Introduction

Naturally Occurring Diseases in Animals: Contributions to Translational Medicine

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The natural world brings to us an array of opportunities to understand the processes of life and disease. Naturally occurring or spontaneous diseases of animals allow us to gain important and fundamental knowledge of human disease and translational medicine. This edition of the ILAR Journal brings together a number of reviews that enlighten us about naturally occurring diseases of animals. These reviews are written in context to lessons learned about disease processes and translating this knowledge to the treatment of human disease. Among these articles are well-documented examples of animal diseases with causes ranging from genetic to infectious. Importantly, these natural animal models provide insight into the pathogenesis of human maladies and offer unique perspectives of how this information can be applied to intervention strategies in people.

Naturally occurring cancers in dogs provide interesting parallels in our understanding of human cancers. Dr. Alvarez’s article on naturally occurring canine cancers provides a current view of the advantage of studying canine cancer to understand the genetic basis of human cancers. Although mouse models are clearly a preferred model for genetic manipulation throughout biomedical science, the canine naturally selected model provides opportunities to study the causes of cancer in context of the same environment as their owners. Dogs provide a novel model in this setting, in part, because of purposeful genetic breeding that amplifies phenotypes pleasing to humans. The reduced generation time of dogs and recent knowledge of the canine genome have accelerated the usefulness of dogs as models of human cancer. The canine cancer model is further focused on in the review by Drs. Fenger, London, and Kisseberth, who document the parallels between canine osteosarcoma and sarcomas in children. Osteosarcoma is the most common malignant bone cancer in children and dogs. Although conventional treatments have greatly improved the survival of children and dogs suffering from osteosarcoma, new treatments are required to further extend the success of therapies against this aggressive cancer. The authors point out the important parallel clinical and biological features of human and canine osteosarcoma. At the molecular level, the canine cancer parallels what we know about pediatric osteosarcoma, making the dog model particularly relevant in the development of new targeted drugs against the cancer. This theme continues in the review by Dr. Knapp and colleagues of bladder cancer in dogs and humans. Urinary bladder cancer affects thousands of human and canine patients each year. Naturally occurring bladder cancer in dogs has many similarities to invasive bladder cancer in humans at the cellular, molecular, and biological levels, making this naturally occurring model attractive to study new forms of therapy against this deadly cancer. This review illustrates the value of combining knowledge about canine bladder cancer with that of induced rodent models to help guide translational approaches to understanding invasive urothelial carcinoma of humans. Bladder cancer studies in dogs have the potential to define heritable and environmental risks for the human disease. In addition, recent clinical trials in dogs suffering from transitional cell carcinoma serve the dual purpose to improve the lives of pet dogs and to inform human clinical trials. Drs. Davis and Ostrander provide an insightful overview of the value of understanding naturally occurring cancers in dogs from a genomics perspective. With more than 70 million pure and mixed breed dogs in the United States, combined with the fact that cancer is a leading cause of death in this species, the value of understanding the genetics of dog cancers is dramatic. As knowledge of the canine genome and of specific mutations in their cancers expands, so too have opportunities to clarify the underlying causes of cancer in people suffering similar cancer types. Improvements in the care of dogs have paralleled their owner’s willingness to seek out new treatments for dog cancers. Through the careful evaluation of breed tendencies, combined with surveys of specific genetic mutations, researchers have provided a new avenue to understand the causes of cancer in both humans and dogs. This review illustrates that genomic analysis in pet dogs may offer new insights.
into human cancers for which human gene mapping studies are complicated by small family sizes and locus heterogeneity.

In parallel with increasing knowledge about naturally occurring cancers in animals, refinements in imaging modalities have greatly improved the diagnosis and evaluation of cancer in animals as well as in people. Dr. LeBlanc reviews the current state of knowledge of comparative imaging studies in cancer-bearing animals and how this information can be translated to improve assessment of human cancers. Her review proposes expansion of the highly successful National Cancer Institute’s Comparative Oncology Trials Consortium (http://ccr.cancer.gov/resources/cop/COTC.asp) to include comparative imaging studies that would complement the drug discovery and development trials in animal patients. Advances in molecular imaging techniques are providing disease-specific signals and individualized data that can refine patient selection and guide patient-specific interventional treatment approaches. Finally, in the review by Drs. O’Connor and Wilson, adoptive immunotherapy is considered as a treatment against a variety of cancers and as a specific treatment against canine lymphoma. Current veterinary therapeutic approaches often include the use of exogenous cytokines to enhance tumor antigen-specific monoclonal antibody therapy. Newer cell-based treatments offer promise against multiple human and canine cancers. This review compares current applications of adoptive T cell therapy in dogs and people and explores how this strategy can overcome the problem of central immune tolerance by combining the natural ability of patients’ T cells to recognize and eliminate target cancer cells while instigating a systemic immune response to block advancing disease.

