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Review

What constitutes an "animal model of osteoarthritis" – the need for consensus?

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SUMMARY

Objective: To review the use of animal models of osteoarthritis (OA) with regard to their utility for investigation of the mechanisms and regulation of structural pathology and pain.
Methods: PubMed searches were conducted using separate clusters of terms to retrieve articles on (i) models of structural joint damage in genetically-modified (GM) mice, and (ii) models of OA joint pain. The papers were reviewed to investigate whether there was evidence that the research outcome was dependent on the model used.
Results: Out of a total of 109 separate GM mice strains identified in which an effect on OA was reported, 15 had been studied using more than one arthritis model. In 10/15 the same effect of the GM on arthritis was reported in at least two different models. In 5/15 the effect of the GM on arthritis structural pathology was different, and sometimes opposite, when comparing two or more induction methods. A total of 112 publications were retrieved in which pain/disability was examined in a model suggested to represent OA. The induction methods used most commonly to study "OA pain" were distinct from those most often used to investigate the pathophysiology and regulation of structural joint damage. Four papers directly comparing pain mechanisms in different models were identified, with 3/4 describing differences in nociceptive pathways.
Conclusions: The available data indicates that the molecular mechanisms of both joint structural damage and pain may be distinct in animal models of OA induced or initiated by different means. This suggests the need to continue using multiple OA animal models but that the subsequent interpretation of the data and its extrapolation to the human condition must be more precise.

Animal models and the ARRIVE guidelines

Animal models are extraordinarily powerful research tools for studying the pathogenesis and potential therapeutic intervention of many different diseases. They provide a key step not only in the knowledge development pathway but also contribute significantly to the "translatability" of drug discovery projects toward clinical realization[1–3]. It is scientifically incumbent upon us as researchers to do everything possible to make certain that our experiments are well designed, controlled, powered, analyzed and reported. In the case of research involving animal models, this is true not only from the perspective of good scientific practice but also to fulfill our responsibility for the appropriate and ethical use of animals i.e., implementing the "3Rs" (**R**educe the number of animals used, **R**efine the procedures and protocols to minimize suffering and maximize the value of the outcomes, and where possible **R**eplace animal studies with an alternative approach). A critical component of "reduction and refinement" in any animal experiment is ensuring that such studies are appropriately planned, evaluated, and reported. Poor reporting is as problematic as poor experimental design in diminishing the value and validity of any scientific research. Recent reviews have highlighted the deficiencies in reporting in many studies using animal models for a variety of diseases, and those for osteoarthritis (OA) are no exception[4–6].

In this edition of Osteoarthritis and Cartilage, the ARRIVE guidelines[4] have been re-published. These guidelines were developed to provide a comprehensive checklist for authors to follow to ensure appropriate reporting of any research using animals, and their use is now a recommendation for submission of such manuscripts to OA&C. While broadly applicable to all animal-based studies, the importance of the ARRIVE guidelines as they

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specifically relate to OA research has been eloquently discussed in the accompanying editorial (Ref OAC6571 – to be inserted once finalized). In the long term, use of these guidelines will promote more consistent publication of OA animal studies, ultimately enabling better comparisons between laboratories and systematic reviews of the literature. Although the emphasis is on "reporting", the ARRIVE and other guidelines[5,6], along with Dr Percie du Sert's editorial, should be consulted BEFORE embarking on a study using animals, not just afterward while writing the manuscript. Considering the checklist items while designing the study will enable researchers to control for factors that can significantly alter the experimental outcomes, and hamper or even invalidate the interpretation of the data.

OA – one disease or many?

