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Studies Focus on a Drug Therapy for DM & Predicting Risk of Hemangiosarcoma

Boxer Owners May Participate in DM Clinical Trial

A clinical trial to test the effectiveness of the drug antisense oligonucleotide in treating dogs in the early stages of degenerative myelopathy (DM) will begin this fall at the University of Missouri School of Veterinary Medicine. Early signs of the neurodegenerative disorder include dragging the hind limbs and uncoordinated gait. Owners must be within driving distance of the University of Missouri to participate in the study. For information, contact the lead investigator, Dr. Joan R. Coates, at coatesj@missouri.edu or 573-882-7821.

Boxers are among the breeds predisposed to degenerative myelopathy, a progressive neurodegenerative disease that affects adult dogs, and hemangiosarcoma, an aggressive, highly malignant cancer. Research of these diseases offers hope that effective treatments may one day help affected dogs. Here is a review of the research.

Testing a Drug Therapy for DM

Degenerative myelopathy (DM) is a heartbreaking neurodegenerative disease that affects adult dogs at least 9 years of age, after many already have been bred. Although the recessive causative mutation in the superoxide dismutase gene (SOD1) was discovered in 2009, leading to a DNA test to help identify carriers and affected dogs at risk for developing the disease, DM continues to be a health concern.

A pilot study recently begun by a veterinary neurologist and neurosurgeon at the University of Missouri College of Veterinary Medicine is testing the effectiveness of a drug treatment for dogs affected by DM. "Our goal is to use ASO (antisense oligonucleotide) therapy to disrupt the coding for SOD1 protein," says Joan R. Coates, D.V.M., DACVIM-Neurology, professor of neurology and neurosurgery.

Although DM was first recognized in German Shepherd Dogs in the 1970s, the disease affects many breeds. Boxers are among the highly susceptible breeds, with an allele frequency of 72 percent. Fifty-seven percent of Boxers tested for the disease are considered at risk. Over 25 dog breeds have been confirmed for degenerative myelopathy.

Responding to the health concern in Boxers, the American Boxer Charitable Foundation has provided funding of $76,000, plus $50,000 directly to the AKC Canine Health Foundation, to support DM research. Joyce Campbell, D.V.M., chair

of the American Boxer Club Health and Research Committee and a trustee of the Foundation, works to encourage breeders and owners to test their dogs for DM. Importantly, she says, breeders can use the DNA test to make informed breeding decisions.

Tracy Hendrickson of Tulsa, Okla., who breeds under the Sunchase prefix, has experienced DM in several Boxers. Today, she uses the DNA test to determine which dogs to breed. Those that carry the SOD1 mutation are bred only to clear, healthy dogs to avoid producing affected dogs. "I recognize the potential of creating a genetic bottleneck, but the goal is to increase the gene pool with more DNA-clear dogs," she says.

DM is similar to some forms of the human disease amyotrophic lateral sclerosis (ALS), more commonly known as Lou Gehrig's disease. It is named for the New York Yankees' first baseman and Hall of Famer Henry Louis "Lou" Gehrig, whose standout 16-year major league baseball career ended in 1939 due to ALS and who died from the disease in 1942.

The first sign of DM that owners notice is their dogs dragging or scuffing the nails of their hind legs. Decreasing muscle control and weakness in the rear limbs lead to frequent falls and difficulty getting up. Usually within 11 months, paralysis occurs. The progressive disease spreads through the central nervous system, damaging the spinal cord, muscles, nerves, and brain.

DM affects the nerve fibers, called axons, and secondarily reduces the nerve insulation, myelin. The process hinders nerve transmission, resulting in hind limb clumsiness and loss of mobility. When the nervous system is no longer able to transmit sensory information or motor commands between the brain and hind limbs, a dog loses complete muscle function.

Coates' study, in which she has received a two-year grant from the National Institute of Neurological Disorders and Stroke, is in collaboration with a neurologist at the Washington University School of Medicine who is leading a clinical trial in ALS patients to test the ASO therapy.

"Our goal is to develop therapeutic treatments that will benefit dogs with DM and people with ALS," Coates says.

Coates currently is performing safety studies, which will lead to a small clinical trial to study the ASO treatment in six dogs at the beginning stages of DM. Although the treatment protocol is still being developed, she expects the injections will be made into the spinal fluid of the lower lumbar region.

Explaining the treatment, Coates says, "Antisensse oligonucleotide is a short strand of complementary DNA that can inhibit mRNA expression and thereby block the transfer of genetic information from DNA to protein. These short strands of synthetic DNA can be used as therapeutic agents or tools to study gene function. When ASO is injected into dogs or people, it suppresses the coding for the SOD1 protein, slowing or possibly halting the disease progression. We want to define how long the ASO drug stays in the spinal fluid cells to help us determine the frequency of injections."

Among the difficulties treating diseases of the central nervous system is getting past the blood-brain barrier, the protective barrier that separates the brain from the circulatory system. "The blood-brain barrier makes it hard to administer drugs through the vein to treat the central nervous system," says Coates. "The challenge is getting the treatment into the spinal fluid and the nervous tissue."