Three articles review and highlight benefits from infectious disease models that provide important insights for translation to medicine. Drs. Yugo, Cossaboom, and Meng, in their review of models of hepatitis E virus (HEV), a cause of hepatitis globally in humans, illustrate the evolving knowledge of new genotypes of HEV in mammalian species. The authors document how comparative studies have yielded insights into human disease caused by human HEV genotypes 1 and 2. Traditional nonhuman primate models were critical to the discovery of human HEV and to study the pathogenesis of HEV infection. Recent advances in genetic identification and molecular characterization of naturally occurring HEV infections in swine, chicken, and rabbits have contributed new tools to understand HEV pathogenesis and to develop new interventions to prevent HEV infection. This review also acknowledges the need for models of fulminant HEV infection during pregnancy and of virus persistence in chronic infections. Dr. Breitschwerdt reviews the current state of knowledge of bartonellosis, focusing on what is known about the transmission and ecology of an array of Bartonella species. The study of the expanding number of Bartonella species that are confirmed to be zoonotic pathogens offer important opportunities to learn more about the human infections. This review illustrates the ecologically diverse animal reservoir hosts and the evolving array of arthropod vectors that have been documented to transmit the bacteria among animals and humans. The complex pathogenesis of bartonellosis provides diagnostic and clinical challenges in animals and people, requiring a One Health approach to understand the disease and to investigate new interventions or therapeutic approaches for this chronic and devastating disease. Equally as complex, respiratory syncytial virus bronchiolitis in preterm infants presents severe challenges to pediatric clinicians. Dr. Ackermann’s review summarizes the pathogenesis of respiratory syncytial virus in humans and various animal models and outlines the developmental, anatomic, cellular, physiologic, and immunologic features in the lamb model that are similar to infection in human infants. This important large-animal model allows the evaluation of novel interventions such as the delivery of cytokines or compounds to block the damaging effects of the infection on the developing lung, as well as assessments of contributory factors such as alcohol consumption during pregnancy or of immune-mediated damage from ineffective immune responses.

Four articles focus on the musculoskeletal and neurologic systems. Dr. Kornegay and colleagues review the current knowledge of Duchenne muscular dystrophy, an X-linked human disorder. Inherited absence of the protein dystrophin causes degeneration of skeletal and cardiac muscle, leading to severe mobility and quality-of-life issues affect patients. In this review, genetic and cell-based therapies are compared with investigations of pharmacologic approaches to block the disease outcomes. This review outlines other mammalian dystrophinopathies and compares their advantages and limitations as models of the human disease. Dr. Patterson’s review of canine epilepsy as a model of human epilepsy compares and contrasts the naturally occurring dog model to the induced model of the disease in rodents. Illustrating the pervasive problem of rodent models that fail to recapitulate the human disease, this review suggest the use of naturally occurring epilepsy in dogs as an alternative approach to understanding the disease and investigating new treatments to block seizure development. In a unique comparative approach, Dr. Patterson-Kane reviews recent advances in the understanding of tendon maturation, aging, and subclinical pathology as determinants of tendon injury and highlights superficial digital flexor tendon injury in equine athletes as an important model of Achilles tendon injury in people. These tendons share similar functional and clinical features that are not reproduced in other animal models. The equine model has particular advantages in understanding tendon matura-
tion, aging, and environmental and biomechanical factors that contribute to the deterioration of tendons before and during tendon injury. Finally, Dr. Kranenburg and colleagues review another common musculoskeletal condition in humans and dogs, spondylosis. This review identifies similarities in the pathology of each but also reviews the disparate terminologies used to describe parallel disease and pathologic features. They focus on dog breeds such as boxers that spontaneously develop spondylosis and intervertebral disk disease and consider how specific genes linked to the development of this disease in boxers may help to define the disorder in humans.
The issue concludes with a review by Drs. Baneux, Martin, and Hallman of animal care and use issues involving clinical trials using patient-owned animals. How to conduct studies ethically in privately owned animals has been debated in several forums. Their review brings a fresh perspective and provides some best-practice guidelines for institutions seeking to conduct clinical trials for the benefit of animals and their owners. Studies with privately owned animals, similar to those with human patients, may warrant mechanisms of oversight that are not clearly covered in current international, federal, or local laws, regulations, or guidelines regarding animal research. Publication of data from clinical trials involving privately owned animals has clear needs for oversight that is ethical, protects the health of the animals involved, is transparent to the owners, and is congruent with the veterinary oath.