Editorial

Discovery Medicine 2025; 37(197): 1139–1142
https://doi.org/10.24976/Discov.Med.202537197.101

Bridging the Translational Gap: Prioritizing the Spontaneous Canine Osteoarthritis Model for Preclinical Studies

Khan Sharun[1,2,*], Shajahan Amitha Banu[3], Luca Melotti[4]

[1]Center for Regenerative Nanomedicine, Northwestern University, Chicago, IL 60611, USA
[2]Graduate Institute of Medicine, Yuan Ze University, 32003 Taoyuan, Taiwan
[3]Stanley Manne Children's Research Institute, Louis A. Simpson and Kimberly K. Querrey Biomedical Research Center, Chicago, IL 60611, USA
[4]Department of Comparative Biomedicine and Food Science, University of Padua, 35122 Padua, Italy
*Correspondence: sharunkhansk@gmail.com (Khan Sharun)
Published: 9 June 2025

Keywords: cartilage; cartilage regeneration; tissue engineering; regenerative medicine; animal model; One Health

Osteoarthritis (OA) remains a leading cause of chronic pain and disability worldwide [1]. Despite decades of research and billions spent on drug development, treatment options remain limited largely to symptom management rather than disease modification. Most preclinical research has failed to yield therapies that consistently translate to human clinical success [2]. This stagnation underscores the limitations of traditional animal models, which often rely on artificially induced joint damage in rodents or large animals [3,4].

The failure to translate promising preclinical findings into effective human therapies represents one of the most significant challenges in OA research [2]. Despite extensive research using rodent models, the development of disease-modifying osteoarthritis drugs (DMOADs) has been hindered by high failure rates in clinical trials [2]. Current preclinical OA research heavily depends on surgically or chemically induced animal models, which lack critical features of human disease progression [4]. While these approaches have contributed significantly to our understanding of disease mechanisms, they fail to recapitulate the complex, multifactorial nature of human OA. The rapid onset and progression of experimentally induced OA differs markedly from the slow, progressive nature of naturally occurring disease in humans, compromising the translational value of these models for therapeutic development [5]. For example, proteoglycan changes in rodent models diverge sharply from those in human OA [6]. Additionally, rodent models inadequately replicate the complex interplay of genetics, biomechanics, and inflammation driving human OA [7]. The U.S. Food and Drug Administration (FDA) has repeatedly flagged these discrepancies, noting that preclinical models must better reflect human OA subtypes and longitudinal disease trajectories [2].

In contrast, spontaneous canine OA is a naturally occurring disease in pet dogs, and it offers a transformative opportunity to bridge this translational gap [8]. The spontaneous canine model provides unparalleled advantages in recapitulating OA heterogeneity, pain pathophysiology, and therapeutic response by aligning research with the One Health initiative, which emphasizes shared biological mechanisms between humans and animals [3,8]. Indeed, this might be considered to be the closest match to a gold standard model with respect to disease progression, anatomical similarities, and translational relevance to human medicine. Fig. 1 illustrates some of the key advantages of using the spontaneous canine OA model compared to experimentally induced OA models.

Advantages of the Spontaneous Canine Model

Spontaneous, slow-progressing OA occurs in multiple species, including rodents, non-human primates, and dogs [8]. However, pet dogs offer unique advantages that position them as exceptional translational models [9]. Unlike laboratory animals, dogs share both environment and lifestyle attributes with their owners. This shared environment is especially relevant in OA, where lifestyle factors like diet, physical activity, and daily routines play a crucial role in disease progression [8]. The prevalence of canine OA is substantial, with surveys suggesting that 11 million dogs in the United States and 5 million in Europe could suffer from the condition [3]. In some breeds, the prevalence of knee OA reaches approximately 20% [9]. This high prevalence and breed predispositions provide researchers access to naturally stratified populations that can inform investigations of genetic and environmental risk factors [9,10]. Spontaneous canine OA manifests in multiple joints, with the hip and knee (stifle) joints being particularly common sites [9].

