Recommendations for the use of preclinical models in the study and treatment of osteoarthritis

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Introduction

Osteoarthritis (OA) is a heterogeneous condition in that a variety of causes result in a common pathogenesis. This involves not only articular cartilage, but the whole joint including subchondral bone, ligaments, muscles, menisci, synovium, the capsule and joint fluid. Primary, or so-called idiopathic, OA is slowly progressing and is the most common form of OA and increases in prevalence and severity as humans and animals age. Often OA develops from a focal lesion, which can be generated traumatically in animals and humans. Post-traumatic OA may develop more rapidly and can be reproduced by mechanical insult and surgically by creating joint instability.

The analysis of animal models of OA traditionally depends on histological assessment of articular cartilage. But there are many other important analyses that are used in characterizing human disease including imaging, biomarkers and symptomatic measurements. Although there are no DMOADs (disease-modifying osteoarthritis drugs) currently available for human use, there are drugs that have been shown to be disease modifying in animals such as diacerhein, matrix metalloproteinase inhibitors, an IL-1-convertase inhibitor, a cathepsin-K inhibitor, and salmon calcitonin.

This conference was held to reach a better understanding and a consensus of how best we can monitor and treat OA in a preclinical setting. Many experts described the principal models presently in use to reproduce OA experimentally. They have been described in detail and debated as to which are appropriate and for what and how should they be analyzed. These discussions and presentations have been summarized and in most cases are...
available on demand by contacting the Canadian Arthritis Network office at 1-416-586-4770 or can@arthritisnetwork.ca. The discussions in the breakout sessions of this conference have also been recorded and edited for clarity and are also included in this web presentation.

In this paper, as in our discussions at the conference, we have always been guided by reference to the human disease. This is because our studies of experimental and natural OA in animals must be conducted in such a fashion that they meaningfully guide us in our understanding and treatment of human OA, as well as in the veterinary care of animals. It is obvious that, wherever possible, common tools and technologies should be used in preclinical and clinical investigations.

We have attempted to summarize our discussions, although these were often inconclusive as a result of diverse opinions from over 160 participants. Hence, this is a guidance document representing work(s) in progress. It is not intended to provide definitive direction since there exists differences of opinion. But there was often a welcome general agreement on many aspects of this challenging research. We sincerely hope that our colleagues will find this document, and the collective information originating from this rare meeting of the minds in this challenging field, of value in determining how to better care for this all too common debilitating condition, which creates so much suffering in humans and animals.

Here we present what we feel is a reasonable consensus of the participants’ views.

**Animal models**

**Animal models and human OA**

Much more work on human OA is essential to understand animal models better: the opposite also applies. Hence, preclinical and clinical studies can and should be conducted in parallel. There are many animal models that reproduce key aspects of human OA in terms of natural history, mechanisms, signs and symptoms. Yet, as not one animal model completely reproduces the signs and symptoms of human OA, we must remain mindful to use the most appropriate model to answer our scientific questions. Nevertheless, animal models are essential for addressing safety and efficacy of various drugs and therapies because, at present, we lack human therapeutic interventions that are structurally modifying and are known to effectively control pain and symptoms. Symptomatic aspects of human OA must, in future, be well characterized in animal models.

Conference presentations confirmed that many good animal models of OA exist, but also revealed that we must be more critical as to what they tell us. In particular, there appear to be opportunities and a mandate to develop new models to better model the patient’s clinical experience. Here we need input from patients/consumers to help us examine, for example, structure/symptom relationships in our models. Biomechanical studies are also essential since the complex structures of joint tissues, such as articular cartilage, determine the special mechanical properties and hence functions of these tissues. The functional biomechanical properties of a tissue, therefore, best reflect the complexity of fundamental structural changes.

The genetic components of human OA are difficult to model at present since information is limited. Genetic differences may manifest not just structurally but also behaviourally. Remember that genetics is a research tool. One of the most promising applications of these tools and principles is in genomic breeding studies of dogs predisposed and resistant to developing arthritis secondary to congenital hip dysplasia.

