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GROWING PCM MEMBERSHIP

The Preclinical Model Section was launched almost eight years ago, bringing together veterinarians and anyone interested in using animal models or potential alternatives in their research. We aim to provide valuable information and insights on various preclinical models, particularly those involving animal models, and to highlight diverse perspectives on animal physiology and welfare to ensure best practices and high-quality science. The joint scientific and ethical discourse and dialogue will enable us to address challenges in animal care, model development, creation of uniform guidance, data quality, public perception, reproducibility, and experimental design.

This work would not be possible without engaged and motivated volunteers who invest their time and efforts to maintain the section’s work and bring it to life. We give a big thanks to all former volunteers from the PCM leadership for their amazing contribution. It is our pleasure to introduce our 2024 Section Leadership!
Upcoming Webinar

Pain 101: Comprehensive Approaches to Musculoskeletal Pain Assessment and Animal Welfare Monitoring in Preclinical Research

Wednesday, June 5, 2024
12:00 PM – 1:00 PM CST

This webinar aims to present a comprehensive methodology for assessing musculoskeletal pain and monitoring animal welfare during experiments. By juxtaposing various assessment methods and approaches, we seek to delineate clear distinctions and elucidate their advantages and limitations. Through the scientific discussion, we intend to foster a broader adoption of these methodologies in both daily research routines and future projects, thereby enhancing the rigor and ethical standards of preclinical research.
Call for Reviewers
Journal of Orthopaedic Research (JOR)

It is our pleasure to announce that Aimee Colbath, from Cornell University and our section's Past Chair, will serve as Associate Editor for the Journal of Orthopedic Research (JOR). Therefore, we are seeking reviewers with expertise in small and large animal models to support her responsibilities as Editorial Board member.

Reviewing is a fundamental part of the publishing process and a cornerstone of academic communication. We want to provide all interested researchers with the opportunity to directly contact us and express their interest and commitment to supporting JOR as reviewers. We aim to grow as a diverse and inclusive community and welcome applications from around the globe - we are excited to get to know you and connect! Moreover, we highly encourage applications from early-stage investigators, as you represent the future of our community, and it is important to begin sharing responsibilities with you. Indicate your interest and expertise at the form below.

Complete the Form

We would like to highlight two articles from the April issue of JOR. Click the title of each below to continue reading.

**Epiphyseal Cartilage Vascular Architecture at the Distal Humeral Osteochondritis Dissecans Predilection Site in Juvenile Pigs**
In this study, Tóth et al. characterize the vascular architecture of the distal humeral epiphyseal cartilage in juvenile/developing pigs. Interestingly, it has been shown that there is a disparity in the predilection site to develop OCD within the elbow across species (e.g., children and pigs). Therefore, this study aimed to generate insights for future comparisons to children and to contribute to a better understanding of the pathogenesis of elbow OCD.

**Obesity Impairs Revascularization and Bone Healing in a Mouse Model of Osteonecrosis**
Deng et al. combined their novel and reliable surgery-induced osteonecrosis mouse model with obesity and weight loss. Since obesity has a high prevalence with osteonecrosis of the femoral head,
Their study can contribute to create new concepts for osteonecrosis treatment in obese patients.

**Inspiration Corner: Embrace the 3Rs**

We are pleased to introduce a new subsection in our quarterly newsletter which highlights exciting approaches and initiatives aligned with the 3R Principle. The 3R Principle (Reduce, Refine, and Replace), introduced by Russell and Burch in 1959, serves as a framework for ethically using animals in research and enhancing scientific quality and integrity in studies involving animals.

**Musculoskeletal Infections: Consensus on Pain Management in Preclinical Models**

Brought to you by Communication Committee Members

The Orthopaedic Research Society's Research Interest Group completed its international consensus meeting (ICM) on musculoskeletal infections (MSKI) following the 2023 Annual Meeting. This resulted in comprehensive work reviewing the literature related to priority questions on MSKI and estimated consensus opinions after voting. One of the workgroups was responsible for questions related to preclinical models for treatment of MSKI, mostly focusing on animal model considerations, outcome measurements, and imaging.