Dogs develop OA through mechanisms similar to humans, including anterior cruciate ligament (ACL) tears, hip

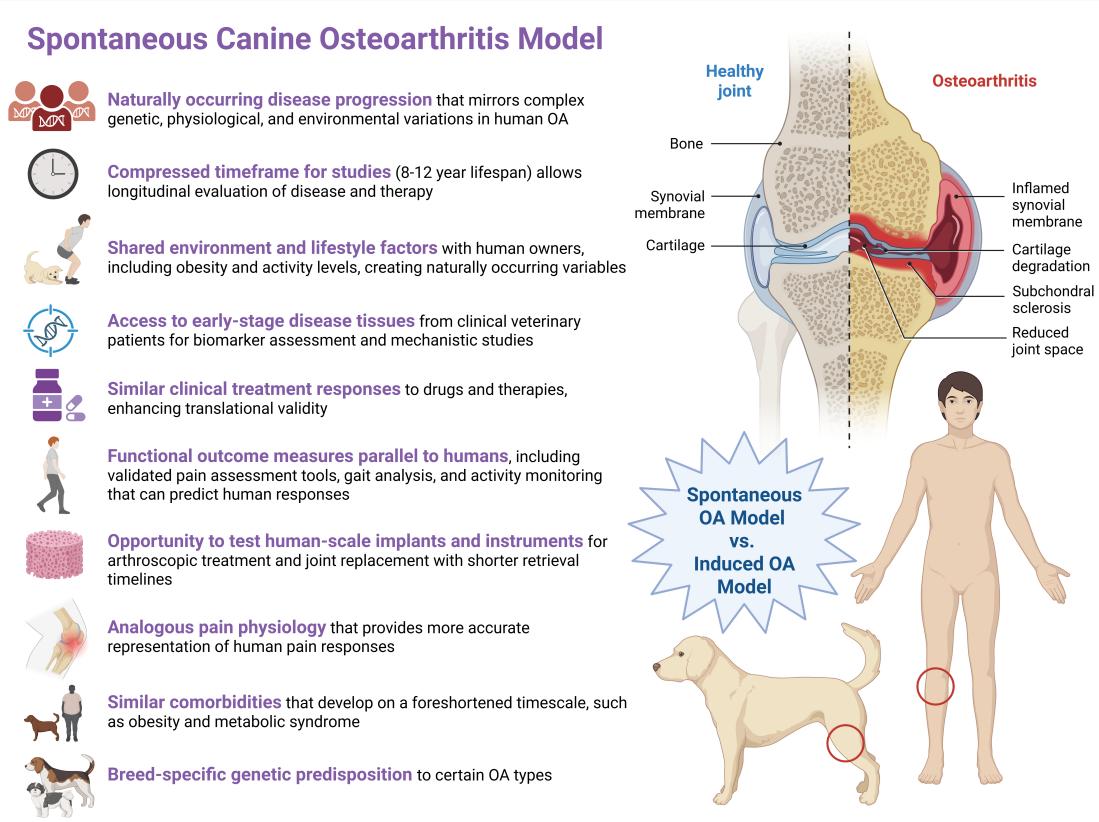

Fig. 1. Key advantages of using the spontaneous canine osteoarthritis (OA) model compared to experimentally induced OA models. Created in BioRender (https://www.biorender.com).

dysplasia, and age-related joint degeneration [6,8]. Their synovial joint architecture, load-bearing patterns, and cartilage biology closely match human tissues, enabling studies of early OA biomarkers and progressive structural damage. Cruciate ligament rupture, a frequent cause of knee OA in dogs, parallels human ACL injuries and subsequent OA development [8]. The spontaneous rupture of the cranial cruciate ligament (CCL, analogous to the human ACL) in dogs often occurs during normal activities such as walking or running, and predisposed dogs show pathological changes in ligament composition before rupture [11]. Notably, similar pathological features have been observed in human ACLs, with approximately 70% of macroscopically normal human ACLs showing histological evidence of early degeneration [12]. The anatomical similarities between canine and human joints provide a strong foundation for translational research [8,11]. Dog knees have human-like anatomy, including an ACL, which is termed the cranial cruciate ligament in dogs due to their quadrupedal arrangement [8]. While a dog's articular cartilage is half the thickness of a human's, this represents a far closer approximation than mouse cartilage, which is approximately 70 times thinner than human cartilage [5].

