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Review

Spontaneous painful disease in companion animals can facilitate the development of chronic pain therapies for humans

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SUMMARY

Objective: To outline the role that spontaneous osteoarthritis (OA) in companion animals can play in translational research and therapeutic pharmacological development.
Outline: Narrative review summarizing the opportunities and limitations of naturally occurring, spontaneous OA as models of human OA pain, with a focus on companion animal pets. The background leading to considering inserting spontaneous disease models in the translational paradigm is provided. The utility of this model is discussed in terms of outcome measures that have been validated as being related to pain, and in terms of the potential for target discovery is outlined. The limitations to using companion animal pets as models of human disease are discussed.
Conclusions: Although many steps along the translational drug development pathway have been identified as needing improvement, spontaneous painful OA in companion animals offers translational potential. Such 'models' may better reflect the complex genetic, environmental, temporal and physiological influences present in humans and current data suggests the predictive validity of the models are good. The opportunity for target discovery exists but is, as yet, unproven.

To anyone who suffers chronic, persistent musculoskeletal pain, the negative impact on their quality of life is constant. In the US more than 100 million people (~one third of the population) suffer from persistent pain with an economic cost of US$600 billion annually, more than for cardiovascular disease, cancer and diabetes combined[1]. The most significant contribution of this comes from the impact of arthritis and other musculoskeletal pain[1]. Fundamentally, existing therapies for chronic, persistent pain have limitations. This lack of options to control pain has fueled another significant social problem – the 'opioid crisis'[2]. Western industrialized countries consume the vast majority of the world's controlled opioids[3]. Although the focus on pharmacology for chronic pain has been described as short-sighted, misleading and, potentially one of the causative factors that led to this crisis[4] there is clear recognition that, among many therapeutic approaches that should be developed, the biomedical research community must work together to produce safe pharmacological alternatives to opioids[5].

However, the current practice of translational biomedical research is not producing new therapeutics for use in humans[6,7]. Within the field of pain research, numerous reviews[8–10] have highlighted the lack of translation of basic research into new approved therapeutics for treatment of persistent pain in humans, and discussed how the processes involved could be optimized to improve the chances of successful translation. There is absolutely no doubt that there have been significant successes arising from basic pain research, as exampled by the well published correlation of anti-nerve growth factor (anti-NGF) strategies (while troubled by safety concerns) showing positive correlation between preclinical

Abbreviations: CBPI, Canine Brief Pain Inventory; CMI, Clinical Metrology Instrument; LOAD, Liverpool Osteoarthritis in Dogs; NGF, Nerve Growth Factor; OA, osteoarthritis; OSA, osteosarcoma; POC, Proof of Concept; QST, quantitative sensory testing; SCI, spinal cord injury; TRPV1, transient receptor potential cation channel subfamily V member 1.

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and clinical efficacy[11]. However, despite the growing number of potential targets for new drug development, the uneasy truth is that few truly new drugs have been brought into clinical practice as a direct result of this research activity. Burgess and Williams[12] reported that out of 54 launches of analgesics between 1990 and 2010, only 4 were analgesics with novel mechanisms of action (alpha 2 delta [Neurontin]; N-type calcium channel modulator [Prialt]; cannabinoid [Sativex]; transient receptor potential cation channel subfamily V member 1 (TRPV1) agonist [Qutenza]) – all the rest were reformulations of existing pharmaceuticals. Duloxetine [Cymbalta], now approved for diabetic neuropathy pain and fibromyalgia, was originally approved for depression, but further basic research showed its potential as an analgesic. Despite newly designed drugs showing efficacy in preclinical models, clinical trials of these drugs have failed[13–15]. For osteoarthritis (OA) pain, it has been stated that evidence for the predictive validity of OA animal models for testing efficacy of novel analgesics under development is extremely limited[16], with potential reasons for this having been eloquently discussed recently[17]. Clearly there is room for improvement. What is strikingly obvious is that in over two decades there have been no novel analgesics approved for the treatment of OA-associated pain or musculoskeletal pain and yet the cost of analgesic drug development is substantially higher than that of many other types of medications[18].

