

“Of mice and men”; converging on a common molecular understanding of osteoarthritis.

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Conflict of interest statement:

Vincent has consulted for GSK, Mundipharma and UCB in the past three years on an ad hoc basis. She directs the STEpUP OA consortium which has financial support from Samumed, Fidia and Galapagos.

Acknowledgements:

Vincent’s lab is supported by the Centre for OA Pathogenesis, Versus Arthritis (grant numbers 20205 and 21621). To Dr Elizabeth Thompson for help with Figures.

Abstract

Despite an increasing burden of osteoarthritis (OA) in developed societies, target discovery has been slow and there are currently no approved disease modifying OA drugs (DMOADs). In part this has been fuelled by a series of misconceptions over the years; that OA is an inevitable consequence of ageing, that damaged articular cartilage cannot heal itself, and that OA 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 has radically reshaped the landscape. Inflammation in OA 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 (FGF18) therapies or Wnt antagonism. Nerve growth factor (NGF) has emerged as a robust target in OA pain in phase II/III trials. These studies, both positive and negative, align well with those in pre-clinical surgical models of OA indicating that pathogenic mechanisms identified in mice can lead us to valid human targets. Several novel candidate pathways are emerging from pre-clinical studies that offer hope of future translational impact. Enhancing trust between industry, basic and clinical scientists will optimise our collective chance of success.

Introduction

The global impact of osteoarthritis (OA), the most common form of joint disease in developed societies, is predicted to rise steadily as obesity and longevity increase(1). OA is a significant societal burden; associated with increased mortality and frequently complicated by multi-morbidity and polypharmacy(2-4). The recent acceptance of OA as a serious disease has helped to drive the therapeutic agenda forward, to garner support from academia and industry, as well as influence health care prioritisation(5). The market for symptomatic and disease modifying treatments is huge 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; the former including pathology, epidemiology and interventional studies in humans. The latter including the study of molecular pathogenesis through in vitro systems, pre-clinical models and ‘omics’ studies at large scale. OA is a mechanically driven disease. This is compellingly described in the epidemiological literature (comprehensively reviewed in (6)), and confirmed in basic science studies, which have

demonstrated: the highly mechanosensitive nature of joint tissues(7-12), the activation of inflammatory signalling by mechanical injury(12, 13), the dependence of mechanics in preclinical OA(14, 15), and the involvement of mechanosensing mechanisms in *in vivo* pathogenesis (16, 17). Several other important aetiological factors, such as obesity, age and genetics, impact the ability of joint tissues to withstand mechanical stress over a lifetime, and affect the ability to repair damaged tissues. These factors may also increase the risk of OA in mechano-independent ways. For example, OA in non-weightbearing joints is increased in obese individuals(18), possibly due to low grade systemic inflammation(19, 20), which may be linked to the gut microbiome(21).

A number of impediments in OA drug development are recognised. OA is an insidious and heterogeneous disease. This inevitably means that clinical trials are often prohibitively expensive, and raises the possibility that one target may 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. Lack of access to human tissue at early stages of disease has necessitated a reliance on preclinical models which has also required substantial refinement; largely moving away from chemical induction methods (monosodium iodoacetate, papain, collagenase injection) in favour of those induced by surgical destabilisation of the joint(22). In the past 15 years target discovery in OA has increased substantially particularly through large agnostic 'omic' studies using end stage human disease tissue, and molecular validation facilitated by pre-clinical mouse models and clinical trials. There has also been significant research into methodological tools for improving clinical outcome measures and OA trial design(23). In this review recent successes and failures in OA clinical trials are considered in parallel with preclinical advances. Together these are helping to unravel the complexities of OA pathogenesis and provide future targeting strategies with a higher chance of translational success.

Targeting inflammation in OA.

Support for the involvement of inflammation in OA 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 associate with clinical outcome(24-26). In addition, a number of inflammatory molecules including cytokines, chemokines and metalloproteinases (MMPs) have been measured in OA cartilage and synovium (27, 28). Clinicians distinguish between inflammatory arthritis and OA, by a relative paucity of leucocytes in OA synovial fluid, which are predominantly monocytes (OA) rather than neutrophils (rheumatoid arthritis). OA patients typically complain of less than 30 minutes of early morning stiffness, and exhibit a very modest systemic inflammatory response(29). These features are used clinically to aid the diagnosis of OA. Whether low grade inflammation contributes to OA pathogenesis, both in terms of pain and structural disease, has been subject to heated debate over the years. A number of recent randomised controlled trials (RCTs) that address different aspects of inflammation have been conducted. All of these tested agents derive from experience in rheumatoid arthritis where there is proven efficacy for such therapies.

