REVIEW

Prevention of posttraumatic osteoarthritis at the time of injury: Where are we now, and where are we going?

Deborah Mason[1] | Martin Englund[2] | Fiona E. Watt[3]

[1]Biomechanics and Bioengineeering Centre Versus Arthritis, School of Biosciences, Cardiff University, Cardiff, Wales, UK

[2]Faculty of Medicine, Department of Clinical Sciences Lund, Orthopedics, Clinical Epidemiology Unit, Lund Unversity, Lund, Sweden

[3]Centre for Osteoarthritis Pathogenesis Versus Arthritis, Kennedy Institute of Rheumatology, NDORMS, University of Oxford, Oxford, UK

Correspondence
Deborah Mason, Biomechanics and Bioengineeering Centre Versus Arthritis, School of Biosciences, Cardiff University, Cardiff, Wales CF10 3AX, UK.
Email: masondj@cardiff.ac.uk

Abstract

This overview of progress made in preventing post-traumatic osteoarthritis (PTOA) was delivered in a workshop at the Orthopaedics Research Society Annual Conference in 2019. As joint trauma is a major risk factor for OA, defining the molecular changes within the joint at the time of injury may enable the targeting of biological processes to prevent later disease. Animal models have been used to test therapeutic targets to prevent PTOA. A review of drug treatments for PTOA in rodents and rabbits between 2016 and 2018 revealed 11 systemic interventions, 5 repeated intra-articular or topical interventions, and 5 short-term intra-articular interventions, which reduced total Osteoarthritis Research Society International scores by 30%–50%, 20%–70%, and 0%–40%, respectively. Standardized study design, reporting of effect size, and quality metrics, alongside a "whole joint" approach to assessing efficacy, would improve the translation of promising new drugs. A roadblock to translating preclinical discoveries has been the lack of guidelines on the design and conduct of human trials to prevent PTOA. An international workshop addressing this in 2016 considered inclusion criteria and study design, and advocated the use of experimental medicine studies to triage candidate treatments and the development of early biological and imaging biomarkers. Human trials for the prevention of PTOA have tested anakinra after anterior cruciate ligament rupture and dexamethasone after radiocarpal injury. PTOA offers a unique opportunity for defining early mechanisms of OA to target therapeutically. Progress in trial design and high-quality preclinical research, and allegiance with patients, regulatory bodies, and the pharmaceutical industry, will advance this field.

KEYWORDS
clinical, disease process, knee, pathophysiology, therapeutics, treatment

1 | INTRODUCTION

This report represents an overview of progress made in understanding and preventing post-traumatic osteoarthritis, first delivered in a workshop with the same title at the Orthopaedics Research Society Annual Conference in Austin, Texas, in 2019. Overviews of the etiology of post-traumatic osteoarthritis, considerations on the design, and conduct of trials after knee trauma, and potential drug targets revealed by preclinical studies were presented, as well as recent progress on clinical trials. Opportunities and challenges in this area were discussed.

2 | THE ETIOLOGY, EPIDEMIOLOGY, AND PATHOGENESIS OF POSTTRAUMATIC OA

Osteoarthritis (OA) is a highly prevalent disease and an increasing burden to public health worldwide. Aging and obesity are established risk factors for OA, but joint trauma is another major contributor to the disease. For example, observational studies link knee injury in young adults to a four to sevenfold increased risk for knee OA by middle age.[1–5] The resulting phenotype of OA following such known joint injury is often referred to as *post-traumatic OA* (PTOA), that is, assuming that the OA is caused by joint trauma. Typical knee injuries that increase the risk of knee OA include intra-articular ligament rupture, such as anterior cruciate ligament (ACL) rupture, an acute meniscal tear in the young and intra-articular fractures; the most frequent clinically significant injuries are thought to be in the ACL, the menisci, and/or the hyaline cartilage.[6] Epidemiological studies estimate the prevalence of major acute knee trauma at 77/10,000 persons per year.[7] ACL tears have an incidence of 8/10,000 persons per year[8,9] and are associated with early subchondral bone changes after injury.[10,11] Thus, there is a potential to observe the onset of PTOA relatively rapidly after trauma in injured patients, offering a unique opportunity to study early disease mechanisms, with the aim of slowing or even halting the cascade of molecular events that occur during its early development.[12,13]

Whether the resulting PTOA phenotype is similar or different from nontraumatic OA remains controversial, but the ability to relate OA development temporally to a risk event is certainly unique to PTOA. It is also important to remember that, even without joint injury, some of these individuals would have developed OA anyway and also that micro injury-related pathways may also be relevant in those with other OA, for example, cases associated with malalignment or obesity. Thus, the distinction between the classification of PTOA and "primary OA" is far from clear. In such individuals, one hypothesis is that a joint injury may accelerate the pathogenesis or just move it earlier as compared with someone with no joint injury exposure.