Concerning the use of animals and those in veterinary practice we should always remember that animals are stakeholders and not just research tools. End points used in clinical veterinary practice may help us when evaluating success of human therapeutic trials. Some of the treatments/surgeries used in veterinary practice replicate the human situation. The Food and Drug Administration may wish to consider developing an OA guidance document for both human and veterinary medicine.

**Ages of animals and disease severity**

OA is a disease of adults, and growing animals, like children, seem to have a better capacity at managing joint damage. Moreover, in controlled experiments, the complexities of changing skeletal size and metabolism during growth can obscure how joints respond to injury and therapy. Thus, to obtain the most meaningful insights into human OA, it is essential to use skeletally mature animals whenever possible. The following minimum ages were proposed for the different species:

- In rats and mice, it is noteworthy that not all growth plates normally close completely. In rats and mice at the ages noted above, longitudinal long bone growth has ceased, though the potential for long bone growth still exists. In such species, scientists should be mindful of treatments that might reactivate senescent growth plates. Genetically modified mice should ordinarily be studied at 9–12 months when natural OA lesions start to appear in wild type mice.
- In working with animals, we must remember the differences to humans. For example, adult human articular cartilage has a cell density one tenth of that in adult rabbits and of intermediate value in dogs. Yet the total number of cells beneath one square millimeter of cartilage surface are remarkably similar between humans and rabbits. Hence, we need to be mindful of various tissue differences between species.

Animal models of OA have a wide range of severity and rate of progression of pathogenic changes. Naturally occurring models (e.g., Dunkin-Hartley guinea pig, C57Bl/6 mice) develop over a much longer period of the animal’s life. Some models exhibit rapid and severe structural changes (e.g., multiple surgical injuries) that can be of value when examining inhibitors of cartilage degradation (e.g., meniscal tear model in guinea pigs). Regardless of the rate of development of pathology, it is important to study selected sites of the joint (e.g., areas of abnormal loading/extreme overload) rather than the whole joint to ensure valid comparisons can be made to test specific hypotheses.

For a variety of reasons, it is advantageous for industry to use more rapid models of OA for drug development. This approach may not be asking too much of the treatment since models of rapid onset inflammation and joint destruction for inflammatory arthritis (e.g., collagen induced arthritis) have proven of value in disease-modifying drug development for inflammatory arthritis. This should be remembered in OA. In contrast, a slower developing OA model, more like human OA, may afford greater opportunities to control joint damage with a less potent drug.

### Recommended minimal ages of animals to enter OA studies (skeletal maturity)

<table>
<thead>
<tr>
<th>Species</th>
<th>Age</th>
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<tbody>
<tr>
<td>Mice</td>
<td>10 weeks</td>
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<tr>
<td>Rats</td>
<td>3 months</td>
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<tr>
<td>Guinea pigs</td>
<td>6 months</td>
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<tr>
<td>Rabbits</td>
<td>8–9 months</td>
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<td>Sheep</td>
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<td>Goats</td>
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<td>Horses</td>
<td>2 years</td>
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Natural/spontaneous vs experimentally induced OA

There is a perceived advantage in using naturally occurring models of OA (e.g., Dunkin-Hartley guinea pig) in that they are more like human OA with slower onset and progression. Yet, like human OA, these models are not necessarily more sensitive when trying to identify the initiating events. Hence, the basis for the joint pathology and the disease onset need to be determined. Some therapeutic compounds may produce better results in surgically induced OA and have no effect on natural OA. Or it may be the reverse. Both possibilities need to be considered. The spontaneous model provides a proof of concept for certain classes of compounds or therapies. For example, aging guinea pigs may be more appropriate than a young injured rabbit for testing a pro-anabolic therapeutic agent. The availability of natural models is, however, sometimes a limitation. Guinea pigs are large enough to use MRI imaging and have been used successfully to examine MMP inhibitors employing single site histological analyses in group sizes of 11–16 animals.

Chemically induced OA models involving iodoacetate

Intra-articular injection of iodoacetate creates an acute model for the study of acute cartilage degradation and joint pain. However, it has limitations as a model for OA. For example, since iodoacetate is a metabolic poison, chondrocyte cell death in this model is extensive, unlike in human OA. It does, however, provide an in vivo model of rapid cartilage degradation mirroring some of the events observed in in vitro organ culture screening studies. The model needs clinical validation (rapidly progressive OA? environmental toxicology Kashin-Beck? iatrogenic arthropathy?).