In an attempt to reverse the poor translational success, there has been an increased focus on several aspects of preclinical research. The induced rodent models and the outcome measures (assays) used in pain research have come under scrutiny, with proposals for improvement suggested in several categories[8,19]: refinement of current models to improve their accuracy and reduce their variability; development of new models that are more directly applicable to prevalent painful conditions; development of assays that more accurately reflect the important outcome measures used in clinical trials; replacement of reflexive measures with non-reflexive (operant) measures; replacement of measurements of evoked responses with measurements of spontaneous behaviors; and the use of a broader range of 'quality of life' measures. However, an important point to note in the context of musculoskeletal pain, communicated by Malfait[20], is that the amount of biomedical research specifically aiming to evaluate pain and pain mechanisms in OA is surprisingly small. It is tempting to think that a simple increase in rodent research in this area would produce advances in the development of pain therapeutics, although enthusiasm for relying solely on this approach, without critically thinking about the approaches used and improving the models and approaches to research, should be tempered by the generally poor success of translational research across all the pain categories.

The majority of rodent models are 'induced' – created to 'model' or 'mimic' the target clinical conditions. These induced animal models of pain appear to have worked well for mechanistic studies but poorly as a basis for selecting new analgesic candidates[8]. One contributing factor may be that the models lack face validity or fidelity to the human condition being targeted – a risk anytime a condition is induced in the model in an attempt to recapitulate the target clinical disease. For example, using the subcutaneous injection of noxious substances, e.g., formalin, carrageenan, to model inflammatory pain seen in arthritis conditions, does not 'look like' arthritis, and the use of monoiodoacetate injections produces arthritis, but through causing the death of chondrocytes that are known to play a role in naturally occurring OA. A follow-on problem with the current rodent models is that they are self-fulfilling as preclinical work progresses. A given model might be used to unravel the mechanisms of 'pain', and once the mechanisms have been elucidated, a candidate analgesic that is developed or chosen based on these mechanisms[21] is then tested in the same model, where it would be expected to show efficacy. In the field of OA, eminent researchers have highlighted the paucity of animal models of OA[20], and emphasized the need to better align preclinical models and the clinical trial population with respect to aspects such as OA disease phenotype, stage, age, sex and confounding co-morbidities[16].

While there is no doubt that induced animal models are a necessary part of translational pain research[22], the concerns around current induced animal models continue to be re-iterated[19,20,23]. The use of highly inbred and genetically modified laboratory animals kept in homogeneous and closely regulated environments is a markedly different situation to humans, who exhibit genetic variability, have diverse diets and personal habits, and live in varied environments. In addition to concerns about the induced rodent models, there are many other aspects of preclinical research that could be improved, including preclinical experimental design (inclusion of different sexes and strains; sample size estimation; randomization; blinding), study quality and reporting of biomedical research, and addressing the issue of data reproducibility[23,24]. These considerations are crucial aspects that could be relatively easily addressed by a concerted effort by the biomedical research community, and those who play a role in the various parts of the process such as journals and funding agencies. However, that still leaves the concern about the reliance on the current induced rodent models as the only predictors of efficacy in humans.

If many current models lack face validity, one approach would be to introduce models that have greater fidelity with the naturally occurring painful disease being targeted. Another approach would be to look for identical *spontaneous* disease conditions in non-human subjects, and utilize these alongside induced rodent models in the translational paradigm. Various species of Guinea Pigs, and some rodent strains spontaneously develop OA[25] but their use in OA-pain research appears very limited (e.g., Ref. 26) possibly due to the unpredictability and variability in the severity of the disease, and the relatively long time it takes to get a mature state of the disease. Another population of animals with spontaneously occurring OA are companion animal pets. They share the same environment and suffer similar co-morbidities as humans and the OA has usually been present for prolonged periods of time. These naturally occurring painful disease 'models' may better reflect the complex genetic, environmental, temporal and physiological influences present in humans. The advantage of this population is that it is well-studied, available, and there is professional veterinary clinician scientist expertise that can be tapped into to optimize their use in translational research. Indeed their use in translational research has been suggested by several authors[23,27–29]. In this narrative review, we build on these suggestions, and propose that companion animal spontaneous 'models' can be useful in two basic ways (1) acting as a bridge between rodent preclinical and human clinical studies, testing drugs for efficacy prior to human clinical studies, with the goal of reducing the failure rates of human clinical trials, thus optimizing and accelerating the approval of new therapeutics (Fig. 1); (2) tissue from naturally occurring disease states may provide vital information in the translational puzzle – information about the neurobiology of pain in the natural disease state (Fig. 2).

Chronic pain is common in companion animals such as dogs and cats, and associated with the same diseases as in people, for example OA, osteosarcoma, intervertebral disk disease. Carefully studying novel interventions in these companion animals, using validated outcome measures, has the potential to lead to important pain treatment breakthroughs for both species. Most drugs fail in the transition from safety-focused studies to efficacy-focused studies, and we suggest that proof-of-efficacy studies could be performed in companion animals at the same time as safety studies in humans, or even earlier, following basic preclinical safety

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