Corticosteroid

Intra-articular corticosteroid is widely used in clinical practice in OA although few historical studies have applied stringent placebo controlled, randomisation and double-blind assessments. In hand OA, an randomised controlled trial (RCT) of intra articular (i.a.) triamcinalone hexacetomide, a long acting steroid preparation, showed clinical improvement up to 12 weeks following injection of drug compared with placebo (lidocaine, a local anaesthetic), meeting the primary outcome of the study, albeit in only two out of eight co-primary endpoints(30). For both groups the injected joint was splinted for 48h immediately after treatment. A phase IIb trial of extended release intraarticular steroid exhibited efficacy over placebo in pain outcomes in knee OA at several time points, even though the primary end point (pain at 12 weeks) was not met(31). Combined Phase II/III studies of

this preparation show an acceptable safety profile and lead to a reduction in use of rescue pain medication (paracetamol / acetaminophen) (32). In 2017 this preparation received FDA approval for clinical use under the trade name Zilretta.

Oral prednisolone has also been tested in hand OA. The first study by Wenham et al, in which 70 patients were randomised to receive 5mg prednisolone or placebo daily found no statistically significant improvement in pain at 4 or 12 weeks(33). However, a recent study in which patients were randomised to receive 10mg prednisolone or placebo daily for 6 weeks showed significant improvement in patient reported pain and function at the primary endpoint (6 weeks). Symptoms returned rapidly after withdrawal of the drug. Interestingly there was a reduction in synovial thickness, but no improvement in synovitis by MRI or power doppler assessment making it unclear as to the drug's primary target tissue(34).

Few studies have attempted to examine the long-term effects of corticosteroid on the joint. In an RCT by McAlindon et al, 140 patients with knee OA were randomised to receive three-monthly i.a. injections of triamcinolone or saline over two years. Clinical outcomes were assessed every three months and cartilage damage measured by MRI at 2 years. No clinical benefit was seen in patients in any of the outcome measures compared with placebo, although it is possible that the periodicity of follow up may have missed transient responses (returning to baseline by 3 months). Importantly this study showed a small but statistically significant increase in cartilage volume loss raising concerns about repeated and long term steroid use on joint health(35). Similar findings were also demonstrated using data derived from the Osteoarthritis Initiative (OAI)(36). A cautious approach to i.a. steroid is indicated by a "conditional type IB recommendation" for this treatment in recent OARSI guidelines for non-surgical treatment of hip and knee OA(37).

Disease modifying anti-rheumatic drugs (DMARDs)

Both hydroxychloroquine and methotrexate are used in patients with rheumatoid arthritis and less commonly on an individual patient basis in OA. Two RCTs using oral hydroxychloroquine in hand OA have been published. Neither met the primary study endpoint (reduction in pain)(38, 39). Nor was a clinical response seen in a pre-defined sub-study in which patients were stratified by presence or absence of power doppler signal, indicative of a more inflammatory phenotype(38). The PROMOTE study(40) has reported, by abstract thus far, a small difference in pain in those with knee OA taking methotrexate, although the effect size was not deemed to be clinically meaningful. A small RCT (n=64) of hand OA patients taking 10mg of methotrexate failed to show a beneficial effect on pain, the study's primary outcome, although some changes to evolution of joint remodelling were suggested in the reported abstract(41). A meta-analysis has concluded lack of efficacy of 'conventional' disease modifying anti-rheumatic drugs across all joint OA(42).

Anti-cytokine therapies.

Lack of efficacy was also evident in four RCTs in hand OA targeting either TNF or IL1(43-46) and two in knee OA targeting IL1(47, 48), one of the latter being via an intra-articular approach. Despite promise from a number of small open label studies, none of the RCTs met the primary study endpoint suggesting that classical cytokine-driven inflammation is neither driving pain nor structural damage in OA. These results are in accordance with preclinical data in which gene deletion of IL1 β , the IL1-converting enzyme(49), IL1R (Vincent, unpublished data), TNF α (50), or inflammasome pathway components (which lead to processing of IL1 family cytokines)(51) do not confer protection from OA after surgical joint destabilisation. Despite a strong rationale based on in vitro studies, evidence to support a direct pathogenic role for IL1 in OA pathogenesis appears, in retrospect, to have been weak (reviewed in (52)).

