AMERICAN KENNEL CLUB
CANINE HEALTH FOUNDATION
PREVENT TREAT & CURE

GRANT PROGRESS REPORT REVIEW

Grant: 00908: *Serotonin Type 2A Receptor Antagonist Therapy for Preventing the Progression of Myxomatous Mitral Valve Disease*

Principal Investigator: Dr. Mark A. Oyama, DVM

Research Institution: University of Pennsylvania

Grant Amount: $81,918.00

Start Date: 1/1/2008 **End Date:** 12/31/2011

Progress Report: 30 month

Report Due: 12/31/2010 **Report Received:** 12/1/2010

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:
Background: Canine myoxmatous mitral valve disease is very common in older dogs and is similar to the human disorder. Serotonin (5HT) related mechanisms has been found in the certain forms of human heart valve disease, and a beginning study by the investigators has shown heightened 5HT signaling in diseased canine mitral valve interstitial cells (MVIC).

Objective: The researchers are investigating the hypothesis that 5HT signaling contributes to the progression of canine myxomatous mitral valve disease. The reseachers seek to 1) further characterize the 5HT signaling pathway in normal and diseased human and canine mitral valve specimens, 2) determine the effects of 5HT-2A receptor antagonism in diseased canine MVIC, 3) perform a dose escalation (Phase I) study of a candidate 5HTR-2A receptor antagonist, ketanserin, in client-owned dogs with myxomatous mitral valve disease, and 4) perform a controlled comparison (Phase II) study in dogs using ketanserin. Ultrasound studies and measurement of neurohormonal markers will assess effects of therapy on progression of mitral valve disease. This study represents a novel translational study that targets a potential underlying pathogenesis of canine mitral valve disease.

Grant Objectives:

Objective 1: Carry out a Phase I dose-escalation study of a candidate 5HT-2A receptor antagonist, ketanserin, in privately owned dogs with moderate myxomatous mitral valve disease (12 dogs, no controls), using echocardiography to detect early effects on progression or regression of myxomatous mitral valve disease.

Objective 2: Carry out a controlled comparison (Phase II) of ketanserin at optimal doses using a treated and placebo group (15 dogs with moderate MVD in each group). Serial echocardiograms and assessment of neurohormonal activity will assess effects of therapy on progression of mitral valve disease.

Publications:

- Oyama, Ma and Levy, Rj (2010) Insights into Serotonin Signaling Mechanisms Associated with Canine Degenerative Mitral Valve Disease. Journal of Veterinary Internal Medicine. 24, 27-36. http://dx.doi.org/10.1111/j.1939-1676.2009.0411.x

Report to Grant Sponsor from Investigator:

The goal of phase I was to establish tolerability and dose of ketanserin in dogs. Phase I has been completed. Fifteen dogs were recruited. Five dogs were withdrawn. None of the withdrawals were thought to be directly associated with the ketanserin administration. Ten dogs completed the six month trial period. While echo parameters of heart size and valve morphology were equivalent at baseline and at the end of the six month period, the Investigators note that this open-label, dose ranging phase was not designed to specifically answer questions of efficacy with respect to severity of MVD. These questions are addressed in phase II. The end result of phase I was that maximum planned dose was well tolerated in dogs, and this dose was established as the target dose for phase II.

Twenty four dogs have been enrolled and randomized into phase II. The final dog was enrolled in August 2010 and will be monitored through August 2011. The study patients and investigators remain blinded and no difficulties or adverse effects have been noted.