In trying to understand the etiology of PTOA, one could classify the consequences of joint injury into two main heavily inter-related pathogenic processes: (1) potentially adverse acute and chronic effects on molecular homeostasis, for example, inflammatory pathway activation within joint tissues by acute tissue injury (contusion or tears), chronic instability (abnormal joint loading), and/or the acute and chronic molecular effects of intra-articular bleeding (hemarthrosis) and (2) acute and chronic consequences of unfavorably altered biomechanical loading patterns and instability due to joint structural damage and associated muscle weakness. Although we know from preclinical models that many of the critical molecular pathways are mechanosensitive, we still know very little about the relative contribution of these inflammatory and biomechanical pathways in the initiation, resolution, or progression of human disease and importantly, about any *interactions* between the two in the etiology and pathogenesis of PTOA. Such knowledge is essential because it is plausible that *both* these processes may need to be considered and targeted to reduce the risk of OA following joint injury. Indeed, restoration of joint stability alone post injury does not appear to reduce the risk of future OA,[14,15] implying that a deeper and multidisciplinary understanding of disease mechanisms is needed for progress in this area. It is tempting to speculate that one might define the pathogenic molecular response within the joint tissues at the time of the injury, including those inflammatory signaling pathways associated with joint pain, dysfunction, and later structural change, and the relevant biomechanical adverse factors (or those which bring about repair). This would then enable the targeting of key biological processes in this early window after the joint injury to ameliorate later disease.

3 | THERAPEUTIC TARGETS AND PRECLINICAL MODELS

Various animal models of mechanically induced OA have been used in preclinical research to identify molecules that could be therapeutically targeted to prevent PTOA. Although OA models vary considerably across species (mouse, rat, rabbit, dog, sheep, and horse) and induction method (spontaneous, injury, and surgical), the vast majority of research testing potential therapeutic compounds has focused on surgical models in rodents.[16] These models destabilize the joint by transection or destabilization of the medial meniscus (DMM), or anterior cruciate ligament transection (ACLT). Since surgical trauma itself contributes to joint degeneration, noninvasive models have been developed to determine whether interventions tested at or close to the time of joint injury could prevent the onset of PTOA. These models use an external loading device to cause ACL rupture (ACLr),[17,18] focal chondral defects,[19] or osteochondral fracture.[20] The advantages of such models in understanding the natural progression of PTOA as well as revealing potential therapeutic targets have been reviewed.[17] However, surprisingly few preclinical studies have tested whether agents given acutely at the time of joint injury prevent subsequent OA progression, even though this would mimic the clinical scenario. The efficacy of drugs used in such studies are often difficult to compare as they use different preclinical models of PTOA, are administered at different times after injury, and use different methods/outcomes to report efficacy. Guidelines on conduct and reporting of experiments using rodent models of OA have been published (design and execution of protocols for animal research and treatment [DEPART], animals in research: reporting in vivo experiment [ARRIVE][21]) and include randomization, blinding to treatment, and reporting of effect sizes with confidence intervals using a validated scoring system such as the Osteoarthritis Research Society International (OARSI) histological scores.[22]

To reveal new potential treatment opportunities for PTOA, a literature review by PubMed search was performed between January 1, 2016 and December 31, 2018 for all articles where new therapies for PTOA were tested in small animals (search terms only rodent/rat/mouse/rabbit; only PTOA; only drug treatments; exclude non-English, Table S1). Results were categorized into whether drugs were given systemically (orally or by intravenous, subcutaneous, or

intraperitoneal [i.p.] injection), or locally (intra-articular [i.a.] injection or topical), the duration of drug treatment and its temporal relationship to the injury/OA. Since OA is a disease of the entire joint accompanied by synovitis and bone changes, as well as articular cartilage loss, and early inflammatory and bone changes appear to be important in driving PTOA,[18] comparisons were made between the effect size of each intervention on bone and cartilage degeneration, synovitis, bone changes, and pain (Tables 1 and 2).

