



AMERICAN KENNEL CLUB
**CANINE HEALTH
FOUNDATION**
PREVENT TREAT & CURE

GRANT PROGRESS REPORT REVIEW

Grant: 00945: *Mucosal Gene Expression Profiles in Canine Inflammatory Bowel Disease*
Principal Investigator: Dr. Albert E. Jergens, DVM, PhD
Research Institution: Iowa State University
Grant Amount: \$60,000.00
Start Date: 6/1/2008 **End Date:** 12/31/2011

Progress Report: 30 month

Report Due: 11/30/2010 **Report Received:** 11/22/2010

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 inflammatory bowel disease (IBD) is a chronic intestinal disorder likely resulting from the interaction between genes and environmental factors. While it is generally accepted that luminal bacteria play a critical role in provoking gut inflammation, genetic factors may also contribute to the bacterial-driven inflammatory response. Several susceptibility genes, such as NOD2/CARD15, have recently been identified in humans with IBD and provide a basis for the development of aberrant immune responses to bacteria in certain individuals. It is reasonable to hypothesize that susceptibility genes also affect clinical disease in dogs with IBD by negatively affecting the interaction with intestinal bacteria and/or their products. Genetic factors are thought to contribute to the pathogenesis of canine IBD as in humans. A role for luminal bacteria is suggested by observations that antibiotics reduce clinical signs, and by reports of increased bacterial numbers in intestinal biopsy specimens obtained from dogs with IBD. Given the recognized breed predispositions, genetic susceptibility to IBD is also likely, although studies are lacking.

Objective: The researchers are utilizing unique molecular biology tools to: (1) identify key genetic factors contributing to disease expression, (2) characterize gene expression profiles which may predict responsiveness to specific therapies, and (3) provide the framework upon which to facilitate identification of IBD susceptibility genes that predispose specific canine breeds to clinical disease.

Grant Objectives:

Hypothesis: Gene expression profiles in intestinal tissue samples of dogs with IBD will provide comprehensive insight into altered gene expression patterns contributing to gut inflammation.

Objective 1: To investigate global gene expression patterns of inflamed intestinal tissues and normal control intestinal tissue using RNA microarrays. The differentially expressed transcripts will identify patterns associated with inflammation and host immune responses.

Objective 2: To utilize quantitative RT-PCR to confirm microarray data and validate unique gene expression signatures in dogs with IBD.

Objective 3: Evaluate the clinical, microbiologic, and anti-inflammatory effects of FOS administration in dogs with IBD. (Appended Objective)

Publications:

- Suchodolski, Js, Xenoulis, Pg, Paddock, Cg, Steiner, Jm and Jergens, Ae (2010) Molecular analysis of the bacterial microbiota in duodenal biopsies from dogs with idiopathic inflammatory bowel disease. *Veterinary Microbiology*. 142, 394-400.

<http://www.sciencedirect.com/science/article/B6TD6-4XNF6FB-1/2/0563bf86e9fc8c4da7851cf9654ac8dd>

Report to Grant Sponsor from Investigator:

Canine inflammatory bowel disease (IBD) is a chronic intestinal disorder likely resulting from the interaction between genes and environmental factors. We propose to utilize unique molecular biology tools to: (1) identify key genetic factors contributing to disease expression, (2) characterize gene expression profiles which may predict responsiveness to specific therapies, and (3) provide the framework upon which to facilitate identification of IBD susceptibility genes that predispose specific canine breeds to clinical disease. We are making good progress towards these goals as evidenced by the following:

We have collected samples from a representative heterogeneous population of 18 IBD dogs for comparison to 6 healthy dog tissues.

We have carefully extracted the genetic material (RNA) from endoscopic samples which will be used in our gene profiling studies.

We have now evaluated gene expression profiles in the normal versus diseased dog groups using sophisticated statistical modeling to help us 'tease out' gene expression patterns which discern healthy versus diseased intestinal tissues. It is our expectation to identify specific genes which serve as biomarkers for diagnosing canine IBD and for monitoring the effects of therapy. We have now identified a grouping of 17 'marker' genes that may be more critically assessed in future studies.

We have noted that IBD dogs show differences in intestinal gene expression as compared to healthy dogs; and these differences in expression may help to explain the mechanisms of chronic inflammation in affected dogs.

We have preliminary evidence that changes in the intestinal bacteria accompany the abnormal gene patterns. It is our belief that this association should be explored more fully with additional studies; since this situation is identical to the association between people and their intestinal bacterial populations causing human IBD (i.e., Crohn's disease and ulcerative colitis).

We have now confirmed the expression patterns of select differentially expressed genes in diseased dogs using sophisticated molecular techniques. This suggests that the observations regarding gene expression patterns using the gene chips are accurate.