RESEARCH PROGRESS REPORT SUMMARY

Grant 02472-A: Effect of Lokivetmab on Tissue Biomarkers of Canine Atopic Dermatitis using RNA Sequencing

Principal Investigator: Frane Banovic, DVM, PhD

Research Institution: University of Georgia

Grant Amount: $9,747

Start Date: 12/1/2017 **End Date:** 10/31/2019

Progress Report: FINAL

Report Due: 10/31/2019 **Report Received:** 3/24/2020

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

Atopic dermatitis (AD) is the most common, chronic, inflammatory and pruritic allergic skin disease that affects dogs worldwide. Treatment of canine AD has a high unmet need for effective and safe therapeutics. The transcriptome investigation of human AD tissues before and after treatment modalities has revolutionized the understanding of the molecular fingerprint of AD, further defining pathogenic immune pathways and identifying disease-specific biomarkers. In the early-phase trial, lokivetmab, a caninized monoclonal antibody targeting interleukin-31 (IL-31) cytokine, markedly improved disease activity, but the effect of IL-31 blockade on AD at the genomic level has not been characterized. The investigators will evaluate lokivetmab modulation of the canine AD transcriptome (defined as differentially expressed genes between lesional and non-lesional skin) using next-generation RNA sequencing (RNA-seq). Findings may suggest that inhibition of a single target has the potential to reverse AD pathomechanisms, opening the door for new targeted treatment for this common and debilitating inflammatory skin disease. Furthermore, transcriptome analysis using RNA-seq may identify novel pathogenic pathways of inflammatory biomarkers as canine AD disease drivers, with potential for development of novel targeted therapeutics.

Publications: None at this time.

Presentations: None at this time.

Report to Grant Sponsor from Investigator:

Atopic dermatitis (AD) is a common inflammatory and pruritic (itchy) skin disease of humans and dogs that affects 15-20% of the population globally. Skin transcriptomic profiling approaches such as RNA sequencing and microarrays of bulk tissue skin biopsy specimens have provided insights into the complex human AD pathogenesis. The transcriptome research revealed human AD-associated cytokines, chemokines and immunological pathways and novel targeted therapies with monoclonal antibodies (biologic therapy) against AD-associated molecules are developed in humans with AD. Whereas the evolving discoveries in the molecular understanding of human AD led to novel therapies that allow better management of patients, the pathogenesis of canine AD has been poorly investigated.

To gain a deeper understanding of the pathophysiology of canine AD, we conducted the first transcriptomic study of AD in 10 dogs with deeply sequenced RNA-sequencing samples using paired-end reads. Similar to recent human AD molecular findings, canine AD is a heterogeneous and complex inflammatory skin disease characterized by the coexistence of abnormalities in cytokine production of T helper (Th) type 1, Th2, Th17, and Th22. The proallergic Th2 axis in canine AD shows dominance of interleukin 13 (IL-13) pathways, but with near undetectable IL-4 expression. In humans, the IL-4/IL-13 inhibition through blockade of the IL-4R by monoclonal antibody dupilumab has been shown in several studies to be a highly effective treatment for human AD. Consistent with our findings of dominant IL-13 signature, anti–IL-13 in canine AD should be further investigated for novel targeted therapy in dogs with AD.

In veterinary dermatology, lokivetmab (Cytopoint, Zoetis, USA), a monoclonal antagonist of canine IL-31, has shown success in reducing clinical and pruritus scores in dogs affected with AD. On the basis of the hypothesis that IL-31 is one of the key drivers of canine AD, we evaluated whether blocking IL-31 reverses the cutaneous molecular pathology of canine AD pathogenesis. This was a controlled, open-label study to assess the efficacy of a single lokivetmab (anti-canine IL-31 monoclonal antibody; Cytopoint, Zoetis) treatment in resolving the pathogenic transcriptome signature (epidermal abnormalities and cutaneous immune responses) in canine AD patients. Our findings show that inhibiting specific Th2 cytokine IL31 with a single lokivetmab administration improved the owner-reported itch scores, but was not able to suppress and reverse the cellular/molecular cutaneous markers of AD inflammation. Our findings are consistent with anti-IL31 inhibitors in human AD; the itch scores are strongly reduced but the clinical scores of skin inflammation are mildly inhibited or un-changed.

To our knowledge, this is the first study using deep transcriptome profiling to reveal inflammatory and pruritic markers of canine AD. Future studies with novel therapies should include transcriptome improvement scores through longitudinal assessments. The generated data will have the potential to provide a more thorough understanding of the disease trajectory for AD responders and non-responders, as well as its heterogeneous nature.