This search revealed 18 unique articles reporting the testing of new treatments. Eleven different systemic interventions were reported (8 given orally and 3 by i.p. injection, and 1 not stated; Table 1), all but one in surgical models of PTOA, with administration starting before induction of OA (4) at the time of surgery/injury (7), or after OA was established (1). Systemic treatment showed 30%–50% reduction in total OARSI scores and 50%–70% reduction in medial OARSI scores, although the variability in species (rat, mouse, and rabbit), surgery (DMM and ACLT), intervention start (from 4 weeks before surgery to 4 weeks after surgery), intervention duration (4–16 weeks), and study endpoint after injury (2–8 weeks), plus a lack of consistent reporting of effect size on OARSI score, or the use of alternative scores such as the Modified Mannkin score, make efficacy comparisons very difficult. All but two studies reported OARSI score, with various effects on bone reported in eight studies, pain outcomes reported in two studies, and synovitis considered in four studies.

Five articles reported the effects of long-term, local interventions delivered to the joint by i.a. or topical treatments, and all of these were in rodent surgical models (Table 2). All treatments were compared with vehicles administered in the same manner. Topical curcumin nanoparticles were applied daily over 8 weeks from induction of OA and reduced medial OARSI score by 27%, OARSI synovitis score by 33%, and reduced bone score and pain. Kartogenin i.a. injections were given weekly, and FGF-9, FGF-18, and 5Z7 i.a. injections were given bi-weekly, at the induction of OA, or 1 or 2 weeks later, for 4–12 weeks. Based on our interpretation of the graphical data where effect sizes were not reported, OARSI severity scores were reduced by 20%–70% (total) or 30%–70% (medial) after repeated i.a. treatments (Table 2). The impact of repeated i.a. injections on other outcomes is difficult to assess as synovitis was only considered in the one of these i.a. studies, and pain not at all.

The final five studies assessed short-term i.a. interventions, delivered one to three times. Four of these studies were in surgical models (rabbit/rat/mouse ACLT), with one in mouse ACLr. Hyaluronan (HA)-binding peptide and micronized porcine urinary bladder reduced medial OARSI score by 30%–50%, but since the interventions were not given until Day 14 (when OA is already established in the mouse ACLT model), these experiments assess their effect on "fast progressing OA" rather than prevention of PTOA. The two studies where treatments were given i.a. at the time of surgery/injury (scaffold and blood in rat ACLT, and HADD-4G/PRP/HADD-4G+PRP in mouse ACLr) were ineffective at preventing degeneration. The final study showed that a single i.a. injection of Avidin-dexamethasone 7 days after surgery in rabbit ACLT reduced OARSI score by 40% and also reduced synovitis and bone score, although effects on pain were not reported.

Despite the major opportunities offered by intervention in PTOA, only three of the preclinical studies reported in 2016–2018 recapitulated the most likely clinical scenario, where a preventative treatment would be administered over a short time at or around the time of acute injury. All but one of these studies was in surgical models of PTOA, where the inflammatory and degenerative effects of sham surgery complicate the interpretation of any protective effects of treatment. Four recent studies published after the systematic PubMed search (Table 3, 2019–2020) exclusively use nonsurgical trauma models where treatment is given at the time of injury either orally (Doxycycline[23] or GKT137831[24]) or as i.a. injection (dexamethasone,[25] 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide [NBQX][26]). Oral doxycycline reduced OARSI score by 30%, improved synovitis by 30%–40% and improved weight-bearing.[23] GKT137831 (Nox4 inhibitor) significantly reduced early bone changes detected by microCT after ACLr.[24] Single i.v. or i.a. injection of dexamethasone did not affect OARSI or bone scores. Two i.a. injections of the glutamate receptor antagonist (RA) NBQX reduced OARSI scores by 50% and bone scores by 75% after ACLr but did not affect end-stage inflammation score or pain.[26]

In summary, these preclinical reports identify promising new therapeutic targets, but comparisons between targets are hampered by variations in reporting and types of outcome measures collected. Reference to ARRIVE guidelines, randomization of treatments, and blinding of investigators to treatments were limited to two studies, whereas eight of the papers do not mention any of these important quality requirements (Tables 1–3). Seven papers considered the effects of treatment in cartilage, bone, and synovium, and only two papers combined this multitissue analysis with indicators of pain (Tables 1–3). Compliance with reporting guidelines and a more holistic approach to the analysis of the effects of interventions is necessary to improve the effective translation of preclinical discovery.

4 | WHY INTERVENE AT THE TIME OF KNEE INJURY?