Mouse models

These may be of special use in the prevention of OA. There is a need to use knock-out or transgenic mice to examine genetic predispositions/contributions to OA. Conditional genetic manipulations should be preferred, particularly those that can be induced in adult animals. The relationship between disease and activity impairment and OA onset requires more study. Remember that genetically altered mice might better be considered as research tools and are not necessarily better OA models. Natural onset OA is clearly more pronounced in the STR/ort and STR/1N mouse strains and these are viewed as effective screening models. However, it is important to recall that the exacerbating effect of joint loading in human OA may not be accurately captured (due to scaling effects) in mouse models.

Drug targets and animal models

As indicated earlier, drugs to address the human condition should be tested in adult animals where the disease is established. Remember that the end point that is used may not always resemble human OA. The molecular target of the drug should be considered when selecting one model over another. More than one model will probably be needed to identify and substantiate the potential therapeutic efficacy. Do not limit studies to only one model. Genetically modified mice may be particularly useful since the genetic change(s) is largely known and fitted to the drug target.

Analyses of animal models

Assessment of structural change

Cartilage offers us an opportunity to detect early change. The importance of measuring and preventing macroscopic changes in articular cartilage structure was clearly recognized since the ultimate goal is to prevent such changes. But at present we are unsure of the relative importance of macroscopic vs microscopic changes when assessing drug effects. This is because macroscopic changes in cartilages only reflect more surface related events. Histology and/or imaging are also required. But if change starts superficially in cartilage, as many human studies indicate, macroscopic measures may suffice. Histological change must be monitored when there is little evidence of structural change. It is necessary to establish a hierarchy of change to measure — what is the minimum that needs to be measured and what are the structural features we should focus on. There was some consensus that the whole-joint cartilage need not be assessed: specific sites should be monitored, such as where joint loading changes and where more severe and less severe lesions are commonly found in a given model. In early human OA, the changes are more prevalent in some parts of the joint than in others. While changes often occur throughout the joint, there are sentinel signs that anticipate the overall pathology of the joint.

We must define and standardize macroscopic changes since this is presently lacking in animal models. Recently, a consensus was reached for scoring human OA macroscopically and we need to define what we should measure and how this should be done in animal models, recognizing the practical differences in assessing small vs large animals.

For a given model (e.g., surgical, chemical, or natural) different species should be compared. There is a desire to identify the most sensitive, specific, fastest and cheapest models and measures. Noninvasive imaging by MRI and microCT using cartilage contrast in CT needs to be tailored to a given model and validated. A best practice of macroscopic assessment of cartilage change is required. Ideally, it will be possible to eventually substitute less invasive technologies for the gold standard of macroscopic and microscopic evaluation.

In terms of a standard histologic grading system we should use one that is similar to that used for human studies. There is a need to define the histological changes observed so that all researchers use the same terminology and mean the same thing. This will facilitate comparisons between results. The Mankin scoring system is of value, but has many limitations — particularly in early OA. Since structural changes in cartilages are similar among species, it would be ideal if the same measurements can be used for all models. At present there is no consensus on a common grading system. But it is agreed that it should include synovial changes as well as changes in cartilage structure, composition and cells. We are unsure of what to measure histologically in bone — this requires definition. It is essential to define a common grading system for each of the features shared between human OA and models of OA.

There was agreement that changes in cartilage, menisci, bone and synovium should all be assessed. The recognition of bone bruises by MRI in humans and animals is a good example of how new technology improves our understanding of how tissues, other than articular cartilage, respond to joint injury. Synovial and bone changes may help improve our understanding of how the whole joint may contribute to OA symptomatology. Sampling techniques, whether for imaging or histopathology, must also be standardized to ensure we are comparing apples with apples. It is important to remember that the scoring system and evaluation outcomes invariably depend on the questions that are being asked and the drug targets being sought.

