



GRANT PROGRESS REPORT REVIEW

Grant: 00741: *Polymicrobial Bacteria-Associated Inflammatory Stifle Arthritis/Degenerative Cranial Cruciate Ligament Rupture in Dogs*

Principal Investigator: Dr. Peter Muir, PhD

Research Institution: University of Wisconsin - Madison

Grant Amount: \$153,742.00

Start Date: 10/1/2007 **End Date:** 3/31/2010

Progress Report: 24 month

Report Due: 9/30/2009 **Report Received:** 9/30/2009

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.)

Original Project Description:

Background: Knee inflammation that develops in dogs with cruciate rupture is little studied and likely underestimated.

Objective: The researchers are determining whether a relationship exists between joint bacteria and development of knee inflammation/cruciate rupture. The researchers will pursue the following specific plan: determine that a relationship exists between bacteria within the knee joint and the development of inflammatory knee arthritis/degenerative CCL rupture. They expect to determine that bacteria reach the knee joint via the blood stream and then induce persistent inflammation of the lining of the knee joint, degradation of joint tissues, and eventual CCL rupture. With this research, the researchers aim to produce improved medical treatment that will prevent cruciate rupture from developing.

Original Grant Objectives:

Objective 1: Determine whether a causal relationship exists between the presence of mixtures of bacteria within the stifle joint and the development of inflammatory arthritis/degenerative cranial cruciate ligament rupture.

Publications:

- Muir P, Fox R, Wu Q, et al. Seasonal variation in detection of bacterial DNA in the knee joints of dogs with inflammatory knee arthritis and associated degenerative anterior cruciate ligament rupture. *Veterinary Microbiology* 2009, epub.

- Muir P, Kelly JL, Marvel SJ, Heinrich DA, Schaefer SL, Manley PA, Tewari K, Plisch EH, Singh A, Suresh M, Hao Z. Lymphocyte populations in joint tissues from dogs with inflammatory stifle arthritis and degenerative cranial cruciate ligament rupture. *Veterinary Surgery*, in review.

IN PREPARATION

- We expect to finalize manuscripts summarizing our radiographic/arthroscopic surgery data from dogs with stable stifles (target journal - *Veterinary Surgery*).

- We also expect to finalize a manuscript describing the results of our correlative study between bacterial load in affected stifles and development of joint inflammation (target journal - *Arthritis & Rheumatism*).

- We also expect to finalize the results of our studies on the synovial pathology of dogs with stable stifles in comparison to the contralateral stable stifle, looking at bacterial load and markers of antigen-specific immune responses (target journal - *Veterinary Immunology & Immunopathology*).

Report to Grant Sponsor from Investigator:

Pathological or degenerative rupture of the cranial cruciate ligament (CCLR) in the stifle joint of the dog is a progressive condition that is often bilateral and is not associated with obvious trauma. In human beings, this ligament is referred to as the anterior cruciate ligament or ACL in the knee joint. Historically, it has been thought that stifle arthritis develops because of joint instability, joint instability develops because of CCL rupture, and CCL rupture develops because of trauma. There is now strong evidence that this paradigm is not correct. Work we have conducted with the support of the AKC Canine Health Foundation strongly suggests that CCLR is preceded by development of chronic inflammation and arthritis in the stifle joint in the majority of affected dogs.

Our long-range goal is to develop new treatments for dogs with stifle arthritis that will reduce joint inflammation and prevent CCL rupture and development of joint instability, as well as develop a treatment that will enable healing of ruptured cruciate ligament to occur. With the support of the AKC Canine Health Foundation, over the last six months, we have moved several steps closer to our goal:

(1) By studying affected dogs with stable stifles, we have now documented that stifle arthritis precedes development of stifle instability associated with CCLR. Furthermore, it is also clear the development of arthritis precedes fraying of the CCL in affected dogs with stable stifles.

(2) Small amounts of material derived from environmental bacteria are commonly found in the inflamed stifles of affected dogs. Additional work suggests that this bacterial material is dead.

(3) Development of joint inflammation in affected dogs includes proliferation of a specific type of inflammatory cell, the T lymphocyte. The presence of T lymphocytes in the stifle joint will promote development of joint inflammation, and also suggests that the joint immune responses

are activated by a specific trigger referred to as an antigen. This type of pathology is typical of other rheumatic diseases, such as rheumatoid arthritis or reactive arthritis in human beings.

(4) Finally, we have learnt that the amount of bacterial material in the stifle joint lining of affected dogs is not directly related to the severity of the inflammation in the joint. This suggests that a specific (likely genetic) susceptibility enables bacteria to trigger joint inflammation in specific individual dogs. We have preliminary data to support this concept and now wish to study this question further in future work.

The presence of large numbers of T lymphocytes within affected joints may represent an important target for drug treatment. We have now initiated a prospective clinical trial using a provisional anti-inflammatory therapy for stifle arthritis. If this medical therapy proves effective at blocking joint inflammation, we expect that it will be possible to prevent development of progressive cruciate rupture in affected dogs, and improve long-term outcome. We expect clinical trial work will be ongoing until an effective medical therapy has been identified. Over time, we expect that fewer dogs will need surgical treatment to stabilize the stifle joint after complete CCL rupture and joint instability has developed. By effective treatment of joint inflammation, we also expect that it will be possible to provide a surgical treatment that will allow the ruptured CCL to heal. All current surgical treatments do not lead to cruciate healing. Enabling cruciate healing may lead to better long-term stability of the stifle joint over time. In the future, further research into genetic susceptibility is needed, as this type of rheumatic disease is typically associated with a patient genetic susceptibility.