However, the use of effective regimens for mitigating pain remains underutilized in MSKI preclinical animals despite the general acceptance of both the ethical imperative and regulatory requirements intended to maximize animal welfare. There are several wrongly believed factors that contribute to actual use of analgia including lack of sufficient evidence-based data on effective regimens, under-dosing due to labor required to dose analgesics at appropriate intervals, concerns that the use of analgesics may impact study outcomes, and beliefs that some animals, such as rodents, recover quickly from invasive procedures and as such do not need analgesics.

However, intentions to model clinical practice, increasing awareness of animal ethics, efforts to apply the 3Rs (replacement, reduction, refinement), and stricter legislation argue for a change in this respect. More research should therefore investigate the pharmacokinetics and pharmacodynamics of different types of analgesia, behavior and physiological alterations in sick animals, and the implementation of humane endpoints to reduce unnecessary suffering.

On this topic, Caroline Constant (Doctor of Veterinary Medicine [DMV] and Diplomate, American and European Colleges of Veterinary Surgeons [DACVS-LA, DECVS]) from the AO Research Institute Davos shares her opinion on pain management for MSKI models.

For researchers, managing pain in animal experiments is not just about alleviating suffering; it is imperative for maintaining research integrity and ensuring the validity of data. Scientific evidence consistently shows that pain can profoundly affect the outcomes of preclinical studies, skewing data and yielding unreliable results. This underscores the critical role of effective pain management as a cornerstone of rigorous scientific methodology.

Good science and animal welfare are intrinsically linked. Preclinical models of infection, for instance, present particularly challenging and painful conditions for the animals involved. These models require exposing animals to pathogens that often cause significant discomfort, distress, and pain due to physiological effects such as inflammation and fever. Managing animal suffering in such studies is complex, as the symptoms of the infection are directly tied to the scientific objectives. Therefore, rigorous standards of care, including proactive pain management and careful welfare monitoring, are essential. Unmanaged pain can trigger stress responses that significantly alter physiological
parameters, affecting the reliability of experimental results and potentially leading to misleading conclusions that could compromise further research and development.

The principles of the 3Rs (Reduce, Refine, and Replace) should guide researchers' practices, particularly Refinement, which emphasizes reducing unnecessary pain and distress. Implementing robust analgesic regimens is a critical aspect of this. A multimodal analgesia regimen, which usually combines two or more types of analgesic agents such as NSAIDs, opioids, local anesthetics, and adjuvant drugs is a standard approach in human pain management and should also be in animal experiments.

In summary, effective pain management is a scientific priority in animal experiments and upholds ethical standards.

Mouse Handling Thought Differently:
Let's Start Using Tunnel Handling and Cupping

by Annemarie Lang, PhD

Tail handling is the traditional and most commonly used method for handling mice. Here, mice are grasped by the base of their tails and transferred into new cages or for procedures. However, mounting evidence suggests that even brief tail handling, as short as two seconds, can have negative effects on the behavior and physiology of these animals. Who wouldn't understand, mice are prey species, and many of you have observed predators such as birds lifting them in the wild. Therefore, implementing refined handling methods is highly beneficial for improving animal welfare, reducing behavioral biases and psychological distress, and increasing job satisfaction among experimenters.

Two of the most common refined methods are Tunnel Handling and Cupping. During Tunnel Handling, the experimenter guides the mice into a tunnel to lift them out of their cage, while Cupping involves lifting mice with cupped hands, requiring only a bit more training. The author of this article can attest that both methods work excellently, even in musculoskeletal procedures such as with an external fixator, elevating animal handling to a new standard that precludes a return to traditional methods. For those interested in delving deeper into the topic, the 3Rs Collaborative offers an excellent overview complete with numerous citations and references, along with a well-crafted “How to” page.

