RESEARCH PROGRESS REPORT SUMMARY

Grant 03194: A Blueprint to Develop Next-Generation CAR T Therapy for Canine Lymphoma

Principal Investigator: Matthew Atherton, BVSc, PhD

Research Institution: University of Pennsylvania

Grant Amount: $174,960.00

Start Date: 2/1/2024 **End Date:** 1/31/2026

Progress Report: End-Year 1

Report Due: 1/31/2025

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

Original Project Description:

High-grade B cell lymphoma is a cancer frequently diagnosed in older dogs, with Golden Retrievers and Bernese Mountain Dogs being particularly predisposed. Standard veterinary care involves chemotherapy and while patients initially respond well, the disease proves to be fatal for most dogs diagnosed. In human medicine, chimeric antigen receptor (CAR) T cell therapy, in which the patient's T lymphocytes are engineered to target and kill their cancer, has been remarkably successful for treating B cell lymphoma. However, a significant number of patients become resistant to this therapy due to loss of target antigen on their cancer cells. To overcome this, next-generation tandem CAR T cells were designed to kill cancer cells by recognizing two separate targets, thereby reducing the ability of cancer cells to escape treatment, and greatly improving the outlook for human patients.

The researchers' prior work revealed that treatment of canine high-grade B cell lymphoma with CAR T cells is feasible and well tolerated, but they have also seen evidence of cancer cell escape after CAR T therapy in dogs. Thus, the goal of this study is to optimize tandem CAR T cells for dogs diagnosed with high-grade B cell lymphoma and to develop a toolbox for monitoring tandem CAR T cell activity and biosafety for use in future canine CAR T trials. The team envisions that the studies will enable the launch of first-in-canine trials using tandem CAR T cells, thus transforming the currently bleak prognosis for dogs with high-grade canine B cell lymphoma.

Publications:

None at this time.

Presentations:

Although we are still at an early stage of this award, Matt Atherton (PI) has been invited to present at the upcoming Penn Vet Cancer Center External Advisory Board Meeting at the University of Pennsylvania in December 2024. The data generated by the funding provided by CHF will form a significant part of his presentation entitled “A blueprint to develop canine CAR T therapy”.

Some of the data generated by the funding provided by CHF has been presented to Penn Vet Cancer Center External Advisory Board Meeting at the University of Pennsylvania in December 2024 by Matt Atherton in a talk entitled “A blueprint to develop canine CAR T therapy”. Brandon Peng also presented data from this project in the form of a poster at Annual Faculty Research Retreat for University of Pennsylvania, School of Veterinary Medicine in October 2024. Matt is also excited to share the progress we are making in an invited talk entitled “Fine tuning CAR T therapy for canine hematologic malignancies” to be delivered at AKC Canine Health Foundation National Parent Club Canine Health Conference, CHF 30th Anniversary in Raleigh in August 2025.

Report to Grant Sponsor from Investigator:

High grade B cell lymphoma is a cancer frequently diagnosed in older dogs, with Golden Retrievers and Bernese Mountain Dogs being particularly predisposed. Standard veterinary care involves chemotherapy and whilst patients initially respond well, the disease proves to be fatal for most dogs diagnosed. In human medicine, chimeric antigen receptor (CAR) T cell therapy, in which the patient’s T lymphocytes are engineered to target and kill their cancer, has been remarkably successful for treating B cell lymphoma. However, a significant number of patients become resistant to this therapy due to loss of target antigen on their cancer cells. To overcome this, next-generation tandem CAR T cells were designed to kill cancer cells by recognizing two separate targets, thereby reducing the ability of cancer cells to escape treatment and greatly improving the outlook for human patients. Our prior work has revealed that treatment of canine high grade B cell lymphoma with CAR T cells is feasible and well tolerated, but we have also seen evidence of cancer cells escape after CAR T therapy in dogs. Thus, the goal of our study is to optimize tandem CAR T cells for dogs diagnosed with high grade B cell lymphoma and to develop a toolbox for monitoring tandem CAR T cell activity and biosafety for use in future canine CAR T trials.

In our second progress report we have continued to make progress in all aspects of our project. Firstly, we have narrowed down our initial selection of four potential CAR constructs to our two most promising (namely TCAR1 and TCAR2). Secondly, we have shown that our tandem CAR T cells can

recognize the targets that they were designed to, are expressed on cancerous canine lymphoma cells and that we can engineer dog T cells to be armed with our CARs. Thirdly, we have completed tests that confirm the presence of the CAR targets in canine patients diagnosed with B cell lymphoma in our clinic. Fourth, we have continued to develop a toolbox of materials that will allow us to safely assess the activity of our next-generation CAR T cells in future clinical trials. In our ongoing studies we will move forwards with the two CAR constructs that have shown promise to date and will identify which of these tandem CARs will have the highest likelihood of success when used to treat canine B cell lymphoma patients. Finally, we will continue to develop our bespoke toolbox to safely launch our future clinical trials of tandem CAR T therapy for canine B cell lymphoma patients.