One of the many items covered in the ARRIVE guidelines is justification for choosing, and recognizing/discussing the limitations of the particular animal model used (guideline items 3b and 18b). The best designed, controlled, and reported study will be scientifically and ethically flawed if the model used does not in fact "do what it says on the label" and model the disease in question. In the case of OA animal models this issue can be particularly vexing. The variety of OA animal models available has previously been reviewed[7–9], and revealed over 20 different induction methods (e.g., spontaneous, surgical, chemical, etc.) in 10 different species of varying strain, age, and gender. Clearly interpreting the data arising from such a diverse experimental background is a daunting task, and will not ultimately be amenable to meta-analysis no matter how consistently and well reported. This would not be the case if one or a much more limited number of OA animal models were routinely used across all laboratories. To date no ideal OA animal model has been described, and the question might be "*whether a single* (*or even limited number of*) *superior OA animal model*(*s*) *exists, and indeed whether it should?*" OA in humans and other species may not be a single disease but rather a syndrome with a characteristic pattern of clinical signs (pain, disability) and pathological changes in joint tissues (typically including cartilage erosion, thickened subchondral bone of reduced mineral density, excessive marginal new bone (osteophytes), synovitis and joint capsule thickening/fibrosis). There is an emerging idea that the syndrome of OA is actually a collection of different disease subtypes, stratified amongst other things by the degree of pathology in different tissues, the rate of progression, the severity of symptoms, the initiating cause(s), the gender of the patient and even the particular joint affected, but all with a similar final clinicopathological endpoint[10].

Stratification such as described above, is only important if it has clinical relevance, being predicated on the hypothesis that the molecular pathogenesis of OA joint damage and its clinical symptomology may be different for each sub-type. This then would lead to the premise that the therapeutic approach for disease modification and/or symptom management may be "OA sub-type specific", and in part could explain the failure rate of human therapeutic clinical trails for OA that have generally approached the disease as a single entity. The alternative hypothesis would be that, at least at some therapeutically applicable stage of disease prior to irrevocable damage, common structural pathology and/or pain pathways come into play irrespective of disease sub-type. This then would suggest that a limited number of therapies would be broadly applicable to structural and clinical disease modification in all/most OA patients. While vital to consider for management of the patient, these two paradigms also have very important implications with respect to the current discussion of appropriate OA animal models. The disease stratification concept supports the need to use many/multiple OA sub-type models with subsequent cautious and precise interpretation of the data, and translation to specific subpopulations of human OA patients. This might perhaps also argue the need for including a prefix to define the particular "OA" being studied, such as early-, late-, post-traumatic-, age-associated-, inflammatory-, cartilage-erosive-, osteophytic-, etc. On the other hand, the second paradigm would suggest we either strive for a reduced number or even single animal model of OA to facilitate meta-analysis, or equally that it does not matter how many models exist and are used, as all would provide information that is globally applicable. Interestingly, both arguments are used in the OA research community and literature when it comes to either defending use of a particular animal model or explaining the lack of efficacy and translation of a given therapeutic from animals to humans. When considering the ARRIVE guidelines and justifying the choice of OA animal model used in an experiment, what arguments can be made for either of the above approaches?

Genetically-modified (GM) mice and models for studying OA structural change

As noted earlier, OA models have been induced by many methods in a variety of animal species, and the pros and cons of these have previously been reviewed[7–9]. It is clear that a huge amount of valuable information on OA pathogenesis and treatment has been gained from the different models and species. For the purposes of the current discussion we have focused on different OA induction methods in mice, not because this is necessarily the best species, indeed there are some significant disadvantages with the mouse[9]. Rather we have restricted this analysis to mice because this species offers the potential to use GM animals, an approach that has had and continues to have, an enormous impact on our understanding of the molecular mechanisms of OA initiation and progression. We previously reviewed the literature on the use of GM mice in OA research to investigate whether cartilage was a suitable therapeutic target to treat global joint pathology[11]. While the particular OA model/induction method used in the various mice was noted in this previous study, they were all considered equally. Thus in one strain the reported effect may have been in spontaneous "age-associated-OA", while in another it was instability induced by intra-articular collagenase injection, and in a third "post-traumatic-OA" following a particular surgical strategy to alter joint biomechanics. In the light of the present discussion, we searched PubMed using the same terms as previously ("mouse/mice/murine" and "OA"), and determined if there was any data comparing the outcome of a given GM using different models that might mimic different OA sub-types. A total of 953 papers were retrieved (November 22, 2011), which on further review yielded reports on 109 separate GM mice in which an effect on OA was reported. In only 15 of these 109 GM strains of mice was the effect on more than one arthritis model reported. In 10 of the GM mice the same outcome (i.e. significantly increased or decreased cartilage erosion) was reported in at least two different models, most commonly surgically-induced post-traumatic- and spontaneous age-associated-OA (Table I). The findings in Table I support the idea of a common molecular pathology irrespective of the initiating cause of OA. Interestingly however, there were five GM mouse strains in which different, indeed sometimes completely opposite effects were reported depending on the model used (Table II). The comparison of OA models were not always done in the one laboratory or described in the one paper, which could contribute to differences observed. However, direct comparison of at least two models was reported either in the one paper or by the one research group, for *Spp1*$^{-/-}$, *Frzb*$^{-/-}$, *Il6*$^{-/-}$ and *S100a9*$^{-/-}$. Divergent effects of the same GM on different models of OA (e.g., *Il6*$^{-/-}$ *increases*

