



RESEARCH PROGRESS REPORT SUMMARY

Grant 02133: Canine Epilepsy: Genetic Variants, Biomarkers, and New Therapies

Principal Investigator: Dr. Ned E. Patterson, DVM PhD

Research Institution: University of Minnesota

Grant Amount: \$104,781.00

Start Date: 10/1/2014 **End Date:** 3/31/2017

Progress Report: End-Year 2

Report Due: 9/30/2016 **Report Received:** 11/28/2016

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:

Epilepsy is a significant seizure disorder affecting all dog breeds. It is the most common chronic nervous system disorder in dogs, with a prevalence of 0.5% - 5.7%, resulting in approximately 2 million affected dogs in the USA. We have assembled a trans-disciplinary team to attempt to improve the fate of dogs that have epilepsy with a special emphasis on dogs with drug-resistant epilepsy. Dog with drug-resistant epilepsy have frequent seizures even when on 2 or more anti-epileptic drugs. The team includes Veterinarians, Canine Geneticists, Pharmacologists, Human Neurologists, Basic Scientists and Biomedical Engineers from the University of Minnesota College of Veterinary Medicine, College of Pharmacy, Institute for Engineering in Medicine, and Departments of Neurology and Surgery, and Mayo Clinic in Rochester, MN. We propose to evaluate traditional DNA genetic markers, blood biomarkers called microRNAs (miRNAs), and potential new drugs for the emergency treatment of seizures in dogs.

In this phase 1 of the Canine Health Foundation Epilepsy initiative, our study goals are; 1. To identify genetic markers associated with epilepsy in Australian shepherds and Vizslas, and identify markers associated with epileptic dogs that are unresponsive to anti-epileptic drug therapy in order to develop genetic screening tests in phase 2; 2. To document microRNA levels in the blood of dogs with epilepsy in order to develop potential blood markers that vary between epileptic and non-epileptic dogs, and dogs with drug-resistant epilepsy; and 3. To



perform initial testing of two new potential drugs for the emergency treatment of canine epilepsy.

Grant Objectives:

1. To identify genetic variants associated with genetic epilepsy in Australian shepherds and Vizslas and develop a genetic screening test for genetic epilepsy risk.
2. To identify genetic variants associated with drug-resistant epilepsy in Australian shepherds and Vizslas in order to develop a genetic test to assist with drug therapy.
3. To identify circulating microRNAs in blood from dogs with naturally occurring epilepsy and correlate miRNA temporal expression with seizure episodes.
4. Perform pilot pharmacokinetic and safety studies in order to determine if one or both are potentially effective for combined initial therapy for canine status epilepticus.

Publications:

Intravenous Topiramate: Pharmacokinetics in Dogs with Naturally-Occurring Epilepsy
Irene Vuu^{1,2}, Lisa D. Coles^{1,2}, Patricia Maglalang^{1,3}, Ilo E Leppik^{2,5}, Greg Worrell⁶, Daniel Crepeau⁶, Usha Mishra¹, James C. Cloyd^{1,2}, *Edward E. Patterson⁴
Accepted and in press. *Frontiers in Veterinary Science: Neurology and Neurosurgery Section.*

Report to Grant Sponsor from Investigator:

Our goal in these studies are to: 1. identify genetic (DNA) mutations associated with epilepsy and/or drug resistant epilepsy in Australian shepherds, and Vizslas; 2. To see if blood micro RNA (miRNA) levels vary within epilepsy dogs and could be used as markers of predisposition to epilepsy and/or response to therapy; 3. To see if novel IV drugs (topiramate or allopregnanolone) might be effective for treatment of seizure emergencies in dogs (and people) by pilot studies with 3-5 epileptic dogs.

To date we have DNA for 86 affected and over 199 unaffected Australian shepherds, and 65 affected and 699 unaffected Vizslas. In initial analysis of 170,000 SNP genetic markers, we have found some chromosomal areas that may contain and epilepsy genes or genes for being less responsive to drug therapy for each breed, but as epilepsy is polygenic in both breeds with likely a number of related genes in each breed, we have not yet identified a marker or area that clearly stands out for a confirmed epilepsy gene. We will continue our studies in



these breeds in the future as genetic technologies have new ways of analysis and we collect more DNA samples from each breed.

In the micro RNA studies we have obtained blood samples from 3 affected and 2 unaffected dogs at various times, and for the affected dogs at various times after a seizure. We have successfully measured miRNA levels and are in the process of final analysis looking for any patterns and associations for possible future use of blood miRNA as a diagnostic marker or marker of how severe epilepsy is in an epileptic dog and/or how well therapy is working in epileptic dogs.

In the IV drug studies for new emergency drugs for life-threatening seizures we have completed all of our IV topiramate studies and we have a paper that is about to be published with the results in the next few weeks. The conclusion is that IV topiramate appears to be safe and potentially effective in this pilot study of 5 dogs, and also gives information that IV topiramate might also be safe and effective for people since dog epilepsy and seizure emergencies are so similar to that in humans. This means IV topiramate could be used for possible future studies in veterinary (and human) emergency rooms for the treatment of seizure emergencies. We have just completed a similar study for IV allopregnanolone and initial results indicate it also is likely safe and effective. Once we have finished our final analysis of the allopregnanolone results we will pick one or the other of the promising new drugs for the emergency treatment on seizures in dogs (and people) for a clinical trial in dogs presenting to veterinary emergency clinics in future funding. We have previously done this (funded by the Canine Health Foundation) with IV levetiracetam in dogs and based on those results IV levetiracetam is now commonly used in veterinary emergencies.