Other putative inflammatory targets from preclinical models.

The above studies force us to conclude that classical inflammation, of the type pathogenic in rheumatoid arthritis, is not driving OA. One exception to this may be IL6. Although the OA phenotype has been inconsistently reported in IL6 knockout mice (56, 57), therapeutic studies suggest that neutralisation of IL6 is disease modifying in murine OA(58). A clinical trial using Tocilizumab, an IL6 neutralising antibody, in hand OA completed in 2019 but has not yet reported (<https://clinicaltrials.gov/ct2/show/NCT02477059>).

Targeting the proteases that degrade the articular cartilage extracellular matrix has long been regarded as an attractive approach to disease modification in OA. A disintegrin and metalloproteinase with thrombospondin motif-5 (ADAMTS5) was identified as the principal aggrecan degrading enzyme in mice(53), and mediates proteolytic activity in human OA chondrocytes (59) (possibly also involving ADAMTS4)(60). Aggrecanase inhibition is being re-explored, after companies abandoned earlier studies at preclinical phase due to adverse cardiovascular events using an anti-ADAMTS5 monoclonal antibody(54). A good safety profile and evidence of target engagement with a small molecule inhibitor(55) is now being followed by Phase II studies in knee OA with structural disease as the primary outcome. (<https://clinicaltrials.gov/ct2/show/NCT03595618>).

Activation of other components of the innate immune system may have more important pathogenic roles in disease and have been examined in preclinical OA (Table 1). A number of chemokine family members have been explored after joint destabilisation, with some, but not others having disease modifying effects in murine OA (Table 1). As these are expressed by chondrocytes and have described chondroprotective and disease causing roles, but do not always correlate with inflammatory cell infiltration of the joint, they are likely acting in canonical and non-canonical fashions(61-63). CCL2 and its receptor CCR2 are the best validated of these targets. Constitutive deletion of CCL2, or its receptor CCR2, delay and suppress pain severity in preclinical OA but have little effect on cartilage damage when induced in 10 week old animals(64, 65). However, a reduction in structural disease has been seen when older (20 week old) CCR2^{-/-} mice are subjected to joint destabilisation(66), and when pharmacological CCR2 inhibition is delivered(67). In another study, disease modification was specifically observed when a CCR2 antagonist was given between 4 and 8 weeks after joint destabilisation, but not between 0-4 or 8-12 weeks(68). Blocking transforming growth factor α (TGF α) signalling, a strong inducer of CCL2 in the rodent OA joint, also reduced structural disease after joint destabilisation in the rat(67). TGF α is of particular interest as it has been identified as a candidate gene determining cartilage thickness and osteoarthritis risk (69) (70). These results point towards a role for CCL2/CCR2 in murine OA pain and a possible role in structural progression. Two human mRNA studies of human synovium have been performed in individuals stratified by having 'painful' or 'non-painful' OA(27, 71). One of these identified CCL2 as significantly up regulated in painful disease(27). CCR2 antagonism in OA pain has been explored clinically (<https://clinicaltrials.gov/ct2/show/NCT00689273>) although the results of this study do not appear to have been reported. A clinical study examining TGF α blockade is currently recruiting (see Table 1 for all current osteoarthritis disease modifying drug trials, taken from clinicaltrials.gov).

Other types of innate immune activation may be important in OA pathogenesis but have, as yet, only been explored as targets in preclinical models (Table 2). Components of the common terminal pathway of complement activation are strongly up-regulated in synovial fluid of individuals with OA(72) with evidence of membrane attack complex formation within human OA cartilage(73). Deletion of C5 (an upstream activator of the common pathway), or deletion of an inhibitor of terminal activation (Cd59a) led to reduced or increased disease severity respectively after joint destabilisation(73). The same group also identified mast cell activity as a pathogenic mediator in murine OA(74). Mast cell activation has previously been described in the OA joint(75) and is associated with structural disease(25).

Inflammasome activation is purported to have a role in OA especially where disease is complicated by a crystal arthropathy. However, studies in mice in which genetic deletion of components of the inflammasome pathway (activated by crystals) has been performed, fail to demonstrate a role for the inflammasome in surgically induced OA (76, 77). Several groups have examined the role of alarmins in OA, through deletion of Toll like receptors (TLR), S1000 proteins or RAGE receptors. Collectively these studies do not support a role for these molecules in surgically induced murine OA(76, 78). Many preclinical studies in this area remain unpublished and this reporting bias has been unhelpful for the field over the years(79).