PTOA represents a significant clinical burden in its own right (c. 12% of all OA cases) but arguably also an unrivaled opportunity for intervention. Unlike more "usual" (nontraumatic) OA where onset is often difficult to define and structural abnormalities often predate symptoms by years,[27] the timing of the joint injury and therefore the initiation of processes in PTOA is known. This means that we can exploit this knowledge in various ways for clinical benefit: to gain a better understanding of the initiating molecular processes and disease pathogenesis, to define prognostic biomarkers, and to identify new therapeutic targets for the disease. In practical terms, as around 50% of individuals develop PTOA after a significant injury,[3] meaningful clinical treatment may benefit from stratification of those at the time of the injury who appear to be at the highest risk of PTOA, focusing early interventions in these individuals to prevent future OA.

TABLE 1 Systemic treatments for PTOA in mice, rats, and rabbits (2016–2018)

Drug	Route	Regime	Model	Assessment	Protection against degeneration	Synovitis score	Bone score	Pain	Reference	ARRIVE	Randomization	Blinding
Rat antimouse IL-6R monoclonal antibody	i.p.	Weekly 0–6 weeks	Mouse DMM	6 weeks	↓ 30% OARSI	↓ 30% OARSI	↓ Osteophyte size	×	Latourte et al.[28]	×	×	×
Stat3 small molecule inhibitor	Oral	Every other day 0–6 weeks	Mouse DMM	6 weeks	↓ 45% OARSI	No effect	↓ Osteophyte size	×	Latourte et al.[28]	×	×	×
Myrtol	Not stated	Daily 0–8 weeks	Mouse ACLr	8 weeks	↓ 25% modified Mankin scores	No effect	↑ density (MicroCT)	×	Duan L et al.[29]	×	✓	×
Guilu Erxian Glue	Oral	Daily 4–8 weeks	Mouse ACLT	8 weeks	↓ 50% OARSI	×	→	→	Chou et al.[30]	×	✓	×
Procyanidins (extracts from pine bark)	Oral	Daily 0–8 weeks	Mouse DMM	8 weeks	↓30–50% OARSI	×	×	×	Wang et al.[31]	×	×	×
Curcumin	Oral	Daily 0–8 weeks	Mouse DMM	8 weeks	↓ 50% medial OARSI	↓ 33% OARSI	→	×	Zhang et al.[32]	×	×	×
LY294002 (PI3K/AKT inhibitor)	i.p.	Daily 0–4 weeks	Mouse DMM	4 weeks	↓ 70% medial OARSI	×	→	×	Lin et al.[33]	×	✓	×
Sivelestat sodium hydrate i.p.	i.p.	Weekly 0–4 weeks	Rat DMM	2/4 weeks	↓50/30% OARSI	×	×	→	Yu et al.[34]	×	✓	×
Olive and grape seed extract diet	Oral	Dietary –4 to 12 weeks	Mouse DMM	8 weeks	↓ ~30% OARSI	×	×	×	Mevel et al.[35]	×	✓	✓
Glucosamine hydrochloride diet	Oral	Dietary –4 to 12 weeks	Mouse DMM	8 weeks	↓ ~30% OARSI	×	×	×		×	✓	✓
Olive and grape seed extract diet	Oral	Dietary –3 to 10 weeks	Rabbit ACLT	10 weeks	↓ ~35% OARSI	×	→	×		×	✓	✓
Glucosamine hydrochloride diet	Oral	Dietary –3 to 10 weeks	Rabbit ACLT	10 weeks	×	×	→	×		×	✓	✓

Abbreviations: ACLr, ACL rupture; ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; OARSI, Osteoarthritis Research Society International; PTOA, post-traumatic osteoarthritis.

TABLE 2 Local treatments for PTOA in mice, rats, and rabbits (2016–2018)