The pilot study could help modify treatment for ALS patients and expedite larger clinical studies of ASO therapy for humans. Coates is optimistic the research will help to identify other disease markers as well.

"As the links between DM and ALS become better understood, it will be important for other veterinary neurologists and ALS researchers to expand treatment approaches with a goal of finding a cure," Coates says. "ALS patients are helping dogs with DM, and dogs with DM are helping to find a therapy for ALS."

Developing Cancer Risk Prediction Tools

Collaborative research, involving key canine cancer researchers, is focusing on developing markers to help diagnose and guide cancer treatment. A two-year, $1.06 million study, funded by the AKC Canine Health Foundation and the Golden Retriever Foundation, is based on newly discovered heritable and acquired mutations. Although the investigation primarily involves Golden Retrievers, a breed in which 20 percent of dogs die from hemangiosarcoma, the findings are expected to apply to all dog breeds.

The researchers are Kerstin Lindblad-Toh, Ph.D., director of vertebrate genome biology at the Broad Institute of MIT and Harvard and professor at Uppsala University in Sweden; Jaime Modiano, V.M.D., Ph.D., the Perlman Endowed Chair in animal oncology at the College of Veterinary Medicine and Masonic Cancer Center of the University of Minnesota; and Matthew Breen, Ph.D., C.Biol., FSB, professor of genomics at North Carolina State University College of Veterinary Medicine.

The study stems from their recently completed research in Golden Retrievers, evaluating the relationship between inherited traits and susceptibility to hemangiosarcoma and lymphoma. Among their groundbreaking discoveries, the researchers identified several regions of the genome that contain heritable risk factors for these cancers. They also identified somatic mutations, alterations in DNA that happen after conception, in tumors that occur recurrently in both cancers. Some of these mutations appear to be linked to how long a dog with lymphoma stays in remission when treated with different types of chemotherapy.

"Our preliminary results indicate that a few heritable genetic risk factors account for as much as 50 percent of the risk for these cancers," Lindblad-Toh says. "We can now look at the tumors in context of the inherited risk factors and start to understand how the tumor process starts. In the coming years, we will have a better understanding of how the mechanisms work and how the tumors continue to grow and spread based on these initial risk factors."

The current study has the potential to produce data that will lead to strategies for determining risk assessment in individual dogs. It also promises to provide insights on how to manage risk across the canine population as a whole. The researchers plan to validate genetic markers that can be used to determine risk in

a large population of Golden Retrievers in the U.S. and Europe. Their goal is to develop robust risk population tools, including a DNA test, to detect dogs susceptible to cancer.

Boxers are among the at-risk breeds for hemangiosarcoma. Others are Bernese Mountain Dogs, Flat-Coated Retrievers, German Shepherd Dogs, Portuguese Water Dogs, and Skye Terriers. The cancer, which comprises 5 to 7 percent of all canine cancers, is called a silent killer because it seldom is detected before the tumor ruptures, causing a life-threatening condition.

Hemangiosarcoma typically starts in the thin layer of cells that line the interior of blood vessels. This intimate access into the blood supply contributes to the cancer's metastasis throughout the body. Tumors in about 50 percent of cases start in the spleen. Other internal organs that are commonly affected include the heart, liver, lungs, kidneys, mouth, muscle, bone, brain, and bladder. Unlike these visceral hemangiosarcomas, tumors that occur in or under the skin typically show less aggressive behavior.

In order to feed their growth, hemangiosarcomas use a process called angiogenesis to create new blood vessels from existing blood vessels. Unlike normal angiogenesis, which is well organized, tumor angiogenesis is disorganized and leads to formation of blood clots as well as hemorrhaging. Mini-hemorrhages within a hemangiosarcoma can heal quickly with dogs showing only mild signs, but severe hemorrhaging from within a tumor can be fatal.

Since signs of hemangiosarcoma are not apparent until the cancer is in advanced stages, it is virtually impossible to detect early. There are no reliable blood tests or imaging technology to identify the presence of this cancer before it is visible or has caused clinical signs.

Without treatment, dogs with visceral hemangiosarcoma usually die in one to two weeks. The standard of care for hemangiosarcoma is surgery and/or chemotherapy, depending on several factors, such as the location of the tumor. Treatment principally is meant to prevent fatal blood loss and to extend life but is seldom curative.

In tumors confined to the spleen, about 50 percent of treated dogs live four to six months after diagnosis. Only 10 to 15 percent survive 12 months or longer. The outcome is less favorable for dogs with tumors that originate in other organs and for dogs that have detectable metastasis at the time of diagnosis.

If the research is successful, owners and veterinarians will be able to follow susceptible dogs and hopefully intervene before life-threatening signs appear. "Identifying the genetic basis of hemanigosarcoma will allow us to better understand the biology of this cancer," Modiano says. "This may lead to preventive measures and effective new treatments."

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