Pain is the primary symptom driving patients to seek medical attention for OA, yet it remains challenging to assess and treat effectively [13]. The spontaneous canine OA model offers unique advantages for pain research that are unattainable in rodent models [8]. Studies comparing pain processing in dogs with spontaneous OA to healthy controls have demonstrated impaired endogenous pain modulation (EPM) in OA-affected dogs [14]. These findings mirror observations in human OA patients, who also show less efficient conditioned pain modulation than healthy controls [14]. Such similarities in altered pain processing mechanisms represent a powerful translational opportunity for developing and testing novel analgesic approaches. The availability of validated assessment tools for canine OA pain further enhances the translational potential. Clinical metrology instruments (client-reported outcome measures) allow for systematically evaluating pain-related behaviours and functional impairments [15]. The Canine Osteoarthritis Staging Tool (COAST) provides a framework for consistent OA classification using owner-reported outcomes, gait analysis, and imaging [15]. Additionally, quantitative sensory testing (QST) protocols have been developed for dogs, enabling the assessment of mechanical and thermal sensitivity in a manner comparable to human pain testing [16]. Another helpful tool in detecting pain severity of OA-affected dogs is the Helsinki Chronic Pain Index (HCPI), which is an owner-based questionnaire for pain assessment and to evaluate the degree of pain [17]. Recent research has shown that widespread somatosensory sensitivity, a hall-

mark of central sensitization in human OA, is also present in dogs with naturally occurring OA [16,18]. This facilitated nociceptive transmission due to central plasticity further validates the canine spontaneous OA model as an appropriate analogue of the human OA pain condition.

One of the most compelling advantages of the spontaneous canine OA model is its relatively compressed timescale compared to human disease. Dogs develop and progress through OA more rapidly than humans yet still follow a naturally occurring disease course rather than the artificially accelerated progression seen in induced models [8]. This compressed timeline enables longitudinal studies that would be impractical in human populations, allowing researchers to track disease progression from early to late stages and assess the impact of interventions at different disease time points. The ability to observe the full disease trajectory within a reasonable research timeframe represents a significant advantage for therapeutic development and testing [8].

Overcoming Challenges in Model Implementation

Despite its considerable advantages, the spontaneous canine OA model faces several challenges that must be addressed to maximize its translational impact. Ethical considerations regarding the use of pet animals in research require careful experimental design [3]. Unlike purpose-bred laboratory animals, companion dogs are family members whose welfare must be prioritized. However, these ethical considerations can be resolved through thoughtful study protocols focusing on minimally invasive procedures and interventions that may benefit the participating animals. Standardization presents another challenge, as genetic and environmental factors may vary considerably across the pet dog population [7]. This variability can complicate data interpretation but also mirrors the heterogeneity seen in human OA populations, potentially increasing translational relevance [7,8]. Resource and infrastructure requirements for conducting research with pet dogs differ from those for laboratory animals [19]. Specialized veterinary facilities, experienced clinical researchers, and systems for owner communication and follow-up are essential to successful canine clinical trials [20]. Developing these resources requires investment but creates valuable infrastructure for ongoing translational research.

Widespread adoption of COAST staging coupled with validated biomarkers could harmonize data across studies [15]. Client-owned dogs enrolled in veterinary randomized controlled trials (V-RCTs) avoid ethical concerns associated with experimental OA induction while providing access to biological samples during routine procedures (e.g., synovial fluid from joint aspirations) [8,21]. Collaborative networks like the Cornell Veterinary Biobank are critical for aggregating samples and data [22].

Recommendations

Several steps should be prioritized to maximize the potential of the spontaneous canine OA model. Regulatory agencies like the FDA must formally recognize veterinary randomized controlled trials (V-RCTs) in client-owned dogs as critical evidence in drug development pipelines and update guidelines to endorse this model. Increased funding for comparative biology initiatives is essential to identify shared biological pathways between humans and dogs, such as through parallel studies of synovial fluid biomarkers. Additionally, cross-species biomarkers and inflammatory cytokines should be validated in canine OA to bridge preclinical and clinical research. Finally, developing breed-specific OA cohorts, such as Labrador Retrievers for hip OA, can accelerate genetic discoveries and precision medicine approaches. Together, these measures will position the canine OA model as a vital tool for advancing translational research and therapeutic development in a One Health perspective.