Drug	Route	Regime	Model	Assessment	Degeneration	Synovitis	Bone score	Pain	Reference	ARRIVE	Randomization	Blinding
Repeated treatments												
Curcumin nanoparticles Topical	Topical (vs. topical vehicle)	Daily 0–8 weeks	Mouse DMM	8 weeks	↓ 27% medial OARSI	↓ 33% OARSI	→	→	Zhang et al.[32]	✗	✗	✗
5Z-7 (inhibitor of TGF β-activated kinase 1)	i.a. (vs. i.a. vehicle)	2 per week 0–4 weeks	Rat DMM	4 weeks	↓ 50%–70% medial OARSI	↓ cytokines	✗	✗	Cheng et al.[36]	✗	✓	✗
Kartogenin	i.a. (vs. i.a. saline)	Weekly 1–12 weeks	Rat ACLT	12 weeks	↓ 60% total OARSI	✗	↓ MicroCT	✗	Mohan et al.[37]	✗	✓	✗
FGF-9	i.a. (vs. i.a. vehicle)	2 per week for 2 to 8 or 12 weeks	Mouse DMM	8 weeks or 12 weeks	↓ 20% total OARSI	✗	↑	✗	Zhou et al.[38]	✗	✗	✗
FGF-18	i.a. (vs. i.a. vehicle)	2 per week 0–8 weeks	Rat DMM	8 weeks	↓ 70% total OARSI	✗	✗	✗	Yao et al.[39]	✗	✓	✗
Short-term intra-articular treatments												
Avidin–dexamethasone (0.5mg)	i.a. (vs. i.a. saline)	Day 7	Rabbit ACLT	3 weeks	↑ 40%	→	→	✗	Bajpayee et al.[40]	✗	✗	✓
Scaffold and blood composite	i.a. (vs. untreated ACLT)	Day 0 / Day 14	Rat ACLT	9 weeks	No effect /↓ 30% total OARSI	✗	✗	↓ Weight-bearing differences	Proffen et al.[41]	✓	✓	✓
HA-binding peptide	i.a. (vs. i.a. saline)	Day 14	Mouse ACLT	4 weeks	↓ 50% medial OARSI	✗	✗	↓ Weight-bearing differences	Faust et al.[42]	✗	✗	✓
HYADD® 4-G alone PRP alone or both combined	i.a. (vs. i.a. saline)	Day 0 or Day 0, 28 & 42 1 to 3x	Mouse ACLr	5/56 days	No effect	No effect	No effect	✗	Duan et al.[43]	✗	✗	✓
Micronized porcine urinary bladder matrix	i.a. (vs. i.a. saline)	Day 14	Mouse ACLT	4/8 weeks	↓ 50/30% medial OARSI	✗	✗	↓ Weight-bearing differences	Jacobs et al.[44]	✗	✗	✓

Abbreviations: ACLr, ACL rupture; ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; OARSI, Osteoarthritis Research Society International; PTOA, post-traumatic osteoarthritis.

TABLE 3 Treatments for PTOA in mice, rats, and rabbits reported after the workshop (2019–2020)

Drug	Route	Regime	Model	Assessment	Degeneration	Synovitis	Bone score	Pain	Reference	ARRIVE	Randomization	Blinding
Doxycycline	Oral	Daily 0 to 4 weeks	Mouse ACLr	4 weeks	↓ ~30% OARSI	↓ 30%–40%	×	↓	Zhang et al.[45]	×	×	✓
GKT137831	Oral	Daily 0 to 1 week	Mouse ACLr	7 days	×	×	↓ (MicroCT)	×	Wegner AM et al.[26]	×	×	×
Dexamethasone	i.v.	Day 0	Mouse cyclic tibial compression	2 weeks	No effect	×	No effect	×	Holyoak, D. T., et al.[27]	×	×	×
DEX-loaded PLGA nanoparticles	i.a. (vs. i.a. saline)	Day 0	Mouse cyclic tibial compression	2 weeks	No effect	×	No effect	×		×	×	×
Hydrogel with DEX-loaded PLGA nanoparticles or hydrogel alone.	i.a. (v s.i.a. saline)	Day 0	Mouse cyclic tibial compression	2 weeks	↓ 30% medial OARSI (hydrogel alone)	×	↓ 40% osteophyte size (hydrogel alone)	×		×	×	×
NBQX	i.a. (vs. i.a. vehicle)	Day 0	Mouse ACLr	3 weeks	↓ 30% total OARSI	No effect	↓ 40%	No effect	Bonnet et al.[28]	✓	✓	✓
NBQX	i.a. (v s.i.a. vehicle)	Day 0 & 1	Mouse ACLr	3 weeks	↓ 50% total OARSI	No effect	↓ 75%	No effect		✓	✓	✓

Abbreviations: ACLr, ACL rupture; ACLT, anterior cruciate ligament transection; DEX, Dexamethasone; DMM, destabilization of the medial meniscus; OARSI, Osteoarthritis Research Society International; PLGA, poly(lactic-co-glycolic acid); PTOA, post-traumatic osteoarthritis.

