RESEARCH PROGRESS REPORT SUMMARY

Grant 02383: Identifying Cellular Mechanisms of Inflammation During Canine Tick-Borne Diseases

Principal Investigator: Christine Petersen, DVM, PhD

Research Institution: University of Iowa

Grant Amount: $207,526

Start Date: 9/1/2017 **End Date:** 12/31/2019

Progress Report: FINAL

Report Due: 12/31/2019 **Report Received:** 12/30/2019

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Original Project Description:

Tick-borne diseases are found in all 50 states of the United States and are the most common vector-borne disease diagnosed in people in the US. The predominant disease is Lyme disease, caused by *Borrelia burgdorferi* and related species (sensu lato). Other important canine tick-borne diseases include those caused by *Anaplasma platys*, *Anaplasma phagocytophilum* (Anaplasmosis), *Babesia canis*, *Babesia conradea* and *Babesia gibsonii* (Babesiosis), and *Ehrlichia canis*, *Ehrlichia chaffiensis* and *Ehrlichia ewingii* (Ehrlichiosis). Many of these diseases also affect people. Dogs can serve as sentinel species for human disease and there are many areas where the immune responses and disease outcomes are very similar in people and dogs, meaning that important lessons can be learned by sharing information between human and animal health (One Health). The researchers will further investigate the dog's immune system to determine which immune cells are responsible for the cure or creation of canine tick-borne disease. Through understanding which cells are responsible for causing disease, the goal is to then specifically target the molecules they produce using immunotherapy or immune modulation to improve treatment of tick-borne diseases in all dogs.

Publications:

Scorza, B.M., Cox, Erin C., Mahachi, K. G., Toepp, A.J., Saucier, J., Tyrell, P., Foltz, J., Lee, D., Petersen, C.A. "IFN-ϒ and not cytotoxic responses from Natural Killer T cells in asymptomatic vs. symptomatic *Borrelia burgdorferi* infection", J. Inf. Diseases (in preparation to submit spring 2020).

Presentations:

Altered circulating NK cell response during Ehrlichia and Leishmania infection and potential role in progressive disease. Breanna M Scorza, Kurayi Mahachi, Erin C Cox, Jennifer Foltz, Dean Lee, Jill Saucier, Phyllis Tyrrell, Christine A Petersen.

- Poster presentation: Great Plains Emerging Infectious Disease Conference. Iowa City, IA. March 2019.
- Oral presentation: World Association for the Advancement of Veterinary Parasitology conference. Madison, WI. July 2019.
- Oral presentation: Center for Immunology and Immune-Based Diseases Retreat. Iowa City, IA. August 2019.
- Oral presentation: Woods Hole Immunoparasitology conference. Woods Hole, ME. April 2019.

Natural Killer cell subsets during Lyme Disease: Pathogen control and pathogenesis. Breanna M Scorza.

- Oral presentation: Immunology Grand Rounds, University of Iowa Hospitals & Clinics, Iowa City, IA. November 2018.

Impact of Tick-Borne Co-Infections on Canine Leishmaniosis: Circulating Natural Killer Cell Populations. Breanna M Scorza, Kurayi Mahachi, Erin C Cox, Angela Toepp, Jennifer Foltz, Dean Lee, and Christine A Petersen.

- Oral presentation: Parasitology Group Meeting, University of Iowa, Iowa City, IA. January 2019.
- Oral presentation: Immunology Student Seminar, University of Iowa, Iowa City, IA. December 2018.
- Poster presentation: American Society for Tropical Medicine and Hygiene Conference. New Orleans, LA. October 2018.
- Poster presentation: Center for Immunology and Immune-based Diseases. Iowa City, IA. August 2018.
- Poster presentation: American Association of Immunology. Austin, TX. May 2018.

Characterization of circulating Natural Killer cells in canines exposed to tick-borne infections. Breanna M Scorza, Kurayi Mahachi, Angela Toepp, and Christine A Petersen.

- Poster presentation: Great Plains Emerging Infectious Disease Conference. Iowa City, IA. March 2018.

Elevated Natural Killer T cells promote asymptomatic *Borrelia burgdorferi* infection in dogs. Breanna M. Scorza, Erin C. Cox, Kurayi Mahachi, Angela J. Toepp, Jill Saucier, Phyllis Tyrell, Jennifer Foltz, Dean Lee and Christine A. Petersen.

- Oral presentation: Wilson lab joint lab meeting. Iowa City, IA. December 2019.

Report to Grant Sponsor from Investigator:

The overall goal of this study was to determine differences between dogs with asymptomatic versus symptomatic Lyme Disease, in order to better understand which cell types, or inflammatory factors produced by them, are helpful for controlling the disease. In this study, we identified sporting and hunting dogs at different clinical stages of Lyme Disease and sampled blood from them in the field. We have confirmed our field diagnoses with specialized assays performed by IDEXX Laboratories. In the lab, we have analyzed the percentage of Natural Killer immune cells and some markers of the activation state of these NK cells in the blood. We have found multiple interesting aspects of the canine immune response to Lyme Disease which were not previously known, and in fact will be novel contributions to the LD immunological knowledge, due to our ability to learn from asymptomatic exposed dogs which has not been done in people. We have found one subset of these cells, NKT cells, increased in dogs exposed to the bacteria that causes Lyme Disease, Borrelia burgdorferi, but do not show symptoms of Lyme Disease (asymptomatic dogs). Therefore, we hypothesize these cells are helpful in preventing Lyme Disease symptoms. The NK cells from dogs with symptomatic Lyme Disease showed a statistically enhanced inflammatory response in the presence of Lyme Disease causing bacteria, indicating that excessive inflammation may contribute to clinical disease. Additionally, a serum cytokine was elevated in asymptomatic dogs, thus this cytokine could be skewing the NK cell subset toward a less inflammatory phenotype to prevent disease. This cytokine may represent a novel therapeutic to help drive the immune response towards a healing phenotype. Finally, we have observed that NK and/or NKT cells from dogs exposed to Lyme Disease causing bacteria are able to kill target cells similar to healthy control dogs. This is further evidence that increased inflammation, and not an inability to kill bacteria, drives most of the clinical symptoms of canine Lyme Disease. Based on these results, therapies targeted towards decreasing NK cell-mediated inflammation, or to increase serum cytokines associated with NKT cell differentiation may help dogs maintain an asymptomatic state following Lyme Disease exposure. Throughout this study, we have established a good working relationship with the caretakers of the hunting and sporting dogs and have collected enough samples to meet our statistical needs for these experiments. We have prepared a strong draft of the manuscript describing our results and we plan to submit the results of these assays for publication this spring.