Summary

The persistent gap between preclinical promise and clinical reality in osteoarthritis research demands a fundamental reassessment of our research models. The spontaneous canine OA model represents a paradigm shift in preclinical research, offering unmatched clinical relevance, ethical advantages, and translational potential. The similarities between canine and human OA in terms of anatomy, pathophysiology, pain mechanisms, and even genomic features provide a strong foundation for translational studies. The compressed disease timeline in dogs, coupled with the accessibility of patients and samples across disease stages, offers unique opportunities to study disease progression and intervention effects that are unavailable in other animal models. We can create a more effective bridge between basic science discoveries and clinical applications by prioritising the spontaneous canine OA model in preclinical research. This approach aligns with the One Health vision and offers practical benefits for both human and veterinary patients. The recommendations outlined in this editorial provide a roadmap for realizing the full potential of this valuable translational model. The time has come to move beyond the limitations of induced laboratory models and embrace the naturally occurring disease models of OA. Doing so may finally bridge the translational gap that has hindered progress in OA treatment for far too long. A coordinated effort to standardize protocols, foster cross-disciplinary collaboration, and secure regulatory buy-in will position this model as the cornerstone of OA drug development.

Availability of Data and Materials

Not applicable.

Author Contributions

KS, SAB and LM conceived this study. KS, SAB and LM were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

All authors gratefully acknowledge their respective institutions and universities for providing the necessary facilities and support for this work. The authors also extend their sincere thanks to Prof. Cristian Pablo Pennisi for his valuable comments on the manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Peat G, Thomas MJ. Osteoarthritis year in review 2020: epidemiology & therapy. Osteoarthritis and Cartilage. 2021; 29: 180–189. https://doi.org/10.1016/j.joca.2020.10.007.

[2] Malfait AM, Little CB. On the predictive utility of animal models of osteoarthritis. Arthritis Research & Therapy. 2015; 17: 225. https://doi.org/10.1186/s13075-015-0747-6.

[3] Vainio O. Translational animal models using veterinary patients - An example of canine osteoarthritis (OA). Scandinavian Journal of Pain. 2012; 3: 84–89. https://doi.org/10.1016/j.sjpain.2011.11.007.

[4] Rios JL, Sapède D, Djouad F, Rapp AE, Lang A, Larkin J, *et al*. Animal Models of Osteoarthritis Part 1-Preclinical Small Animal Models: Challenges and Opportunities for Drug Development. Current Protocols. 2022; 2: e596. https://doi.org/10.1002/cpz1.596.

[5] Cope PJ, Ourradi K, Li Y, Sharif M. Models of osteoarthritis: the good, the bad and the promising. Osteoarthritis and Cartilage. 2019; 27: 230–239. https://doi.org/10.1016/j.joca.2018.09.016.

[6] Liu W, Burton-Wurster N, Glant TT, Tashman S, Sumner DR, Kamath RV, *et al*. Spontaneous and experimental osteoarthritis in dog: similarities and differences in proteoglycan levels. Journal of Orthopaedic Research. 2003; 21: 730–737. https://doi.org/10.1016/S0736-0266(03)00002-0.

[7] Lascelles BDX, Brown DC, Maixner W, Mogil JS. Spontaneous painful disease in companion animals can facilitate the development of chronic pain therapies for humans. Osteoarthritis and Cartilage. 2018; 26: 175–183. https://doi.org/10.1016/j.joca.2017.11.011.

[8] Meeson RL, Todhunter RJ, Blunn G, Nuki G, Pitsillides AA. Spontaneous dog osteoarthritis - a One Medicine vision. Nature Reviews. Rheumatology. 2019; 15: 273–287. https://doi.org/10.1038/s41584-019-0202-1.

[9] Johnston SA. Osteoarthritis: Joint anatomy, physiology, and pathobiology. The Veterinary Clinics of North America. Small Animal Practice. 1997; 27: 699–723. https://doi.org/10.1016/s0195-5616(97)50076-3.