Embrace the latest trend in science and give these refined methods a try!

For more inspiration on refinement in mouse fracture models, check out our recent publication in JOR: Embracing ethical research: Implementing the 3R principles into fracture healing research for sustainable scientific progress.

One Medicine, One Orthopaedics, One Community

In another new subsection of our quarterly newsletter, we will highlight exciting topics and scientists from the field of comparative medicine to foster translational science.

Osteosarcoma Immunotherapy Research in Dogs Helps Advance Pediatric Trials

by Lynn Pezzanite, DVM, MS, PhD, Diplomate ACVS-LA
Despite years of research, approximately 30% of pediatric patients with osteosarcoma (OS) still succumb to metastatic disease. Researchers at Colorado State University led by Dr. Steven Dow, DVM, PhD and Dan Regan, DVM, PhD at the Flint Animal Cancer Center at Colorado State University are using dogs with spontaneous OS as a uniquely valuable animal model to test promising new immunotherapy combinations, particularly those that target immune suppressive myeloid cells in the tumor microenvironment (TME). Spontaneous canine OS is a well-defined large animal model of human OS, exhibiting similar biology, clinical progression and metastatic sites, and molecular aberrations. Indeed, canine OS has historically been used to help develop novel limb spare techniques, to evaluate non-specific immunotherapeutics and assess the efficacy of targeted therapeutics to prevent the outgrowth of metastatic disease. Despite best efforts, progress in the prevention and treatment of metastatic disease has essentially stalled for the past three decades; 30% of people and 90% of dogs still die of tumor spread, primarily to the lungs.

Numerous clinical trials have been undertaken in people with macroscopic metastases as well as in human patients and dogs with both microscopic and macroscopic disease, yet all have failed to demonstrate improved outcomes. This is particularly evident with respect to immune checkpoint inhibitors, which are largely ineffective in pediatric OS patients, despite their effectiveness in many other tumors. One particularly daunting challenge for immunotherapy-based therapeutics for OS relates to the immunologically “cold” TME, which greatly suppresses effective T-cell responses.

In recent studies supported by the NCI Moonshot initiative, the first NIH supported research program specifically targeting canine cancer immunotherapy studies, the CSU research program in collaboration with Dr. Cheryl London, DVM, PhD (Tufts University) has advanced a novel triple drug combination to deplete myeloid cells to trials in dogs in both the adjuvant and metastatic disease settings. The studies employed a combination of three drugs targeting myeloid cells, including two repurposed drugs (losartan and toceranib, targeting monocytes and MDSC and T-regulatory cells, respectively). A third drug designed to inhibit signaling by the chemokine receptors CXCR1 and CXCR2 was included to block neutrophil and monocyte migration into the TME. Continuous oral treatment with the triple drug immunotherapy combination induced significant, measurable antitumor activity in dogs with metastatic OS, and significantly improved survival when administered following amputation compared to the current standard of care in dogs with OS. These studies will form the basis for additional combinations of myeloid and T-cell targeted immunotherapy for this devastating disease of both kids and dogs.
The Orthopaedic Events Calendar on the ORS website lists events that are of potential interest to those in the orthopaedic community. ORS Members are welcome to submit applicable events at no charge through the Submit Event button at the top of the calendar on the site. This is an excellent opportunity to spread the word about your orthopaedic-related events, ensuring they reach a wider and engaged audience.

Find or Post Events

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**Growing the PCM Membership**

The Preclinical Models section continues to grow. Over 80% of our members are US based and are mostly established investigators. We are seeking early-career individuals interested in advancing preclinical models research and related sciences to improve patient care through basic, translational, and clinical research.

If you know someone who might be interested in representing the voice of preclinical models research within the ORS community and beyond, spread the word. Your personal endorsement and enthusiasm can inspire potential members to be part of this community. Let's expand our network!

Preclinical Model Section Membership

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