Our own work has highlighted an important role for ‘mechanoflamination’(80); demonstrating that mechanical injury directly drives inflammatory signalling and inflammatory genes in joint tissues, including the articular cartilage and synovium(81, 82). Joint immobilisation after destabilisation surgery attenuates induction of pathogenic proteases and prevents OA development(14). Mechanoflamination drives TGF β -activated kinase (TAK1) and down-stream activation of the inflammatory mitogen activated protein (MAP) kinases (JNK and p38) and NF κ B(12). The NF κ B signalling pathway has long been considered an important inducer of inflammatory gene regulation in OA. It is a complex pathway with canonical and non-canonical pathways that mediate anti-apoptotic as well as pro-inflammatory functions. This is confirmed in vivo in a dose dependent manner where heterozygous deletion of RelA (p65), a transcription factor activated upon canonical NF κ B activation, displays chondroprotection whereas homozygous deletion leads to accelerated disease through suppression of apoptosis (85). The latter is mediated through Pik3r1, itself a GWAS candidate gene contributing to cartilage thickness(86). Deletion of IKK α (Inhibitor of κ B kinase alpha, an upstream NF κ B pathway activator), leads to disease protection and anti-apoptotic effects in vivo(87). Whilst NF κ B may be important in transcriptional regulation of proteases in OA, JNK activation controls the bioavailability of aggrecanase activity in vitro (59)and in vivo(88) by a mechanism that appears to involve re-uptake of aggrecanases by the cell surface scavenger receptor, LRP1. Targeting protease activity through Zip8, a zinc transporter, has also been demonstrated in murine OA(89). Zip8 is regulated by the hypoxia transcription factor Hif2 α (90), which has also been shown to be disease modifying in preclinical OA(91).

Promoting anabolism/repair in OA

The inability of articular cartilage to repair is famously attributed to Hunter in 1743 who stated that “...ulcerated Cartilage is universally allowed to be a very troublesome disease and when destroyed, it is never recovered.”(92). The essence of this statement has been reiterated in textbooks for decades, but recent years have seen a paradigm shift. Improved imaging (MRI) 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 cartilage defects spontaneously regress over time (reviewed in (93)). Regression of OA, by Kellgren & Lawrence X-Ray score, over a 14 year period has been documented in the Chingford population cohort(94), and preclinical studies show evidence of intrinsic repair of focal cartilage defects in a mouse strain (genetic) and age-dependent manner(95, 96).

Load altering procedures (joint distraction, high tibial osteotomy)

The best clinical evidence of intrinsic cartilage repair in individuals with OA, comes from open label studies of joint distraction. The largest study to date involves 20 patients. Applying a distraction frame for 6 weeks across the OA knee joint, resulted in an impressive clinical response (reduced pain and improved function assessed by WOMAC), and regrowth of tissue that resembled articular cartilage by MRI at 1 and 2 years(97, 98). Extended follow up of this cohort showed that trial participants were less likely to undergo joint replacement surgery(99). Similar, albeit smaller, studies have been performed by other groups (reviewed in(100)). The procedure results in a reduction of

compressive load through the joint and complete prevention of surface shear stress (no joint flexion). These concepts fit well with observations in mice where immobilising the knee joint in a fully extended position prevents protease regulation and protects the mouse from OA after joint destabilisation. Maintaining some compressive force, is likely to be more effective than complete joint immobilisation as it promotes the release of matrix bound chondroprotective growth factors such as FGF2(14, 16). Interestingly, when 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 (101). 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(102). Moreover, where studies have examined the cartilage macroscopically via arthrotomy, histologically, or by MRI, evidence of cartilage regeneration is observed in the now off-loaded part of the joint(103-105).

Intraarticular sprifermin (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 (reviewed in(106)). 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 OA studies(107-109). Of note, polymorphic variants in FGFR3 have been identified in two genome wide association studies (GWAS); a population study associating a polymorphic variant with articular cartilage thickness(69) and another that identified it as an 'at risk' allele in OA(110). The latter study also identified FGF18 as a candidate gene associated with OA risk(110).

