RESEARCH PROGRESS REPORT SUMMARY

Grant 01418: Harnessing a Dog's Own Immune System to Kill Lymphoma Tumor Cells

Principal Investigator: Heather Wilson-Robles, DVM

Research Institution: Texas A&M Research Foundation

Grant Amount: $143,440.19

Start Date: 1/1/2011 **End Date:** 12/31/2018

Progress Report: FINAL

Report Due: 12/31/2018 **Report Received:** 3/22/2019

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

Original Project Description:

Lymphoma is the most common malignancy of dogs representing up to 25% of diagnosed cancers. Dogs often develop an aggressive form of lymphoma that is rarely curable, with most unfortunately succumbing to disease within 12 months of diagnosis despite best-available chemotherapies. Dr. Wilson-Robles will develop a new treatment to re-train the dog's own immune system to attack the most common type of canine lymphoma, B-cell lymphoma. In order to accomplish this they will obtain a small number of circulating white blood cells, called T-cells, from the blood of affected dogs and insert a gene that will cause the T-cell to express a receptor which recognizes the tumor "fingerprint". After docking with the lymphoma, the T-cell will be triggered to mount an immune response against the tumor cells with the specific fingerprint. This therapy could be used alone or in combination with chemotherapy. Preliminary data demonstrates that it is possible to genetically modify T-cells. Further, they have been able to successfully harvest and grow T-cells in the laboratory and return them safely to the dog. These infused cells can be found in the blood and tumor weeks after infusion, showing that it is possible for these cells to survive in the dog. If successful this study will be the first to develop an "in-dog" T-cell therapy targeting a tumor that has historically thought to be untreatable.

Publications:

O'Connor, C. M., Sheppard, S., Hartline, C. A., Huls, H., Johnson, M., Palla, S. L., . . . Cooper, L. J. (2012). Adoptive T-cell therapy improves treatment of canine non-Hodgkin lymphoma post chemotherapy. *Sci Rep*, 2, 249. doi:10.1038/srep00249

O'Connor, C. M., & Wilson-Robles, H. (2014). Developing T cell cancer immunotherapy in the dog with lymphoma. *ILAR J*, 55(1), 169-181. doi:10.1093/ilar/ilu020

Presentations:

Heather Wilson-Robles, New tricks old dogs can teach us about cancer research. TAMU Immunology consortium invited speaker, 9/21/18.

Wilson-Robles, Heather; Gottschalk, Stephen; O'Conner, Colleen; Adoptive T Cell Therapy in dogs; Clinical experience and lessons learned. Texas Regional Immunology Conference, M D Anderson Cancer Center, Houston, Texas November 10-11, 2016.

O'Connor CM, Wilson HM. Developing T-cell Cancer Immunotherapy in the Dog with Lymphoma. ILAR 2014 Jan (Manuscript Invited and Submitted).

O'Connor CM, Ang S, Maiti SN, McNamara G, Sheppard S, Miller T, Huls H, Champlin R, Wilson H, Cooper LJN. Immune Reconstitution with Activated T cells Significantly Improves Survival in Companion Canines Post Various Treatment Modalities. American Society of Hematology Annual Conference, New Orleans, LA, December 2013.

O'Connor CM, Ang S, Maiti SN, McNamara G, Sheppard S, Miller T, Huls H, Champlin R, Wilson H, Cooper LJN. Adoptive Therapy of Activated T cells Influences T-cell Gene Signatures in Companion Canines Diagnosed with Non-Hodgkin Lymphoma. Genomic Medicine Conference, MD Anderson Cancer Center, Houston, TX, October 2013.

Maiti SN, Zhuang Z, Deniger D, O'Connor CM, Bueso-Ramos C, Pappanicken K, Singh HS, Ang S, Torikai H, Huls H, Lee DA, Radvanyi L, Cooper LJN. Amplification-free multiplexed high-throughput digital profiling of low abundance transcripts and non-coding miRNAs in small amounts of biological samples. Genomic Medicine Conference, MD Anderson Cancer Center, Houston, TX, October 2013.

'Connor CM, Personalized Canine Cancer Therapy, 3rd Annual Post Doc Symposium, MD Anderson Cancer Center, Houston, TX, August, 2013.

O'Connor CM, Personalized Canine Cancer Therapy, American Veterinary Medical Association Annual National Conference, Chicago, IL, July, 2013.

O'Connor, CM; Olivares, S; Ang, S; Champlin, RE; Wilson-Robles, HM; Cooper, LJN. Chimeric Antigen Receptor T-cell Therapy for Companion Canines with Spontaneous B-cell Non-hodgkin Lymphoma. American Society of Gene and Cell Therapy, Salt Lake City, UT, May 2013.

PET 1.1: Providing engineered T cells to dogs with B cell lymphoma. Presented by Dr. Colleen O'Conner, Co-Investigator and Post-Doctoral Fellow at MD Anderson. Presented October 31st, 2010 at Veterinary Cancer Society meeting in San Diego, CA.

Report to Grant Sponsor from Investigator:

Initially the investigators set out to build on the knowledge we had gained from the PET 1.0 study using a dog's own T lymphocytes (white blood cells important in immune responses) to combat their lymphoma (a malignant cancer of lymphocytes). In the initial studies we were able to demonstrate a potential survival advantage to infusing high numbers of CD8+ T cells (like the special forces of your immune system) back into the dog after we grew them up into the large numbers and activated them in the lab. Our initial goal was to then genetically modify these cells so that they would specifically target B cell lymphoma cells (a common type of lymphoma). We were able to successfully generate these cells and demonstrate effective cell killing, however, revised NIH guidelines prevented us from putting genetically modified T cells into pet dogs. For this reason we switched gears and decided to see if using our original T cell product in dogs with a shortened chemotherapy protocol would provide similar or even better remission times than with chemotherapy alone. The goal would be to spare the patients chemotherapy side effects and have fewer visits to the vet for dogs with this devastating disease. With the permission of the AKC Canine Health Foundation, we performed a pilot study in 5 dogs using an abbreviated CHOP chemotherapy protocol that was half as long as what is normally done (9 weeks instead of 20) followed by T cell infusions. These infusions were well tolerated but we had logistical difficulties generating a final T cell product that met our strict sterility standards and contained the correct percentage of CD8+ T cells. For this reason, every dog in the study experienced some form of treatment delay. Three of the 5 dogs enrolled have had progression of their disease at 257 days (suspected progression), 120 days, and 132 days after starting chemotherapy. Two dogs are still alive and in remission at 175 and 182 days after starting therapy. At this time we cannot say how this compares to the average survival time reported for similar cases in one study of 330 days because only one of the dogs in this study has succumb to disease. We plan to continue following the remaining two dogs until progression is noted. We also plan to continue optimizing our protocol and searching for ways to make it more cost effective and efficient.