RESEARCH PROGRESS REPORT SUMMARY

Grant 02165-MOU: Identification of Biomarkers and Therapeutic Targets for Canine Degenerative Myelopathy: The Search for A Cure

Principal Investigator: Joan Coates, DVM
Research Institution: University of Missouri, Columbia
Grant Amount: $154,077.00
Start Date: 1/1/2015 End Date: 6/30/2019
Progress Report: End-Year 4
Report Due: 12/31/2018 Report Received: 1/2/2019

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Original Project Description:

Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that converts superoxide to water and hydrogen peroxide, superoxide dismutase 1 (SOD1), have been linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig's disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. Dr. Coates proposes developing a test that would assay the blood and cerebrospinal fluid (CSF) for proteins that are exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. The investigators will correlate the concentrations of neurofilament proteins in CSF and blood with disease stage, and anticipate that neurofilament protein concentration in blood and CSF will increase as disease progresses. Such a test will allow for minimally invasive monitoring of disease. Furthermore, such a diagnostic test could be used to measure the success of therapy, which may be underway in a cohort of DM-affected dogs [Boxers and Pembroke Welsh Corgis (PWC)] (funded by NIH/NINDS). This work will complement the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. These are functional disease markers that are also being studied in ALS patients.

Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.
Publications:


Presentations:

Joan R. Coates, Curt Mazur, Eric Swayze, Gayle C. Johnson, Daniella Vansteenkiste, Katherine F. Bibi, Stefanie Lim, Frank Bennett, Timothy M. Miller. Antisense oligonucleotide therapy targeting SOD1 for the treatment of canine degenerative myelopathy: A disease model of ALS. 29th International Symposium on ALS/MND. December 7-9, 2018; Glasgow Scotland, UK. Poster presentation (in-vivo models section).

Melissa J. Lewis, James Holland, Jeremy L. Shomper, Baye G. Williamson, Daniella Vansteenkiste, Katherine F. Bibi, Stefanie Lim, Janice Robertson, Joan R. Coates. Diffusion tensor imaging detects brain pathology in canine degenerative myelopathy. 29th International Symposium on ALS/MND. December 7-9, 2018; Glasgow Scotland, UK. Poster presentation (Imaging section).


Coates JR, Sah D. A gene therapy approach targeting SOD1 in a canine disease model of ALS. Workshop Translational Approaches for SOD1-ALS. December 7, 2017; Boston MA, USA.


Coates JR. 2016 Georgia Veterinary Medical Association Fall Convention. Diagnosis and treatment of canine degenerative myelopathy. Westin Atlanta Perimeter North, Atlanta, GA, November 4-6, 2016. (1 h)


Coates JR. 29th Annual Symposium of ESVN and ECVN 2016. Applied Translational Neuroscience. Canine degenerative myelopathy as a disease model of ALS from laboratory to practice; ‘How research has changed my clinical practice’. Royal College of Surgeons of Edinburgh. Edinburgh, Scotland, September 15-17, 2016. (Keynote Speaker)


Coates JR. Canine degenerative myelopathy. Brain Camp 2016 – Noteset. ACVIM/The Ohio State University, July 29, 2016. 1 h


Coates JR. Clinical trials on canine degenerative myelopathy. 2016 ACVIM Forum Proceedings, Denver, CO, June 10, 2016. Specialty Research Session. 1.0 h


Christine M. Sibigtroth, Maria R. Jones, Virginia B. Garcia, Joan R. Coates, Gayle C. Johnson, Eric L. Villalón and Michael L. Garcia. Lumbar spinal cord neuroprotective microglia and fractalkine are increased with disease progression in canine degenerative myelopathy. 2016 American College of Veterinary Internal Medicine Annual Forum. Denver, CO June 9, 2016. Accepted Oral Presentation. Won the ACVIM neurology resident research abstract award.

C.M. Sibigtroth, V.B. Garcia, G.P.J. Shaw, G.C. Johnson, J.R. Coates, M.L. Garcia. Increased phosphorylated neurofilament heavy (pNF-H) in CSF is a disease marker of canine degenerative


Christine M. Sibigtroth, Virginia B. Garcia, Gerry P.J. Shaw, Joan R. Coates, Michael L. Garcia. Increased phosphorylated neurofilament heavy (pNF-H) in CSF as a potential disease marker of canine degenerative myelopathy. 26th International Symposium on ALS/MND; December 11-13, 2015; Orlando FL, USA. Submitted 5/30/2015. Accepted: Poster Presentation (SW9; online page 8)


Coates JR. 2015 National Parent Club Canine Health Conference. Canine degenerative myelopathy: A disease model for ALS therapy development. St. Louis, MO Hyatt Regency at the Arch, August 7-9, 2015. 1 h CE

Coates JR. Kansas City University of Medical and Biosciences. Science Friday Talks. Canine degenerative myelopathy: A disease model of amyotrophy lateral sclerosis. May 22, 2015. (1h)

Coates JR. The Linus Pauling Institute (Dr. Joe Beckman) and Small Animal Rehabilitation Foundation (Dr. Wendy Baltzer), Oregon State University College of Veterinary Medicine. Canine degenerative myelopathy: A disease model of amyotrophic lateral sclerosis (Lou Gehrig’s disease). April 9, 2015. (1h)

**Report to Grant Sponsor from Investigator:**

Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that protects the spinal cord from oxidative stress are linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig’s disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Monitoring the progression of disease is critical for development of effective therapies, but currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. We have developed a test that would assay the blood and cerebrospinal fluid (CSF) for proteins exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. Preliminary data suggest that measuring neurofilament proteins in CSF is a diagnostic marker for DM but we need to establish specificity data to distinguish between other central axonopathies. We have shown that neurofilament proteins in CSF remain elevated through all 4-disease stages but trends may show a longitudinal increase in pNF-H in
individually monitored dogs affected by DM. We will measure neurofilament proteins in CSF to evaluate efficacy of an SOD1 silencing by antisense oligonucleotide therapy approach in a cohort of DM-affected dogs.

We are complementing the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. We continued to collect preliminary data from DM affected dogs using magnetic resonance spectroscopy and diffusion tensor imaging to evaluate for difference in metabolites in the brain. After evaluation of more DM affected and normal dogs, detectable differences in variables were observed in some areas of the brain and cervical spinal cord using diffusion tensor imaging. No detectable differences were observed on magnetic resonance spectroscopy or electrodiagnostic testing.

Six companion dogs affected by DM have been enrolled in a double-blind, vehicle controlled closed trial to evaluate an ASO treatment. Dogs were treated by monthly intrathecal lumbar injections of cSOD1 ASO or aCSF and longitudinally monitored with neurologic examination, electrodiagnostic testing, MRI and CSF analysis. Companion dogs affected by DM showed continued disease progression based on gait monitoring. Nonetheless, the study is statistically under-powered to detect a clinical difference during the interim analysis. Longitudinal monitoring of pNF-H in CSF and MRI variables are still pending.