[10] Anderson KL, Zulch H, O'Neill DG, Meeson RL, Collins LM. Risk Factors for Canine Osteoarthritis and Its Predisposing Arthropathies: A Systematic Review. Frontiers in Veterinary Science. 2020; 7: 220. https://doi.org/10.3389/fvets.2020.00220.

[11] Binversie EE, Walczak BE, Cone SG, Baker LA, Scerpella TA, Muir P. Canine ACL rupture: a spontaneous large animal model of human ACL rupture. BMC Musculoskeletal Disorders. 2022; 23: 116. https://doi.org/10.1186/s12891-021-04986-z.

[12] Trompeter AJ, Gill K, Appleton MAC, Palmer SH. Predicting anterior cruciate ligament integrity in patients with osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy. 2009; 17: 595–599. https://doi.org/10.1007/s00167-008-0701-0.

[13] Saxer F, Hollinger A, Bjurström MF, Conaghan PG, Neogi T, Schieker M, *et al*. Pain-phenotyping in osteoarthritis: Current concepts, evidence, and considerations towards a comprehensive framework for assessment and treatment. Osteoarthritis and Cartilage Open. 2024; 6: 100433. https://doi.org/10.1016/j.ocarto.2023.100433.

[14] Chiu KW, Hash J, Meyers R, Lascelles BDX. The effect of spontaneous osteoarthritis on conditioned pain modulation in the canine model. Scientific Reports. 2020; 10: 1694. https://doi.org/10.1038/s41598-020-58499-1.

[15] Cachon T, Frykman O, Innes JF, Lascelles BDX, Okumura M, Sousa P, *et al*. COAST Development Group's international consensus guidelines for the treatment of canine osteoarthritis. Frontiers in Veterinary Science. 2023; 10: 1137888. https://doi.org/10.3389/fvets.2023.1137888.

[16] Knazovicky D, Helgeson ES, Case B, Gruen ME, Maixner W, Lascelles BDX. Widespread somatosensory sensitivity in naturally occurring canine model of osteoarthritis. Pain. 2016; 157: 1325–1332. https://doi.org/10.1097/j.pain.0000000000000521.

[17] Della Rocca G, Schievano C, Di Salvo A, Hielm-Björkman AK, Della Valle MF. Psychometric Testing and Validation of the Italian Version of the Helsinki Chronic Pain Index (I-HCPI) in Dogs with Pain Related to Osteoarthritis. Animals. 2023; 14: 83. https://doi.org/10.3390/ani14010083.

[18] Cunningham RM, Park RM, Knazovicky D, Lascelles BDX, Gruen ME. Assessment of Sensory Thresholds in Dogs using Mechanical and Hot Thermal Quantitative Sensory Testing. Journal of Visualized Experiments. 2021. https://doi.org/10.3791/62841.

[19] Iadarola MJ, Sapio MR, Raithel SJ, Mannes AJ, Brown DC. Long-term pain relief in canine osteoarthritis by a single intra-articular injection of resiniferatoxin, a potent TRPV1 agonist. Pain. 2018; 159: 2105–2114. https://doi.org/10.1097/j.pain.0000000000001314.

[20] Klosowski M, Haines L, Alfino L, McMellen A, Leibowitz M, Regan D. Naturally occurring canine sarcomas: Bridging the gap from mouse models to human patients through cross-disciplinary research partnerships. Frontiers in Oncology. 2023; 13: 1130215. https://doi.org/10.3389/fonc.2023.1130215.

[21] Ruple A, Sargeant JM, Selmic LE, O'Connor AM. The standards of reporting randomized trials in pets (PetSORT): Methods and development processes. Frontiers in Veterinary Science. 2023; 10: 1137774. https://doi.org/10.3389/fvets.2023.1137774.

[22] Rizzo KM, Jaramilla DA, Roberts LC, Castelhano MG. Small samples, large impact: inside Cornell's cutting-edge Biobank. American Journal of Veterinary Research. 2024; 85: ajvr.24.05.0149. https://doi.org/10.2460/ajvr.24.05.0149.