Similarly, the characterization of the microscopic anatomy of joint tissues (e.g., histological preparation, tissue sampling sites,
staining techniques, etc.) requires standardization to ensure reproducible staining, staining intensity and chromaticity and hence reproducible grading (e.g., metachromasia as an index of proteoglycan concentration). There was a consensus that it is desirable to introduce histomorphometric measurements of cartilage and bone changes (e.g., by quantitative digital image analysis and stereology), to achieve better standardization and to ensure unbiased evaluation.

There was no consensus whether osteophytes should be included in the assessment of osteoarthritis, as in human studies (e.g., Kellgren/Lawrence grading on X-ray), as they are of uncertain significance. Yet, osteophytes are a hallmark of human osteoarthritis. If osteophytes are to be assessed, their presence, location, and extent should be noted; if they are to be quantified, then a volumetric or planimetric record should be made. Whether bone or cartilage changes of osteoarthritis are first observed in animal models is unclear, though the formation of the marginal osteophytes in OA begins at the chondro-osseous junction and is likely controlled primarily by a combination of mechanical and biochemical factors.

Current imaging technologies clearly have an important role to play in assessing early lesions in experimental OA. As more specific and sensitive imaging protocols and contrast agents are developed, the easier it will be to study the pathogenesis of OA longitudinally. It is likely that a sensitive metric for treatment efficacy will be altering the trajectory of the natural history of whole-joint changes in OA.

**Assessment of pain**

The control of OA pain and fatigue is viewed by patients/consumers as the greatest unmet need in this condition (Canadian Arthritis Network and Institute for Musculoskeletal Health and Arthritis, Canadian Institutes of Health Research jointly sponsored OA Consensus Conference, Toronto, 2002). It is therefore imperative that new models (in vitro and in vivo) be developed that enable the objective testing of OA symptoms. Over the past several decades, substantial advances have been made in objectively assessing distress in animals. Such methods can be employed as surrogates of human pain, discomfort, and fatigue. Moreover, such models need to be combined in studies with new drugs that can better control joint pain, whether or not they have structure- or disease-modifying activities. In humans there is evidence of an association between structural joint damage and joint symptoms contrary to some earlier reports. It is unclear whether pain is linked to disease initiation or progression. There was a consensus that a fuller understanding of OA pain in humans was needed so that the appropriate animal models could be developed to enable the assessment of OA symptoms in preclinical studies.

In human OA we also need to determine:

- Whether pain status and mechanisms change over time. Can they be modeled in animals?
- Do pain conditions show the same pharmacology over time?
- We must determine whether different pain mechanisms are operative in a patient at different times.

We must clarify the clinical measures of pain and tenderness in a manner similar to a functional WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) analysis.

**Animal models for the study of pain: recommendations**

In an animal model, it is important to include multiple time points when assessing pain. For the study of pain, mechanisms and pharmacological interventions to treat pain may change over time in models. Some participants felt that naturally occurring models may better represent pain than surgically induced models. Yet it was felt that in view of the early involvement of meniscal damage in idiopathic OA, and the presence of nerve endings in the peripheral portion of the meniscus, meniscus-based models may be particularly relevant to studies of OA pain. Chronic OA has a large component of microinjury and surgical models may therefore represent this. Instability in idiopathic OA is similar, though not necessarily identical, to surgical instability. Overall, surgical models were considered relevant and acceptable for pain measurement, though sham surgery is mandated to control for the possible effects of iatrogenic neurectomy.

There was agreement that the intra-articular moniodiacetate model does not produce the typical pathology of human OA, but is a clinically relevant model of arthritis pain. Iodoacetate is an example of how the mode of action of a compound can influence the choice of outcome measures in a particular animal model. To best study pain in OA, there should be a close collaboration between pain and OA researchers.

**The measurement of pain**

There was agreement that scientists’ need suitable standardized testing procedures to detect and document “total” animal nociceptive behaviour. We need to develop methods to assess animal behaviour that reflects pain, joint instability, and function. A hierarchical approach to assessment is needed.