In 2014, a proof of concept study was reported in which 192 individuals with OA were randomised to receive intraarticular sprifermin (FGF18) (at three doses) or placebo with follow up at 6 and 12 months. The study failed to meet its primary endpoint (a difference in articular cartilage thickness in central medial femoro-tibial compartment), but did show delayed loss of cartilage overall and thickening in the lateral compartment(111). In 2019, the FORWARD trial, in which 549 participants received 6 or 12 monthly intraarticular sprifermin, reported a significant increase in total femoro-tibial cartilage volume compared with placebo at 2 year follow up, albeit without significant clinical improvement(112). In a recent post hoc analysis (thus far reported in abstract form) of the three year data involving a subgroup of 161 patients defined as being at high risk of progression, sprifermin treatment demonstrated a statistically significant clinical as well as structural improvement over placebo(113). Whilst these studies do not specifically demonstrate reversal of cartilage damage (true repair), they do show that damage can be arrested and are therefore structure modifying OA drugs. Whether these agents turn out to be true disease modifying OA drugs (DMOADs) is not clear. The apparent discordance between structure and symptoms in OA is discussed further below.

Intraarticular SM04690 (a Wnt antagonist).

Wnts are a complex family of cellular signalling molecules that direct a broad range of cellular responses particularly with regard to bone development. Wnts are activated upon mechanical stress of articular cartilage (114, 115) and are thought to drive the dedifferentiated chondrocyte phenotype, bone remodelling and induction of catabolic enzymes seen in OA(116-118). Canonical Wnt signalling involves stabilisation of the signalling molecule beta catenin within the cell. Interfering with beta catenin has conflicting outcomes in experimental OA indicating that this molecule is not readily amenable to therapeutic translation (reviewed in(119)). Interfering with natural inhibitors of Wnt signalling such as DKK1 and DOT1L in mice does reveal the disease modifying potential of this pathway(120-123). SM04690 is a synthetic Wnt inhibitor with undisclosed (unknown) primary mechanism of action showing success in murine models of OA(124) (125). A Phase I study of single dose i.a. SM04690 in 61 subjects with moderate OA demonstrated acceptable

safety with exploratory clinical endpoints that demonstrated a positive trend towards improvement in pain and joint space narrowing(126). A phase II study of 455 individuals with unilateral knee OA demonstrated improvement in pain as well as an increase in joint space indicative of disease modification(127). In May 2019 the company launched their Phase III studies.

Other putative anabolic targets from preclinical studies:

Recent studies in murine OA identify the YAP/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 (reviewed in (128)). Genetic and pharmacological enhancement of this pathway protects joints from OA after joint destabilisation(129), which may in part be due to it controlling the generation of chondroprogenitor cells arising from the synovium (130). YAP/TAZ also reciprocally controls TAK1 (129) (strongly induced by cartilage injury, see above) and this may be an important mechanism by which inflammation suppresses repair (Figure 1).

Targeting nerve growth factor (NGF) to treat OA 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. It is also known to be a neurotrophic factor; directing the growth of new nerves (reviewed in(131)). The use of anti-NGF neutralising antibodies to inhibit OA pain has been heralded as a huge breakthrough for OA patients who have struggled for years with inadequate pain relief. Several biological agents, all delivered systemically (intravenously or subcutaneously), have been tested in Phase II studies with a meta-analysis demonstrating efficacy across the different studies. Two companies have now published phase II/III studies using NGF neutralising antibodies(132-134); Fasinumab and Tanezumab showing efficacy over placebo. Concerns over patients developing rapidly progressive OA in index and non-index joints (ranging from 2-10% 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 (NSAIDs). The community now awaits a decision from the FDA to see whether this class of drug, which was designated “Fast Track” in 2017, will be approved for patient use.

Other strategies to target NGF signalling have also been tested. In 2019 two RCTs targeting TrkA, the receptor through which NGF signals, were published. In the first, 215 participants were randomised to receive twice daily oral dosing with ASP7962 for four weeks. The study failed to meet its primary endpoint (WOMAC-pain subscore)(135). A second study randomised 108 participants to intraarticular GZ389988A. This study did demonstrate improved pain outcomes with drug compared with placebo although the effect size was small and of questionable clinical value. Neither study was accompanied by evidence of target tissue drug bioavailability(136).

