RESEARCH PROGRESS REPORT SUMMARY

Grant 01787: Clinical Advancement of a Cancer Vaccine in Dogs

Principal Investigator: Dr. Nicola J Mason, BVetMed, PhD

Research Institution: University of Pennsylvania

Grant Amount: $96,660.00

Start Date: 1/1/2013 **End Date:** 12/31/2016

Progress Report: End-Year 3

Report Due: 12/31/2015 **Report Received:** 2/4/2016

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. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:

Canine lymphoma is the most common hematopoeitic cancer in dogs with an estimated annual incidence of 30/100,000. Chemotherapy induces remission in 75-85% of patients; however, the majority relapse with drug-resistant lymphoma within 8-10 months of diagnosis and most dogs die of their disease shortly thereafter. Cell-based vaccine strategies that stimulate anti-tumor immunity have shown promise in the treatment of many different cancer types including non-Hodgkin's lymphoma (NHL) in humans. We have used a cell-based vaccine to induce anti-tumor immunity in dogs with NHL. This vaccine given three times after successful induction chemotherapy significantly prolonged overall survival. However, in the majority of dogs the vaccine did not prevent relapse but significantly prolonged second remission duration induced by rescue chemotherapy when compared to unvaccinated controls. These findings suggest that the lymphoma vaccine stimulated anti-tumor immunity but that this was insufficient to prevent relapse and only upon immunological boosting (through a poorly defined but previously recognized chemotherapy effect) could prolonged cancer free survival be realized. Here we aim to optimize our cell-based vaccine approach to induce functional, long lasting tumor-specific immune responses that aim to prevent relapse and prolong survival in dogs with NHL. This cellular vaccine will be generated in the presence of a potent immune stimulant and will be given every 2 months to dogs with NHL. The effects on tumor specific immunity will be evaluated. The goal is to optimize our vaccine/protocol to stimulate more effective anti-tumor immunity that will prevent relapse and prolong overall survival in dogs with NHL.

Grant Objectives:

To optimize our cell-based vaccine approach to induce functional, long lasting tumor-specific immune responses that aim to prevent relapse and prolong survival in dogs with non-Hodgkin's lymphoma .

Publications:

None at this time.

Report to Grant Sponsor from Investigator:

The goal of this proposal is to build on our previous work developing a cell-based vaccine that aims to stimulate potent tumor-specific immune cells (known as T cells) that will kill lymphoma cancer cells. Our previous work has shown that white blood cells known as B cells found in the peripheral blood can be activated and grown outside of the body using special “feeder cells” that express an important molecule known as CD40L. The stimulated B cells (known as CD40-B cells) can be loaded with genetic material (RNA) that has been extracted from the patient’s tumor. When re-injected back into the patient, the CD40-B cells are able to present the tumor material to the body’s immune system and stimulate an anti-tumor immune response. We have previously shown in a phase I clinical trial that this approach has produced promising results with respect to prolonging overall survival in dogs with lymphoma. Since then we have been working to further improve this vaccine in 2 important ways: firstly we aimed to generate a more robust system that induces greater B cell proliferation and produces B cells that have improved capacity to stimulate the patient’s T cells against the cancerous cells; and secondly to generate a more user-friendly system of B cell activation and expansion that would only require basic laboratory equipment to make these vaccines for canine patients. This is an important step towards potential commercialization and distribution of the feeder cell product enabling its use for many more dogs.

Our work has focused on optimizing the feeder cells that are used to stimulate B cells from the patient’s blood. Our proposed clinical trial involves repeat vaccination of dogs with lymphoma (rather than just 3 initial vaccines as per our first, phase I trial). Thus generation of a robust system that allows for optimal B cell activation and expansion aims to supply more B cells that can be cryopreserved for repeat vaccinations.

Current methods of generating the CD40-B vaccine from lymphoma patients are labor-intensive and require specialized laboratory equipment that is not available in most facilities. Therefore, we have explored ways to enable use of these feeder cells without the need for special equipment. To this end, we have developed protocols that utilize KTCD40L cells that

have previously been irradiated (using a Cs-137 irradiator) and cryopreserved. This eliminates the need for irradiation and maintaining a fresh stock of KTCD40L cells and provides a more off-the-shelf product that could be used by standard laboratories to stimulate canine PBMCs.

We have performed several experiments to evaluate whether these pre-irradiated, cryopreserved feeder cells can effectively expand canine B cells. We have found that canine B cell expansion using thawed, previously irradiated KTcCD40L feeder cells is possible however it is sub-optimal when compared to freshly irradiated feeder cells. However, the moderate drop in B cell expansion efficacy is off-set by the easy of use and potential for commercialization enabling any facility with standard laboratory to equipment to generate autologous CD40-B cells.

We have now re-opened our clinical trial and have since enrolled 13 dogs following optimization of our B cell culture system. Three dogs have completed their induction chemotherapy (CHOP) and have begun their immunotherapy. Five are receiving chemotherapy and will be vaccinated within the next couple of months. Five dogs have failed chemotherapy and are therefore no longer eligible. Over the next year, we will perform trial follow up, continue to generate and administering autologous CD40-B cells every 2 months to patients remaining in remission and will perform anti-tumor immune function testing to determine whether our approach is able to induce and maintain clinically relevant, anti-tumor immunity.