Q4. Can/should we define an optimal set of species (rodents *vs*. large animal models) in which to model, study mechanisms, and test treatment of OA pain?

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Response: YES. Each animal model of OA has specific advantages and limitations, but by studying pain across multiple species and strains, we can gain a better understanding of the mechanisms underlying the human disease. While certain animal models of OA are well-suited for studying joint degeneration, they may not be appropriate for investigating symptoms. Pain is also not a single discrete entity but is multifactorial, encompassing multiple different phenotypes (nociceptive, inflammatory, neuropathic). Thus, using a range of different animal species will allow us to interrogate the various aspects of OA pain subtypes.

Level of Evidence: Low

Delegate Vote: Agree: Disagree: Abstain:

Rationale: Modelling OA pain in preclinical animal models is challenging because animals cannot communicate the intensity and quality of their pain (1, 2). While no animal model fully recapitulates disease pathobiology, using multiple strains and species will allow us to better understand pain neurobiology in this complex disease (1, 3). Each animal model has specific advantages and limitations, but by studying pain across multiple species and strains, we can gain a better understanding of the mechanisms that contribute to the human disease. While certain animal models of OA are well suited for studying joint degeneration, they may not be appropriate for investigating symptoms (4, 5). Pain is also not a single discrete entity but is multifactorial, encompassing multiple different phenotypes (nociceptive, inflammatory, neuropathic) (6, 7). Using a range of different animal species will allow us to interrogate the various aspects of OA pain subtypes.

Although the primary goal of scientific research is to identify novel pain targets and develop approaches to manage human disease, it is important not to lose sight of the necessity to discover new treatments that can be applied to the veterinary community to help improve the well-being of our companion animals and livestock (8). This is best achieved through modelling OA in larger animals. Smaller animals belonging to the orders Rodentia and Lagomorpha are attractive because we can artificially manipulate their genetic composition and because a plethora of molecular tools is available to probe the pain pathway (9). As such, there is no single species or order of animals that is optimal for studying the complexity of OA pain mechanisms.

Considerations:

1. **Large Animal Models (e.g. horse, sheep, dog):**

Advantages:

- One of the primary read-outs for OA pain assessment is changes in mobility. Trauma to the joint followed by progressive OA development has a negative impact on gait parameters, kinematics, and joint biomechanics. Large animals are easier to train and retain a high degree of willingness to move in spite of having an OA joint. This inclination to move facilitates analysis of joint function including dynamic weight bearing/gait (force plate analysis), and kinematics (video capture).
- Large animals naturally have larger joints. Thus, induction of post-traumatic OA by surgical derangement of the joint is easier to perform and is highly reproducible. This consistency in being able to induce post-traumatic OA will ultimately lead to a more uniform pain response.
- Relevant to veterinary medicine.

Disadvantages:

- High cost.
- Ethical approval is constrained when using higher order animals.
- Housing infrastructure of larger animals may be prohibitive in smaller institutions

2. **Small Animal Models (e.g. mouse, rat, rabbit, guinea pig):**

Advantages:

- Relatively inexpensive.
- Greater number of molecular tools and genetically modified strains enable detailed interrogation of pain mechanisms.
- High throughput for treatment validation.

Disadvantages:

- Prey animals so they may suppress their pain behaviour.
- Some female models of OA do not show a pain phenotype.

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