AMERICAN KENNEL CLUB
CANINE HEALTH FOUNDATION
PREVENT TREAT & CURE

RESEARCH PROGRESS REPORT SUMMARY

Grant 01760: Use of Gene Therapy to Treat Dilated Cardiomyopathy

Principal Investigator: Dr. Margaret M. Sleeper, VMD

Research Institution: University of Pennsylvania

Grant Amount: $146,774.00

Start Date: 1/1/2013 **End Date:** 12/31/2014

Progress Report: Mid-Year 2

Report Due: 6/30/2014 **Report Received:** 6/30/2014

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:

Dilated cardiomyopathy (DCM) is the second most common cause of heart disease in dogs and medical management of the secondary signs is the only therapeutic option. The prognosis for affected dogs depends on the stage of disease and the breed. Doberman pinschers exhibit particularly rapid and uniform progression once congestive heart failure (CHF) has occurred, with most living less than 6 months. Heart function is critically dependent upon calcium-dependent signaling. During heart disease, malfunctioning of calcium channels within cardiac cells promotes calcium cycling abnormalities, further inhibiting heart function. Gene transfer strategies to reduce calcium cycling abnormalities ameliorate heart disease in animal models as well as in human clinical trials. We propose a placebo-controlled, double blinded study to evaluate gene delivery approaches for treatment of Doberman pinschers affected with DCM and CHF. Dogs will be treated with intramyocardial injections of saline (control group) or a vector expressing two proteins targeting the myocardial calcium pathway. Medical heart failure management will continue in all dogs and statistical analysis will be performed every 2 months. If a clinical benefit is recognized in the treatment group, the control group will undergo gene delivery. If our results show that the gene delivery to improve myocardial cell calcium handling slows progression of heart failure in Dobermans with DCM, the results will have significant ramifications for this breed as well as the potential to benefit dogs with many forms of heart disease, since calcium handling proteins are abnormally expressed in dogs with heart disease of varying causes.

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Grant Objectives:

Objective 1: Assess efficacy of therapeutic gene transfer to improve the quality of life of Doberman pinschers with symptomatic DCM using a questionnaire that has been specifically developed and validated for evaluating dogs with cardiac disease.

Objective 2: Assess efficacy of therapeutic gene transfer to normalize myocardial structure and dysfunction in DCM using physical examination, echocardiography and electrocardiography.

Objective 3: Assess efficacy of therapeutic gene transfer to prolong the life of Doberman pinschers with symptomatic DCM.

Publications:

None at this time.

Report to Grant Sponsor from Investigator:

All objectives for the project remain the same but there has been a delay in starting this clinical trial because of some new data, which became available after the initial grant was submitted in late 2012. These data showed very successful myocardial transduction using a less invasive approach (the vector was infused into the left ventricle rather than directly injected into the myocardium), however the subjects were puppies rather than adult dogs. We are further investigating this less invasive delivery method in adult dogs to determine whether it will also be effective in adult dogs (the population we plan to treat in this study). Unfortunately the government sequestration and closure in 2013 severely impacted Rob Kotin at the NIH (the collaborator producing vector), which caused significant delays in completing our studies. He then left the NIH and is now working at the University of Massachusetts, causing another delay. However, we have now treated 4 adult dogs confirming that the less invasive delivery technique is effective. We are planning on treating two more within the next month to further optimize the delivery technique and plan to begin advertising the clinical trial in September 2014. Our results show we will be able to use this less invasive technique for gene delivery, which will significantly benefit the dogs that are treated and may reduce the study cost.