Anti-NGF clinical trials align well with evidence of NGF-mediated pain-like behaviour in rodent OA. 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 can be measured by assessing the amount of weight transmitted through each hind limb. Using this technique, in our hands, mice display two phases of pain behaviour post 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)(137-139). Late OA pain in rodents is NGF dependent (140, 141), and TNF-independent(141). The driver of NGF-dependent late OA 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(142). Whilst this may be surprising in view of broadly held views that OA pain originates from inflammatory processes in the synovium or subchondral

bone, emerging molecular data from human tissue also support cartilage as the principal source of NGF in the OA joint. Using agnostic approaches, NGF was not regulated in synovium of individuals with painful compared with non-painful OA(27, 71), nor was it found in bone marrow lesions from samples taken at the time of arthroplasty(143). It was found to be regulated in damaged articular cartilage in early microarray studies of OA cartilage(144) and it does define one of seven subsets of chondrocytes identified by single cell sequencing of human OA cartilage(145). NGF is regulated by direct cartilage injury (mechanoflammentation) in a TAK1-dependent manner and it is tempting to speculate that damage to chondrocytes near the osteochondral junction is an important trigger for NGF-driven neoinnervation of the articular cartilage that is seen late in both murine and human disease(146, 147). Neoinnervation of this region also requires a permissive subchondral bone to support axonal extension. This has recently been shown to be dependent upon netrin-1, secreted by osteoclasts during the course of murine OA(148). An overall model for the development of pain in OA has been proposed(149).

Conclusions

There are many reasons to be optimistic about new therapeutic developments in OA. Whilst it is true that much of what we have learnt in the past few years from clinical studies is what not to use in disease, these negative studies have been highly informative in reminding ourselves that OA is quite distinct from inflammatory arthritides, such as rheumatoid arthritis. We have learnt that inflammation in OA is nuanced; classical immunomodulatory pathways are not good targets, but there are several other inflammatory pathways that await clinical exploration, including those driven by direct mechanical injury of the cartilage, so called mechanoflammentation, complement and mast cells.

The nature and role of inflammation in OA pathogenesis thus remains unclear. Clarification is vitally important, not only so that we can develop appropriate targeted therapies for patients but also to decide whether patients require stratification prior to treatment. There has been a popular move to try to phenotype patients with a view to personalising their treatment to improve efficacy of a given drug. However, these phenotypes currently lack cohesion; some being defined by clinical features ("inflammatory OA"), by co-morbidity ("metabolic OA"), by precipitating factor ("post-traumatic OA"), or by anatomical site ("hand OA", "hip OA" etc). There is little or no evidence that stratification by any of these change 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 likely help.

Clinical successes are pointing towards a focus on regenerative/anabolic pathways rather than anti-inflammatory ones (Figure 1). This agrees well with pre-clinical studies although the reciprocal relationship between repair and inflammation in the chondrocyte suggests that targeting one will likely affect the other(129). Recent large GWASes in OA are also supporting the concept that OA 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 predicting regulation of classical inflammatory genes(110, 150). Newer targets identified by genome studies including the retinoic acid pathway also look promising(151).

NGF targeting for pain relief is the most 'oven-ready' target in OA. Clinical success in late OA indicates analgesia is largely as a result of nociceptor desensitisation. It remains to be seen whether interfering with this pathway at earlier stages of disease could affect the neoinnervation of the cartilage due to NGF's neurotrophic functions, and to what extent this could prevent painful disease developing. This type of strategy would need to be considered in the context of current safety concerns around the development of RPOA which remains a real concern. Other molecules that appear to have a role in the neoinnervation of the osteochondral junction in OA models include netrin-1(148), a molecule secreted by osteoclasts that guides axonal growth through the

subchondral bone. Blocking bone remodelling with a bisphosphonate early in murine OA development appears to block pain without affecting structural disease, according well with clinical studies in OA in which bisphosphonates are not disease modifying when given in established disease(152, 153).

One major outstanding issue remains the apparent discordance between structural and symptomatic disease, and this 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 and what the relative contribution is of factors that drive central sensitisation of pain, is currently unknown. Of the few examples we have available to us at this stage, cartilage structure modifying drugs e.g. sprifermin, are largely arresting disease progression rather than regenerating the cartilage so perhaps we would not expect symptoms to reverse. Where structural damage is appearing to reverse e.g. after joint distraction, symptoms also appear to improve (albeit with no placebo control). Targeting pain alone is most unlikely to improve structure in the short term and indeed, may worsen damage through mechanical overuse. In preclinical models there tends to be better accordance between structural damage and pain-like behaviour (reviewed in (149)) with some clear examples emerging which may identify true disease modifying OA drugs (DMOADs) of the future e.g. involving the YAP/TAZ pathway.