Table I
GM mice in which the same effect on OA-like articular cartilage (AC) damage was reported irrespective of the model. Where indicated changes in other joint tissues such as subchondral bone (SC bone), osteophytes or synovium/joint capsule were also described

Gene/mutation	Notes	References
Matrix proteins		
Tnc$^{-/-}$	Increased aaOA AC damage Increased ptOA (ACLT/MCLT) AC damage	[34]
Matrix degrading enzymes, enzyme inhibitors & enzyme cleavage sites in substrates		
*Adamts5*Δ*cat* (catalytically inactive)	Decreased ptOA (DMM) AC damage Decreased AIA AC damage (no change in synovial inflammation)	[35–40]
Jaffa (aggrecan ADAMTS-site mutation)	Decreased ptOA (DMM) AC damage Decreased AIA AC damage (no change in synovial inflammation)	[41]
Sulf1$^{-/-}$	Increased aaOA AC damage Increased ptOA (DMM) AC damage	[42]
Sulf2$^{-/-}$	Increased aaOA AC damage Increased ptOA (DMM) AC damage	[42]
Growth factors, cytokines, effector molecules & their receptors and converting enzymes		
Cd59a$^{-/-}$	Increased ptOA (DMM and MM) AC damage and synovitis Increased aaOA AC damage and synovitis	[43] [44]
Fgf2$^{-/-}$	Increased aaOA AC damage Increased ptOA (DMM) AC damage	
Tnfrsf11b$^{+/-}$ (osteoprotegerin)	Increased aaOA AC damage Increased ptOA (TMCL/MM) AC damage	[45]
Cellular proteins & transcription factors		
Epas1$^{+/-}$	Decreased ptOA (DMM) AC damage; (no change in subchondral bone) Decreased ciOA AC damage	[46]
MicroRNA		
miR-140$^{-/-}$	Increased aaOA AC damage (and PG loss) Increased ptOA (DMM) AC damage (and PG loss)	[47]

OA MODELS: (1) Spontaneous – age-associated-OA (aaOA); considered age-associated if a progressive worsening of disease with age was reported. (2) Surgical instability – post-traumatic-OA (ptOA): various methods (DMM = surgical destabilization of the medial meniscus; MM = medial meniscectomy; TMCL/MM = transection of the medial collateral ligament and partial or complete medial meniscectomy; ACLT/MCLT – anterior cruciate and medial collateral ligament transection; MULTI = transection of anterior and posterior cruciate ligaments, medial and lateral collateral ligaments and medial and lateral meniscectomy). (3) Collagenase-induced instability – collagenase-induced arthritis (ciOA). (4) Post-inflammatory arthropathies; AIA = antigen-induced arthritis; only included if compared with 1, 2, or 3 above.

age-associated-OA but *decreases* post-traumatic-OA in male mice) suggest that the stratification of at least some sub-types of OA associated perhaps by age at the time of joint insult, or the degree of inflammation or joint instability, may be important. Furthermore this data demonstrates that the molecular mechanisms regulating cartilage damage and therefore its potential treatment, may be different in sub-types of OA.

Models for studying OA symptomology

The key *clinical* feature of OA is joint pain and disability, and the prevailing paradigm is that OA becomes a clinical syndrome when there is sufficient joint damage to cause pain and impairment of function. However, the relationship between pathology in different joint tissues and existing, incident and progressive OA pain in

Table II
GM mice in which *a different effect* on OA-like AC damage was reported depending on the model. Where indicated changes in other joint tissues such as subchondral bone (SC bone), osteophytes or synovium/joint capsule were also described