Functional gait analysis may be influenced by pain and, therefore, could be used as a surrogate pain measure. It should also be noted, however, that it may be difficult to interpret kinematic measures in instability models since changes may be related to an alteration in joint function rather than due to musculoskeletal pain per se. Intra-articular anesthetic challenge might be one strategy to decouple gait mechanics from pain physiology.

It was noted that spontaneous pain behaviour is different from evoked pain behaviour. Both should be measured over time and used in testing potential therapeutic agents. Since patients have a difficult time distinguishing pain and function, this may be similar in animal models. The emotional component of pain should be measured using a behavioural output. Neuropathic pain has standardized clinical tests, but OA pain does not. Quantified sensory tests for OA should be developed and used in clinical and preclinical studies. Since pain has different manifestations (stabbing, throbbing, searing, burning, overall, general, etc.) we should try and measure these objectively in animals, possibly electrophysiologically.

It is essential that the research community identify what is a clinically significant reduction in pain in animals for the guidance of researchers and regulatory agencies.

In conclusion, we need gait analyses, electrophysiological and behavioural tests to distinguish evoked pain from spontaneous pain.

**Gene expression vs biochemical analyses in assessing joint injury and repair**

Besides humans, complete genomic analyses are now available in mice, rats and dogs and will be available soon for an increasing number of species. In any analysis of joint tissues in OA, we should examine the balance between matrix synthesis and degradation and identify any alterations in the regulation of these molecules since these changes occur in human OA. We should be analyzing menisci, ligaments, periarticular tendons, synovia, capsules and subchondral bone, as well as articular cartilage — because OA is a condition involving and affecting all these tissues.

In the study of joint tissues, gene expression analysis results should be questioned as to their value: they sometimes only
represent the potential for change and not change itself. Biochemical analyses can detect and measure functional products of gene expression that are responsible for structural and compositional changes. Gene expression can be viewed as what the cells are thinking about in the short term; changes in matrix proteins and carbohydrates are the more long-term changes in the biochemical and mechanical milieu. It is noteworthy that the turnover of some structural macromolecules in the extracellular matrix may take many months or even years. So the presence of a molecule in the matrix does indicate whether it was synthesized at birth or made yesterday unless this can be demonstrated. Hence, molecular markers of newly formed or newly degraded matrix molecules are highly valuable. So too are changes in the gene or protein expression of molecules that influence tissue metabolism in joint injury, repair and degeneration and which are associated with phenotypic changes in cells such as chondrocyte hypertrophy and its association with collagen cleavage.

Functional repair and degradative processes should be identified and recorded rather than non-functional processes. Be aware of the lack of intrinsic repair capacity in adult articular cartilage. Gene expression analyses in the dorsal root ganglion and spinal cord in animal models may prove of value in studying pain in both spontaneous and surgical models. Unlike connective tissues, tissues of the nervous system have rapid turnover of proteins, so protein biochemistry and immunochemistry of nerves is an important and informative indication of recent nerve activity. Researchers should remember that OA models at present represent models of damage rather than repair. For example, the elevated expression of structural macromolecules can be viewed as anabolic, yet, since catabolism is also elevated, the reality is a state of high turnover.

In summary, the focus should, wherever possible, be on functional products and their balance reflecting degradation, repair, disease onset and progression.

The use of biochemical biomarkers to predict OA progression

In animal studies, biochemical/molecular markers in body fluids are viewed as useful indicators for studying tissue dynamics, in particular cartilage and bone turnover and synovitis. But they need to be complemented with imaging and histology over multiple time points to assess their predictive value and determine relationships to disease onset and progression.

We should distinguish diagnostic biomarkers (which may be qualitative) from those predictive of disease progression or response to treatment (that need to be quantified). Again, the time at which a given biomarker may be of most value probably depends on the time point at which it is used to predict progression (see above for discussion on how altering the trajectory of natural history of OA may be a useful tool for establishing efficacy).

Biochemical markers should be classified: a classification system has been proposed.

Biomarkers are needed to identify disease activity prior to radiographic change as revealed by MRI, DEXA or other radiological methods. The use of skeletally immature animals in OA models is not only inappropriate due to the demographics of OA, but also confounds biochemical marker analyses since biomarkers can be elevated during growth (increased matrix turnover/remodeling) and we may be evaluating growth more than identifying the pathological changes in OA.