5 | PROGRESS IN INTERNATIONAL CONSENSUS ON THE DESIGN AND CONDUCT OF INTERVENTIONAL TRIALS AFTER KNEE TRAUMA

Current interventions at the time of acute knee injury, including rehabilitation and surgical interventions, such as ligament reconstruction, aim to improve knee pain and instability, and restore function as rapidly as possible. There has been much controversy about the relative benefits and risks of different types and timings of interventions in the posttraumatic period, particularly surgical, and whether certain surgical approaches could in some circumstances exacerbate an injury response or delay recovery.[46–48] Physiotherapy approaches have been reported[49] and exercise intervention trials started (NCT04363476). However, to date, there is a lack of high-quality evidence for the efficacy of any existing interventions that follow the injury reducing an individual's risk of later PTOA.

There is also a lack of guidance or internationally agreed approach on the design and conduct of interventional trials at the time of knee trauma, which seek to prevent PTOA, representing an unmet need. Guidance would need to be appropriate for various different types of interventions, which potentially seek to target different mechanisms, and which might be used either alone or in combination. As well as exercise/rehabilitation and surgical interventions, these could include pharmacological, cellular or biological approaches, or devices and orthotics.

Several current barriers to interventional studies exist in this area. Probably, the biggest is that there is no Food and Drug Administration label for "prevention of (PT)OA". There are few precedents in this area, particularly for clinical trials of investigational medicinal products (CTIMPs) and a lack of academic or pharma funding or activity because of this. Uncertainties span many aspects of trial design: the study population to be included, the timing of intervention, and its appropriate comparator and the use of outcomes, which are both sensitive, reproducible, and feasible.

The lack of guidelines and consensus in this area was identified as a roadblock for those working in clinical translation in PTOA. In collaboration with Versus Arthritis (then Arthritis Research UK, the U.K.'s largest musculoskeletal research charity), an international workshop was convened in London, UK, in November 2016 to outline considerations and research needs around the design and conduct of interventional studies at the time of knee injury. The 32 stakeholders present included clinicians (orthopedic surgeons, rheumatologists, sports and exercise physicians, physiotherapists), pharmaceutical industry representatives, patient representatives, discovery and preclinical scientists, bioengineers, and clinical triallists.

Considerations were to be relevant to all forms of interventional study but not quasi-controlled studies or cohorts. On the day, a systematic literature review and summaries of key areas from leading experts in the field were presented. Workshops and then an iterative process developed considerations in four main areas: eligibility, outcomes (including biomarkers), the definition of injury and timing of intervention, comparator, and multimodality interventions. Knowledge gaps and research needs were also outlined. The output of this exercise is reviewed here; the detailed report has now been published.[50]

The literature review considered all published interventional randomized controlled trials (RCTs) or non-RCT trials. Thirty-seven articles were identified, which included mainly surgical studies of ACLR, patellar dislocation, tibial fracture, and a minority of other injury types. The studies were generally of small size (median category 20–50 participants), of long duration (11 studies of over 5 years), with only a minority of studies stating a priori power calculations and primary outcome. Just 2 of the 37 were classical CTIMPs.

5.1 | Summary of considerations

The application of existing published international guidelines on the conduct of trials in OA was encouraged where possible[51–53] and also the use of existing design and international reporting guidelines such as CONSORT and STROBE.[54,55] Key (or more controversial) points are included below.

5.2 | Study populations

It was felt important to include patients in studies who had a definable structural acute injury and represented common groups with a modifiable process. An example of this was ACL injury with an associated acute meniscal tear. There was an awareness that the inclusion of extreme phenotypes, perhaps those with "inevitable" disease should be avoided, as well as those likely to have degenerative meniscal tear/established OA, as they would confound the outcome. A discussion around an upper age threshold to exclude cases more likely to have OA proposed, including only those age 35 or younger initially in such studies. Since some injuries have a lower risk of future OA than others, stratification was desirable to avoid overtreatment. Ideally, those at the highest risk of OA should be identified, although predictive biomarkers or other algorithms for doing so are currently lacking.

5.3 | Timing of the intervention

An appropriate "window of opportunity" for any given intervention should be defined. This needs to be specific not only to the target, the route, and nature of the treatment but also acceptable and feasible for patients and clinicians. At an early stage of development, smaller experimental medicine studies (with molecular rather than patient-reported outcomes), or feasibility studies of agents should be considered to answer such questions. These should refine and enable study design, and help to triage more robustly likely new targets ahead of larger, more costly "classical" clinical trials. At a more general level, such studies will grow and establish confidence in

optimal study design for any given target. Patients should also be involved at an early stage in the design of studies.

5.4 | Comparator

Interventional studies should always use a carefully designed comparator, placebo, or sham. Surgical placebo was noted as both supported and possible in this area.[56,57] Although multimodality interventions were commonplace in clinical practice, it was felt essential to test and understand the individual effects of interventions before testing multimodality interventions, which was acknowledged as challenging.