Gene/mutation	Notes	References
Matrix proteins		
Spp1$^{-/-}$ (osteopontin)	No change aaOA AC damage (but increased PG loss, SC-bone density, decreased chondrocytes) Increased ptOA (TMCL/MM) AC damage (but NO change PG loss, decreased chondrocytes)	[48]
Matrix degrading enzymes, enzyme inhibitors & enzyme cleavage sites in substrates		
Mmp3$^{-/-}$	Decreased aaOA AC damage Decreased ciOA AC damage (and synovial macrophages) No change ptOA (DMM) AC damage	[49] [50]
Growth factors, cytokines, effector molecules & their receptors and converting enzymes		
Frzb$^{-/-}$	No change aaOA AC damage (or SC-bone but increased diaphyseal BMD) Increased ciOA AC PG loss	[51]
Il6$^{-/-}$	Increased aaOA AC damage (and SC-bone sclerosis but decreased joint BMD; no change AC PG; male only) No change ciOA AC damage Decreased ptOA (DMM) AC damage	[52] [53]
Cellular proteins & transcription factors		
S100a9$^{-/-}$	No change ptOA (DMM) AC damage Decreased ciOA AC damage Decreased AIA AC damage (and synovial inflammation)	[54] [55]

OA MODELS: (1) Spontaneous – age-associated-OA (aaOA); considered age-associated if a progressive worsening of disease with age was reported. (2) Surgical instability – post-traumatic-OA (ptOA): various methods (DMM = surgical destabilization of the medial meniscus; MM = medial meniscectomy; TMCL/MM = transection of the medial collateral ligament and partial or complete medial meniscectomy; ACLT/MCLT – anterior cruciate and medial collateral ligament transection; MULTI = transection of anterior and posterior cruciate ligaments, medial and lateral collateral ligaments and medial and lateral meniscectomy). (3) Collagenase-induced instability – collagenase-induced arthritis (ciOA). (4) Post-inflammatory arthropathies; AIA = antigen-induced arthritis; only included if compared with 1, 2, or 3 above.

humans, at least in the knee, is not entirely clear[12–20]. The conflicting data on the source and regulation of OA pain may be due to peripheral and central sensitization or adaptation/tolerance, and changes in the molecular mechanisms and tissues contributing to pain at different stages of disease. The complex temporal and tissue interactions mean that pre-clinical study of the causes as well as local and systemic regulation of pain in OA relies almost exclusively on *in vivo* studies. Despite this, the questions surrounding the most appropriate and valid animal models for OA pain study are as unclear as those described for investigation of joint tissue destruction pathways. The data in GM mice presented above, supports the concept of distinct sub-types of OA disease and therefore OA model-stratification for at least some aspects of joint structural damage. Whether the same is true for studying the mechanisms of OA pain has not been established.

We undertook a literature search in PubMed using the key words/phrases "animal model/models" and "OA" and "pain" (November 25, 2011). This search retrieved 209 publications, and a review of these papers revealed 112 in which some aspect of pain/disability was examined in a model purported to represent OA. In these papers 18 different arthritis induction methods were used and a total of nine different species were examined (Table III). A variety of outcome measures of "OA pain" were used including changes in: spontaneous locomotor (and other) activities, gait, limb loading, locomotor endurance, grip strength, ipsi- and contra-lateral mechanical allodynia and mechanical and thermal hyperalgesia, and spontaneous and evoked joint afferent nerve activity. In some studies only a single pain outcome was evaluated while in others up to five different pain measures were used. In many of these studies changes in pain outcomes were measured longitudinally and also before and after administration of various analgesics and/or inhibitors of endogenous opioids.

It is noteworthy that the animal models used most commonly to study "OA pain" were distinct from those most often used to investigate the pathophysiology and regulation of structural joint damage (e.g., Tables I and II). In the latter it is generally accepted that the model should reflect both the global joint tissue pathology seen in human OA, AND that the induction method has some physiological relevance to naturally-occurring initiating events or risk factors such as aging, obesity and joint injury[7–9]. In the reports of OA pain research in contrast, there was an over representation of studies using intra-articular injection of monoiodoacetate (MIA), with 50% of all studies using this model. MIA inhibits the glycolytic pathway causing rapid widespread chondrocyte death, extensive neovascularization and invasion of the deep cartilage layers, subchondral bone necrosis and collapse, as well as profound and prolonged inflammation[21,22]. The initiating event and many of the pathology changes are not typical of OA, and recent studies have highlighted the differences in the cartilage transcriptome between MIA-induced arthritis and human OA[23]. A further 17% of the papers use other induction methods that also induce joint pathology that would not be widely accepted as typical of OA, largely inducing an acute inflammatory arthropathy (e.g., intra-articular injection of carrageenan/kaolin, Freund's adjuvant or sodium urate). Only a minority of the publications retrieved used models generally accepted to broadly mimic human OA: 25% used surgically-induced instability models, one paper evaluated pain in the collagenase-induced instability model, three papers examined age-associated-OA and only one obesity-induced OA.