We should be assessing both anabolic and catabolic markers and those of synovitis to determine imbalances in preclinical OA models (as reflected above) and not a single biomarker. Thus, a combination of changes in biomarkers (e.g., balance of cartilage type II collagen synthesis vs degradation) may well be more predictive than a change in any one biomarker. It is essential that assays be standardized to enable comparisons of results. Normal values and standard deviations are required for comparison. The threshold for a significant biochemical marker change should be identified as should changes thereof that are products of pathology. Biomarker changes should be related to behavioural outcomes to explore the possible interrelationships between pathology and pain. Biomarkers of pain (hyperalgesia and allodynia) should be identified and measured.

The assessment of synovial and capsular changes and inflammation in models of OA

Although OA is not considered an inflammatory arthritis (like RA), it is not a non-inflammatory process. Indeed, classic inflammatory changes clearly occur in the synovium and capsule and a variety of inflammatory changes (such as upregulation of proinflammatory cytokines) involve other connective tissues including cartilage and bone. Blood flow in a joint is confined mainly to the bone, synovium and capsule. It is an index of inflammation since it involves angiogenesis, vasomotor tone, and changes in vascular/endothelial cell permeability. These parameters should be measured in OA models. Thermography and early phase scintigraphy are valuable methods to measure blood flow. Laser Doppler measurements can detect the hyperaemia of inflammation. The biochemical biomarker hyaluronic acid (hyaluronan) generated by synovial cells is increased in serum in synovitis and this can be measured.

It is important to determine how joint innervation and peripheral neuropeptides may change in OA models in association with synovitis. Ultrasound and MRI and early phase scintigraphy are used in human studies to detect synovitis and may be of value in animal studies too.

Biomechanical analyses of joint tissues

The biomechanical properties of joint tissues are measures of what is most important — the functional properties of a tissue — and should therefore be monitored in OA models both in vivo and ex vivo. These measurements should include cartilage compressive stiffness and elasticity and their time-dependant changes. The natural variation of biomechanical properties of cartilage with age and joint site (condyle vs tibial plateaus) needs to be distinguished from pathological changes by carefully controlled testing of comparable carefully defined regions. The mechanical strength of the cartilage may be a final common denominator with respect to these measures. The mechanical properties of the subchondral bone, menisci, ligaments and the capsule also need assessment. Correlations should be made with structural and biochemical properties and symptoms. Determinations of whether biomechanical properties are related to joint movement are required. The effect of load on a diseased tissue needs to be understood.

New biophysical techniques to measure cartilage functional quality such as in vivo arthroscopic determination of streaming potentials could be applied to OA models in larger species.

Clearly there is a need for an integrated approach to the assessment of joint damage; a given drug may only influence one important parameter.

Other general assessments and recommendations for overall strategic analyses

In modeling the process and end points of human OA, we should also assess symptoms such as lameness (gait analysis), joint loading (incapacitance) and range of motion together with pain, nociceptive behaviour (hyperalgesia/allodynia), evoked vs
spontaneous and referred pain, synovial effusions, joint swelling and temperature.

Tissues comprising the whole joint should be structurally assessed using imaging, macroscopic assessment, histopathologic assessment at defined sites of change (with histomorphometric methods), biochemistry, molecular biology/gene expression, physiological and biomechanical properties of joint tissues as well as joint function, (kinetics, kinematics, stability).

Methods used in both human and animal studies need to be standardized to permit the evaluation of change in both situations so that meaningful comparisons can be made. Change must be quantified to permit parametric statistical change to be identified. End points must be defined and meaningful (either individual or composite).

**Essential safety issues in animal models of OA**

In dealing with pharmaceutical therapies, we must examine the toxicology related to the route of delivery and include the musculoskeletal system in these analyses. We must analyze the pharmacogenetics and pharmacodynamics (catabolism and anabolism) as well as the pharmacokinetics.

In systemic treatment, especially for molecular targets of joint health, we should study in normal animals the effects of drugs on the structure and biochemical composition of the musculoskeletal system including joints. For intra-articular delivery, specific toxicological concerns are reduced but must still be addressed, especially for local tolerability.