Finally, it is reassuring to conclude that, where there is overlap, research in surgical pre-clinical OA models aligns well with findings in clinical trials (Figure 2). This provides valuable validation of the models and will help grow mutual trust between the different OA research disciplines. It is increasingly difficult to claim that “mouse OA is fundamentally different to human OA”, or that “post-traumatic OA 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(154). Part is due to the acceptance that OA has disease-specific molecular targets. Regardless, this is an important time for OA research with tangible translational benefits within reach.

Search strategy and selection criteria:

This is a narrative review based on clinical trials performed in hand and knee/hip OA by searching PubMed terms “Phase” and/or “Trial” and “Osteoarthritis” in the title from 2012-2019. Further information was sought through clinicaltrials.gov, searching for “osteoarthritis” studies where the intervention was “drug”. Preclinical studies were interrogated through skeletalvis.ncl.ac.uk. The review was not intended to be a comprehensive review of all clinical trials in OA nor on all pathways identified through murine studies. Rather its intention was to focus on those targets where there was overlap between murine and human studies. In addition, 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 working with preclinical surgical models, human tissue and patients with OA.

Figure 1. Emerging therapeutic targets in OA.

Pathological targets largely cluster into those promoting repair, those neutralising pain, and those suppressing tissue inflammation. A reciprocal relationship exists between inflammatory and repair pathways in the OA joint and both of these impact on pain. Targets that show efficacy in mouse and where there are therapeutic strategies being tested in clinical trial are shown in green; solid lines representing those with proven efficacy in human studies, hashed lines indicating where clinical study outcomes are not yet known. Putative pathways identified in mice that haven’t yet been tested in clinical studies are shown in red. Load altering procedures include surgical joint distraction and wedge osteotomy to correct joint malalignment. These probably suppress mechanoflamination. Peripheral pain

arises from joint pathology and may 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.

Figure 2. Concordance between tested targets in mouse and human OA studies.

Several pathways have been or are being tested in human OA having also been tested in murine surgical models. Yellow – therapies showing treatment success, or target engagement, in each respective study. Grey – therapies that have failed in to modify symptomatic or structural disease. Note 100% concordance between mouse (outer ring) and human (inner ring) studies.

	Target tested	Study details	Cartilage modifying?	Symptom modifying?	Ref
Complement	C5	KO data confirmed by pharmacological approach	Yes	Not examined	(73)
	Cd59a		Yes	Not examined	(73)
Chemokines	CCL2/CCR2	Constitutive gene deletion inconsistent across different studies but appearing to show modification at later time points. Pharmacological studies point towards a critical treatment window.	Inconsistent	Yes	(64-66, 68, 155)
	CCR5 or CCL5	Inconsistent cartilage degradation scores. Neither saw a difference in synovitis scores.	Inconsistent	Not examined	(61, 66)
	CCR7	modest structural role, KO have reduced pain behaviour	Yes	Yes	(63)
	CXCR2.	Structural increase at 8 weeks in KO i.e protective	Yes	Not examined	(62)
	CXCR4	inhibition in bone abrogates surgically induced OA	Yes	Not examined	(156)
Mechano- inflammation	I κ B ζ subunit of NF κ B.	over expression worsens disease. Conditional deletion leads to decreased disease (both on Col 2 promoter)	Yes	Not examined	(157)
	RelA (p65) NF κ B transcription factor	Dual action of RelA in disease – heterozygotes protected. Homozygotes increased disease by preventing anti-apoptotic mechanisms induced by PIK3R1 (a GWAS hit for cartilage thickness).	Yes	Not examined	(85)
	IKK α	cKO (aggrecan cre). disease protection associated with increased apoptosis	Yes	Not examined	(87)
	JNK2	Chondroprotection observed at 4, 8 and 12 weeks post surgery.	Yes	Not examined	(88)
Mast cell activation	cKit Mcl1	Deletion produces functional deletion of cKit dependent and cKit independent mast cells. Chondroprotection was also observed with APC366, a tryptase inhibitor.	Yes	Not examined	(74)
	IgH7 Fc ϵ r1	Both targeting IgE mediated activation of mast cells. Indicating that IgE induced mast cell activation is driving OA pathology.	Yes	Not examined	(74)

Table 2. Putative innate immune targets showing disease modification in preclinical studies.

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