It appears there is a significant disconnect in the animal models used to study structural versus symptomatic aspects of OA, indeed separate models are sometimes used in the one publication[24]. The question is whether this separation of animal models to study

Table III
Animal models used to study the pain of OA

Animal Model	Species	Outcome measures
Spontaneous		
Age associated	Guinea pig	Mechanosensitivity (EP)
Obesity	Mouse	Grip strength meter, motor coordination (rotarod), gait analysis, spontaneous locomotor activity
Intra-articular injection		
MIA	Rat, Mouse	Grip strength meter, thermal hyperalgesia, mechanical hyperalgesia, HL weight distribution (incapacitance), mechanical allodynia (VF), mechanosensitivity (EP), gait analysis (CatWalk)
Na Urate	Cat, Parrot	Weight distribution, subjective pain scores
AIA	Mouse, Rat	HL weight distribution (incapacitance), mechanical allodynia (VF), 1° mechanical hyperalgesia (PAM), 2° mechanical hyperalgesia (DPA), range of motion (VRA), gait analysis
Adjuvant	Rabbit, Rat	HL weight distribution; Mechanical hyperalgesia (VF)
Carrageenan/Kaolin	Mouse, Guinea pig, Rat	Thermal hyperalgesia (Hargreaves & hotplate)
Instability (surgical)		
ACLT	Rat, Dog, Rabbit	Gait analysis
MCLT	Rat	HL weight distribution (incapacitance)
MMT, MM (unilateral)	Rat, Sheep	HL weight distribution (incapacitance), mechanical allodynia (VF)
MM (bilateral)	Sheep	Ground reaction force
MM (partial)	Rabbit, Rat, Mouse	HL weight distribution (incapacitance), tactile allodynia (VF)
DMM	Mouse	HL weight distribution (incapacitance), mechanical allodynia (VF), thermal hyperalgesia, locomotor activity (LABORAS)
IA OC fragment	Horse	Clinical observation of lameness
ACLT & partial MM	Rat, Guinea pig	Gait analysis (CatWalk), mechanical allodynia (VF)
ACLT/MMT/MCLT	Rat	Rotarod
MCLT & MMT	Rat	Mechanical allodynia (VF), thermal hyperalgesia (Hargreaves apparatus), HL weight distribution (incapacitance), mechanical hyperalgesia (paw pressure device)
Instabilty (enzymatic)		
Collagenase	Mouse	Visual gait analysis (treadmill), joint tenderness (palpometer)
Genetic modification		
IL1B over expression	Rat	Thermal hyperalgesia, mechanical allodynia (VF), gait analysis (Catwalk), foot printing, HL weight distribution, treadmill
Col9a1 (−/−)	Mouse	Motor coordination (rotarod), gait analysis, mechanical allodynia (VF), thermal hyperalgesia (hotplate, tail flick), grip strength

Key: HL = hind limb, VF = Von frey filaments, EP = electrophysiological recordings from knee joint afferents, PAM = pressure application measurement device, ROM = range of motion analysis, VRA = videoradiographic analysis, DPA = dynamic plantar aesthesiometer (automated VF), LABORAS = laboratory animal behavior observation registration and analysis system, MIA = monoiodoacetate induced arthritis, ACLT = anterior cruciate ligament transection, MCLT = medial collateral ligament transection, MMT = medial meniscal transection, MM = medial meniscectomy, DMM = destabilization of the medial meniscus, IA OC fragment = intra-articular osteochondral fragment.