5.5 | Outcome measures

One of the known challenges in this area and also in OA as a whole is that "traditional" outcomes such as X-rays are insensitive to change, necessitating large numbers of participants in long studies, which are expensive and unfeasible. There is a need to identify earlier "surrogate" endpoints. To this end, interventional studies and cohort studies should be encouraged to include multiple early measures (biomarkers, alternative imaging outcomes, patient-reported outcome measures [PROMs]) to build knowledge. Assumptions about the relationships and relevance of, for example, PROMs and structural outcomes should be avoided, but rather evidence sought, aiming for sensitive, specific measures of any form, which shorten studies.There should be close liaison with industry and regulators about what is acceptable to them.

5.6 | Translational studies

While the potential for biomarker stratification and for early molecular or imaging-based surrogates of longer-term outcomes in studies was identified, there are none currently with sufficient evidence to support their use. Studies that incorporate longitudinal bio-sample collection (synovial fluid, plasma, serum, DNA, RNA, and tissue) and magnetic resonance imaging (MRI), X-ray, or other experimental imaging were encouraged.

High-quality cohort studies may provide us with a greater understanding of processes and potential novel prognostic markers of outcomes. Two studies identifying associations between synovial fluid markers and outcomes were given. Amano et al. conducted a small study of 26 participants undergoing ACL reconstruction, examining a number of inflammatory response proteins in the synovial fluid at this time. The outcome was T1ρ and T2 values on cartilage MRI, where a higher score correlated with abnormal cartilage integrity. Of note, a "high GAG cluster" was identified (which was associated with lower interleukin (IL)-6, tumor necrosis factor-α, and matrix metalloproteinase 3 than the "inflammation cluster"), which was associated with higher T1ρ/T2 in medial tibial/patellar cartilage.

In another longitudinal cohort study, the knee injury cohort at the Kennedy study, 150 individuals with a variety of clinically significant acute knee injuries were followed over time. Baseline synovial fluid biomarkers were shown to be associated with patient-reported symptoms at the time of injury and also with early clinical outcomes.[13] The markers tested had been selected from a surgically induced mouse model of PTOA. Appropriate use of preclinical animal models represents an opportunity to improve translation in this area.

6 | CLINICAL TRIALS

The only published human trials for the prevention of PTOA to date in man have focused on anti-inflammatory treatments: primarily dexamethasone and anakinra, and IL-1 RA. The first was a proof of concept RCT using i.a. anakinra in just 11 subjects[58] (NCT00332254). The second RCT was in adolescent/pediatric cases with an ACL injury, with short-term patient-reported outcomes and biomarkers collected after i.a. dexamethasone or placebo.[59] The evidence review to identify interventional studies with specific reference to PTOA of the knee[50] identified a deficiency in this area with only five pharmacologic trials of any nature for treating ACL rupture (MSCs + HA vs. HA; IL-1RA vs. saline; IL-1 inhibitor vs. placebo, femoral nerve block + ACL reconstruction vs. ACL reconstruction; oral glucosamine for acute knee injury).

There has been recent concern that several biologically active or cellular therapies are gaining credence for use at the time of knee injury and for other indications without sufficient testing in an RCT setting or formal licensing, with the hope that they may prevent OA. Minimum reporting standards for therapies, such as stem cells and platelet rich plasma (PRP), have since been published.

Anakinra (IL-1RA) has progressed to Phase 1/2 trials for the prevention of injury-induced OA after ACL rupture (ClinicalTrials.gov: NCT02930122, NCT03968913), whereas dexamethasone (ClinicalTrials.gov: NCT02318433) has completed a Phase 1 trial for this indication in radiocarpal injury (data not yet published).

The evidence from animals to support these targets is of interest. IL-1RA given as a single i.a. injection reduced degeneration and inflammation after mouse tibial fracture,[60,61] and this effect was enhanced using sustained i.a. release.[62,63] However, a recent systematic review on the use of corticosteroids in vivo at the time of injury[64] revealed that methylprednisolone appeared to be degenerative in an equine exercise model, while it was protective in a canine model where the ACL was sectioned. In healthy rabbits, prednisolone acetate was found to be detrimental, while after surgical drill injury, dexamethasone (i.a. 0.5 mg/kg) was protective if given every 3 days for 3 weeks[65] or at the time of drill injury[66] but was not protective when given 7 days post-ACLT.[40] Recent reports show that Avidin-dexamethasone 7 days after surgery in rabbit ACLT reduced OARSI score by 40%, and also reduced synovitis and bone score,[40] but that dexamethasone was ineffective in a mouse tibial compression model.[25]