**Reminders**

**Structure/function/symptom interrelationships**

These should be explored and included in OA modeling. Wherever possible, we should pay careful attention to the time course of disease, when symptoms develop and when symptom modification with therapy may occur. We must examine the biomechanical properties and geometry of joints so that we can better understand joint function and changes thereof in relationship to structure and symptoms. Such integrated studies are sorely needed. They may help to determine whether the treatment of symptoms can improve function.

**Treatment of experimental OA: prophylaxis, progression, reversal**

It is important to recognize different treatment options that address prophylaxis (pretreatment), slowing of progression (early treatment) and reversal. Phasic treatment and crossover studies should be addressed in the experimental design. Attention to activity and diet should be included as part of the treatment protocol. Both anti-catabolic and pro-anabolic options are available. Early treatment is considered to produce the greatest opportunity for success in both experimental and human studies based upon our experience with rheumatoid arthritis.

**Markers of disease onset, activity and progression**

It is important to identify and use indicators of risk, onset, activity and progression, which may include genomic/metabonomic, biochemical, genotype/phenotype and imaging markers. These offer insights in vivo that may pinpoint changes in progression that then predict structural or symptomatic or functional alterations. It is important to remember that biochemical markers of skeletal turnover usually identify process whereas imaging markers tend to recognize outcome. New spectroscopic imaging techniques may be developed sufficiently to enable the identification of both process and outcome.

**What can the Canadian Arthritis Network, OARSI and others do to help?**

They can offer a forum for the exchange and dissemination of knowledge with various stakeholders, including patients. This addresses self-education, training, and the promotion of interdisciplinary approaches. The importance of negative results needs to be addressed. Access to this information is important. The coherence of methodologies between preclinical and clinical studies should be promoted, as well as knowledge exchange among stakeholders, including researchers, practitioners, industry, government, regulatory agencies and patients.

**Concluding remarks**

It is important to remember that some models can mimic aspects of the human disease, but no single animal model is able to mirror all variants and aspects of human OA. There was some consensus that we should treat and model subsets of OA such as inflammatory OA.

There are different subsets of animal models, as in human OA. There are primary idiopathic models of natural, age-related disease onset and secondary experimentally induced disease. Secondary models of OA include: surgical instability, chemical, and impact models.

There is the natural occurrence of OA in veterinary patients, be it because of aging, trauma or genetic causes.

The best model on face value, in terms of natural occurrence and animal size permitting multiple assessments of the kind used in humans, is spontaneous OA in the Dunkin-Hartley guinea pig, though the influence of body mass and obesity are complications yet to be resolved.

There was a general consensus that, ultimately, less severe models are required to better evaluate potential therapies for use in human OA.

In primary models we need to examine whether we can model risk factors for OA, namely diet (obesity), genetics, activity, age, gender, stress and joint loading. These variables should be considered with the design and outcome of all models of OA onset and intervention.

Our goal has been to reach some consensus on the appropriate use of animal models for the detection, study and treatment of OA. We have made progress towards this goal although much remains to be done. We also need to further enhance the existing high standards of the three “Rs” in animal experimentation, namely:

1. Reduce — use fewer animals;
2. Refine — enhance efficiency of the experimental protocol; and,
3. Replace — employ *in vitro* over *in vivo* whenever possible.

We recognize that adequate severity of disease is achieved in existing models. But there should be awareness that overly severe experimental models can be counter-productive in presenting us with greater challenges than we meet in human disease. The reduction of disease by experimental intervention needs clear definition so that severity and responses to treatment can be better defined, standardized and compared. The use of standardized experimental methods and different joint tissues to identify changes in joint signs, symptoms, structure, turnover and function...
should be maximized to obtain more comprehensive and more meaningful information of relevance to the human disease. We should be aware that in some surgical models, the contra-lateral joint can represent a model of less severe and more slowly progressive degenerative change modeling human OA. Remember that the literature contains validated studies of animal models — they should be carefully noted.

Conflict of interest
No author has any conflict of interest related to this work.

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