly informative in reminding the medical community that osteoarthritis is distinct from inflammatory arthritides, such as rheumatoid arthritis. Research has shown that inflammation in osteoarthritis is nuanced and that classical immunomodulatory pathways are not good targets, but that there are several other inflammatory pathways awaiting clinical exploration, including those driven by direct mechanical injury of the cartilage (so-called mechanoflamination), complement, and mast cells.

The nature and role of inflammation in osteoarthritis pathogenesis thus remains unclear. Clarification is crucially important, not only so that we can develop appropriate targeted therapies for patients, but also to decide whether patients require stratification before treatment. There has been a popular move to try to phenotype patients, with a view to personalising their treatment to improve the efficacy of a given drug. However, these phenotypes currently lack cohesion; some are defined by clinical features (eg, inflammatory osteoarthritis), and others by co-morbidity (eg, metabolic osteoarthritis), precipitating factor (eg, post-traumatic osteoarthritis), or anatomical site (eg, hand osteoarthritis, hip osteoarthritis). There is little or no evidence that stratification by any of these features changes the response to treatment. Further carefully considered phenotypes that take into consideration molecular pathways are probably required. Large-scale molecular endotyping of patient samples is currently in its infancy, but will probably help.

Clinical successes point towards a focus on regenerative or anabolic pathways rather than inflammatory ones (figure 1). This suggestion fits well with preclinical studies, although the reciprocal relationship between repair and inflammation in the chondrocyte suggests that targeting one will probably affect the other.¹³² Recent large genome-wide association studies in osteoarthritis also support the concept that osteoarthritis is a failure of repair. Several at-risk loci have been attributed to genes in the TGF β and FGF pathways, and there is a notable absence of loci that predict the regulation of classical inflammatory genes.^{113,154} Newer targets identified by genome studies, including the retinoic acid pathway, also look promising.¹⁵⁵

NGF-targeting for pain relief is the target closest to being ready to use in osteoarthritis. Clinical success in late osteoarthritis indicates that analgesia occurs largely as a result of nociceptor desensitisation. It remains to be seen whether interfering with this pathway at earlier stages of the disease could affect the neoinnervation of the cartilage

Search strategy and selection criteria

This is a narrative Review based on clinical trials done in hand and knee or hip osteoarthritis by searching PubMed with the terms “Phase” with “Trial” and “Osteoarthritis” in the title from Jan 1, 2012, to July 31, 2019. Further information was sought through Clinicaltrials.gov, by searching for “osteoarthritis” studies in which the intervention was “drug”. Preclinical studies were interrogated through Skeletalvis.ncl.ac.uk. This Review is not intended to be a comprehensive review of all clinical trials in osteoarthritis or all pathways identified through murine studies. Rather, its intention is to focus on those targets for which there is overlap between murine and human studies. Additionally, the Review highlights a few emerging pathways that have strong preclinical evidence for a role in pathogenesis and which could be amenable to clinical targeting. Inevitably, an exercise of this sort reflects the author’s personal views on pathogenesis, based on 20 years of working with preclinical surgical models, human tissue, and patients with osteoarthritis.

due to the neurotrophic functions of NGF, and to what extent this could prevent painful disease from developing. This type of strategy would need to be considered in the context of current safety concerns around the development of rapidly progressive osteoarthritis, which remains a real concern. Other molecules that appear to have a role in the reinnervation of the osteochondral junction in osteoarthritis models include Netrin-1,¹⁵² a molecule secreted by osteoclasts that guides axonal growth through the subchondral bone. Blocking bone remodelling with a bisphosphonate early in murine osteoarthritis development appears to block pain without affecting structural disease, according well with clinical studies in osteoarthritis in which bisphosphonates are not disease-modifying when given in established disease.^{156,157}

One major outstanding issue remains the apparent discordance between structural and symptomatic disease, which raises questions about whether validated drugs need to be able to, or indeed could ever, target both. Whether different joint pathologies give rise to different types of symptoms at different stages of disease is currently unknown, as is the relative contribution of factors that drive central sensitisation of pain. Of the few examples available at this stage, cartilage structure-modifying drugs (eg, sprifermin) mainly arrest disease progression rather than regenerating the cartilage, so perhaps symptoms could not be expected to reverse. Where structural damage appears to reverse (eg, after joint distraction), symptoms also appear to improve (albeit with no placebo control). Targeting pain alone is unlikely to improve structure in the short term and might worsen damage through mechanical overuse. In preclinical models, there tends to be better accordance between structural damage and pain-like behaviour,¹⁵³ with some clear

examples emerging that might identify true disease-modifying osteoarthritis drugs of the future, such as those involving the YAP–TAZ pathway.

Finally, it is reassuring to conclude that, where there is overlap, research in surgical preclinical osteoarthritis models aligns well with findings in clinical trials (figure 2). This concordance provides valuable validation of the models and will help develop mutual trust between the different osteoarthritis research disciplines. It is increasingly difficult to claim that mouse osteoarthritis is fundamentally different to human osteoarthritis, or that post-traumatic osteoarthritis does not inform age-related disease in humans. Part of this reassurance has emerged through improved awareness of bias mitigation in clinical and preclinical studies.¹⁵⁸ It is also partly due to the acceptance that osteoarthritis has disease-specific molecular targets. Regardless, this is an important time for osteoarthritis research, with tangible translational benefits within reach.

Declaration of interests

TIV has consulted for GlaxoSmithKline, Mundipharma, and Union Chimique Belge in the past 3 years on an ad-hoc basis. She directs the STEpUP osteoarthritis consortium, which has financial support from Samumed, Fidia, and Galapagos.

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