7 | CHALLENGES AND OPPORTUNITIES

7.1 | Translation

This review highlights some promising potential therapies for the prevention of PTOA, but also some challenges while interpreting the literature. All but one of the reported studies on PTOA between 2016 and 2018 were performed in surgical models of OA, with different intervention times, routes of administration, and start and endpoints. There is a need to ensure that the animal model and intervention regime matches the potential clinical application. The majority of studies did not clearly state effect sizes and did not measure all clinically relevant outcomes (degeneration, synovitis, bone score, and pain). More recently, nonsurgical PTOA models offer new opportunities to delineate the relationship between inflammatory and mechanical drivers of pathology. However, the use of such noninvasive models in testing the efficacy of interventions to prevent PTOA has been limited.

To translate this preclinical work effectively, it is essential that the methods for assessing the efficacy of each drug are consistent and that the way in which the drug is tested is applicable to the ultimate clinical application. As noted by others, universal adoption of experimental design and execution (DEPART) and reporting (ARRIVE) guidelines are needed to ensure that study quality is high, design aspects transparent, and bias is not unwittingly introduced. The reporting of power calculations, effect sizes, and confidence intervals using standard scoring systems and the preregistration of all preclinical studies to facilitate the reporting of negative results would accelerate the prioritization of new potential therapies for the prevention of PTOA.

7.2 | Clinical

The knee-injury "model" of OA in humans is a highly attractive model for PTOA research: acute knee trauma is common and relevant injuries well-defined and the onset of PTOA of the knee is relatively rapid. The extent of injury necessary to "cause" OA and the relative importance of different types of injury could be better understood. There are accepted imaging protocols and scoring systems for MRI of this joint in the context of injury and knee X-ray outcomes (albeit with its limitations, discussed elsewhere). The synovial fluid analysis provides a window on the joint at this time and is relatively straight forward in large joints such as the knee. Assessment of the presence of hemarthrosis is also possible via this invasive monitoring, which may represent an important prognostic factor at the time of joint injury.[67] Following those at the time of knee injury thus offers a unique opportunity to prevent joint degeneration by measuring and modulating molecular and structural events arising from the trauma.[12,13]

However, there are also important hurdles in the field of PTOA research of the knee. These include challenges in designing longitudinal cohort studies and clinical trials given the large heterogeneity of patients with knee injuries and the current long follow-up time needed for observing OA development (even if PTOA may develop more rapidly than other forms of OA). In addition, following the earliest disease processes has traditionally involved expensive, time-consuming imaging methods, such as MRI, which limits feasibility. There are also further challenges in monitoring and characterizing the often subtle changes in the joint over time and in interpreting which changes may be part of the disease process as opposed to what may be considered "normal response to injury" or "normal aging" of the joint, that is, not necessarily related to symptoms or disease.[68] Furthermore, it may be hard to determine whether disease-related changes in the posttraumatic joint are in fact attributable to the injury, especially in the presence of other OA risk factors in an individual. Having sufficient numbers to allow the consideration of all other relevant clinical and demographic factors in individual outcomes in analyses is essential.

8 | CONCLUSIONS

In contrast to many other risk factors for OA, such as age, obesity, and genetic factors, the risk posed by joint trauma is relatively well-defined and usually easy to pinpoint in time, offering a unique opportunity for understanding the early mechanisms of OA. The first considerations for interventional trials in this area were published in 2019[50] and provide much-needed foundations for work on future guidelines to progress this field. The key to achieving a breakthrough in this field is arguably cross-disciplinary research involving epidemiologists, orthopedic surgeons, biomechanical experts, molecular scientists, rheumatologists, physiotherapists, pharmacologists, radiologists, and other medical imaging experts, to achieve a comprehensive understanding of the etiology and pathogenesis of PTOA relevant to a successful translation. It is imperative that we work closely with patients, regulatory bodies, and the pharmaceutical industry to reach these goals. Preclinical models in this area should fuel translational and experimental medicine research in this area. Research testing interventions in models should report effects on all joint tissues and comply with the highest conduct and reporting standards. Despite the challenges, there remains a real opportunity: the prevention of OA at the time of joint trauma, which may bring about much-needed traction in the treatment of OA as a whole.

ORCID

Deborah Mason https://orcid.org/0000-0003-4926-3365

Fiona E. Watt https://orcid.org/0000-0002-6066-7590

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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