2015 Summary
Research of Canine Degenerative Myelopathy
American Boxer Charitable Foundation and American Boxer Club
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I have been asked by Dr. Joyce Campbell to provide a summary to the ABCF and ABC of the research accomplishments over the past year. I would like to especially acknowledge the ABCF and ABC for the continue support of the research through grant funding and donations.

Update on current research
We continue to move forward with the grant funded by the AKC Canine Health Foundation through the ABCF entitled, *Biomarker development in canine degenerative myelopathy for diagnosis and longitudinal monitoring of a therapeutic approach*. We have another potential diagnostic marker, which will assist with the early diagnosis of DM. We also continue to evaluate neuroimaging through MRI and electrodiagnostic techniques in monitoring DM progression. We also continue to work on a project funded by the Missouri Spinal Cord Injury Research Program and study histopathologic studies of different motor units (nerves and muscles) so that we can learn more amount the pathophysiology of DM. The Boxer is one of the breeds that the studies are focusing on. We are still in need of CONTROL tissues that represent older Boxers (> 9 years) that pass from another disease process and considered to be neurologically normal.

Through finding the associated mutation in a protein called superoxide dismutase 1 (SOD1), we now have a target for therapeutic study. We continue to evaluate a molecular approach using antisense oligonucleotides to halt the production of SOD1, which may slow DM progression. This has been shown in transgenic ALS mouse studies. This study is being funded by the NIH/NINDS. The above mentioned AKC CHF grant will fund the untreated control group so that we can study the therapeutic approach as a randomized, double-blinded, placebo control study. This is the best way to evaluate therapeutic efficacy. The same therapeutic approach also will be underway in human patients also with SOD1-associated ALS. After completion of additional safety studies, **this study is now underway**. The main inclusion criteria are Boxers in the early disease stage and within driving distance to receive monthly treatments.

Through the ALS Association (ALSA) we received funding to also pursue an immunization study that targeted the misfolded SOD1. Researchers at the University of Toronto have isolated part of the misfolded protein whereby the animal's own immune system develops antibodies against it. The clinical trial is almost completed and we are assimilating the data.

I also have a PhD student who is studying the neuroinflammation associated with canine degenerative myelopathy. Accurate knowledge of neuroinflammation characteristics in relation to disease stage will be vital to test the ability of potential anti-inflammatory therapeutics to slow or halt the disease progression. This project was moved forward by Joyce Baker Brown and received funding through the Million Dollar Round Table Foundation with her platform as *Man and Man's Best Friend, In Pursuit of One Dream to cure ALS and DM.*

Dr. Coates continues to study DM through tissue collections and archiving those tissues so the disease can be researched also by other DM and ALS research groups. The ABCF has kindly donated additional funding to enable the archiving to be continued.

Newly funded research:
This year we received additional funding also from the ALS Association (these funding opportunities are made possible through the 'Ice Bucket Challenge'):

Coates JR (Co-PI), Gerdes JM (Co-PI), Bryan JN, Johnson GC. ***Temporal regional PET imaging of the CNS EAAT2 Protein in canine degenerative myelopathy as a disease model of ALS.*** *The ALS Association (Investigator Initiated Research Grant)* This research explores brain function and a receptor known to be affected in ALS. We will longitudinally follow DM participant dogs using this diagnostic marker.

Sah D (Co-PI), **Coates JR (Co-PI),** Johnson GC, Govindarajan R. ***Development of an AAV Gene Therapy Targeting SOD1 for the Treatment of ALS –Translation of Delivery.*** *The ALS Association TREAT ALS ™ Drug Development Contract.* We will be using a gene therapy approach to treat DM affected dogs. This project is in collaboration with a company that focuses on treatment approaches for neurodegenerative diseases.

Dr. Coates and her collaborators also have continued to publish the completed research:

Zeng R*, Coates JR§, Johnson GC, Hansen L, Awano T, Kolicheski A, Ivansson E, Perloski M, Lindblad-Toh K, O'Brien DP, Guo J, Katz ML, Johnson GS. Breed distribution of *SOD1* alleles previously associated with canine degenerative myelopathy. *Journal of Veterinary Internal Medicine*.2014;28:515-521.
http://onlinelibrary.wiley.com/doi/10.1111/jvim.12317/abstract

Morgan BR*, Coates JR§, Johnson GC, Shelton GD, Katz ML. Characterization of thoracic motor and sensory neurons and spinal nerves in canine degenerative myelopathy, a model for amyotrophic lateral sclerosis. *Journal of Neuroscience Research*. 2014;92:531-541.
http://onlinelibrary.wiley.com/doi/10.1002/jnr.23332/pdf

Morgan BR*, Coates JR§, Johnson GC, Bujinak AC, Katz ML. Characterization of intercostal muscle pathology in canine degenerative myelopathy: A disease model for amyotrophic lateral sclerosis. *Journal of Neuroscience Research*. 2013;91(12):1639-1650.
http://onlinelibrary.wiley.com/doi/10.1002/jnr.23287/pdf

Lovett MC, Coates JR, Oglesbee M, Fenner W, Moore SA. Quantitative assessment of HSP70, IL-1β and TNF-α in the spinal cord of dogs with E40K SOD1-associated degenerative myelopathy. *The Veterinary Journal*. 2014; 200(2):312-317.

When provided the opportunity, she lectures on canine DM at veterinary CE, research meetings and breed clubs. She also is invited by the ALS Association to share her research on canine DM in order to enhance collaboration and open doors for shared therapeutic approaches. The ALS Association acknowledges canine DM as a disease model for ALS. This year she was invited to a 'think tank' that took place at The Cold Springs Harbor Laboratory, NY.

We continue to investigate for disease modifiers in collaboration with Dr. Gary Johnson and Dr. Kerstin Lindblad-Toh and colleagues, which was also funded by the AKC-CHF and the ABCF. We have a manuscript under review for a potential genetic disease modifying gene. We continue to explore the genetic intricacies of DM.

Dr. Coates continues to build collaborations with other veterinary and ALS researchers. Through study of DM, she is able to open collaborations with ALS researchers who are investigating therapeutic approaches for ALS. Hopefully, canine DM as a disease model for ALS will help treat DM and ALS.

The progress of DM research could not be made possible without the support of the ABCF and ABC. I wish to thank all the members. I also want to thank all the companion animal owners, breeders and the dogs who have given their lives so more can be learned about DM. I will always be grateful for the support.