OA structure and pain matters? The answer likely depends on whether the mechanisms and importantly pharmacological control of pain are similar in all models of chronic joint disease, or whether the distinct temporal pattern of structural damage in early and progressive OA drives particular pain mechanisms. Recent studies of post-traumatic-OA in mice using multiple outcome measures suggest that in this sub-type of OA there are quite distinct phases of inflammatory and non-inflammatory pain, and accompanying changes in dorsal root ganglia (DRG) gene expression, sensitization and endogenous opioid driven adaptation[25–27]. Comparison of different OA models in GM mice suggested there may be distinct molecular mechanisms regulating cartilage erosion dependent on the sub-type of disease (Table II). We found very few studies in which pain outcomes in different arthritis models were directly compared[28–31]. All four of these studies were done in rats, two comparing MIA-induced arthritis with a post-traumatic surgical model, and two MIA versus intra-articular Freund's adjuvant injection. Differences were noted between MIA and adjuvant in terms of response to specific analgesic therapies (TRPA1 receptor antagonist, diclofenac). When comparing MIA- and surgically-induced arthritis, one study reported similar changes in DRG gene expression although comparative pain outcomes were not reported[29], while the other found differences between the two models for alteration in gait, mechanical allodynia, and concentration of substance P in the DRG[28]. This small cohort of comparative studies tends to suggest there are distinct nociceptive mechanisms in different models of joint disease, and argues for use of more appropriate models in OA pain research.

Conclusions and a call for consensus

Attempts are being made to standardize pre-clinical OA studies particularly those that use animal models. OARSI recently published guidelines for histological evaluation of OA models in a variety of species[32], which will hopefully enhance cross-publication and cross-laboratory comparisons. The re-publication of the ARRIVE guidelines in this journal is a further step toward the same goals, by promoting better uniformity in the factors controlled and reported in OA animal model research. In the present review we have tried to address the question of whether more widespread use of a reduced number of specific OA animal models might also be possible and facilitate research outcomes. The available data suggests that the molecular mechanism of both joint structural damage and pain may well be distinct in OA induced or initiated by different means. This then argues the need to continue using and studying multiple OA animal models rather than pursuing a single "ideal" but also that the subsequent interpretation of the data and its extrapolation to the human condition must be more precise. As noted earlier, it may be helpful to more formally classify the possible sub-type of OA that is being modeled. In some cases, particular arthritis models should perhaps not use the term "OA" at all if this cannot be justified based on pathophysiological relevance to a naturally-occurring human condition. We would suggest based on available evidence, that there should be better convergence of the models used to investigate structural OA pathology and those for pain. That a given arthritis model induces more robust and easily studied pain outcomes should *not* be an argument for its continued use and then extrapolation of the findings to "OA pain", rather it is a reason to improve the methods for measuring pain so that these can be reliably used in a more physiologically relevant OA model.

In spite of the above recommendations there remains a vast array of animal models of OA to choose from, with selection of one over another being driven more by convenience or past experience than merit. Even within a particular OA sub-type e.g., surgically-induced post-traumatic-OA, there may be multiple available models with little data to indicate whether or not they are directly comparable for pain and structural disease outcomes. This has obvious implications for advancing scientific understanding of OA and defining new therapeutics but also the relative "strength" of the animal model data feeds directly into metrics that may be used by industry or possibly funding bodies in making decisions to continue particular research or drug development programs[1–3]. The Canadian Arthritis Network[33] and Arthritis Research UK (in press) have held workshops on pre-clinical OA animal models providing very useful discussion on their merits and limitations. In the drive for better standardization and research outcomes, we suggest there is now a clear need for guidelines on OA animal models, similar to those that have been developed for histopathology and reporting/publication. In order to facilitate this, we are initiating a Delphi process to collect and distil the knowledge from an international group of experts with the aim to produce a consensus document on OA animal models. An initial series of "yes/no" questions on what factors are considered important in an ideal OA animal model will be developed through a repeated opinion feed back process. The final agreed questions will then be used to rate all existing OA animal models and the results published, hopefully to improve not only standardization but also research outcomes and translation. Invitations to participate in this process will be sent in 2012, and those interested in potentially taking part are invited to contact Dr Chris Little.

Author contributions

Both authors were involved in collecting data, reviewing the literature and drafting the article or revising it critically for important intellectual content, and both authors approved the final version to be published.

Conflict of interest

Dr Little provides consulting services on pre-clinical animal models of OA to both Universities and pharmaceutical companies. No funding was received with respect to the writing or publication of this manuscript. Dr Little is an Associate Editor of Osteoarthritis and Cartilage.

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