RESEARCH PROGRESS REPORT SUMMARY

Grant 02321: Clinical Trial of Procaspase-3 Activator (PAC-1) in Combination with Hydroxyurea for Treatment of Canine Meningioma

Principal Investigator: Timothy Fan, DVM, PhD
Research Institution: University of Illinois
Grant Amount: $55,375
Start Date: 2/1/2017  End Date: 1/31/2021
Progress Report: End-Year 3
Report Due: 1/31/2020  Report Received: 3/24/2020

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Original Project Description:

Primary brain tumors are a significant cause of illness and death in pet dogs, with meningioma accounting for approximately half of the cases seen by veterinary neurologists and oncologists. Although surgery remains the best treatment for dogs with meningioma, some dogs are not good candidates for this approach based on their tumor size and/or location. Dogs also may experience tumor regrowth after an attempt is made to surgically remove the tumor. In these situations, effective treatment options are limited. Thus, new treatments that are both safe and effective are needed for dogs with meningioma.

A team of investigators from the National Cancer Institute's Comparative Oncology Program (NCI-COP) and selected veterinary academic centers will work together using state-of-the-art imaging and a novel therapeutic approach for dogs with meningioma that are good surgical candidates. Dogs enrolled in this study will receive an investigational combination of chemotherapy agents (PAC-1 + hydroxyurea) and will be monitored with magnetic resonance and non-invasive molecular imaging techniques. Dogs will then undergo tumor removal and tissue analysis. This approach is the first to validate and advance a new therapy that is directly applicable to dogs, and potentially also to humans, with advanced, locally-recurrent, and/or non-resectable meningioma.

Publications:

Presentations:
On September 18, 2017 at the second annual Comparative Brain Tumor Consortium hosted by the NIH, the following oral presentation slide deck was delivered to the attending audience.

Flint Animal Cancer Center Seminar Series, Fort Collins, DE, October 5, 2018; Direct Procaspase-3 Activation as a Novel Anticancer Strategy.

Paws For A Cure, Boston MA, November 12, 2018; The inclusion of pet dogs with cancer in the translational development of PAC-1, a procaspase-3 activating compound.

Mari Lowe Comparative Oncology Seminar Series, November 29, 2018; Inclusion of companion animals with cancer for developing novel anticancer drugs.

Presented by Dr. Amy LeBlanc
• Annual Veterinary Cancer Society meeting. “Functional Cancer Imaging in Veterinary Oncology & Updates on NCI activities in Comparative Oncology” Houston, TX, Oct 18, 2019.
• Monthly seminar series for FDA veterinarians “The NCI Comparative Brain Tumor Consortium: Progress and Plans”, FDA Center of Devices and Radiological Health (CDRH), FDA Campus @ White Oak, MD, September 18, 2019.
• ONCOVET X conference: “The Role of Comparative Oncology in Cancer Drug Development and Precision Medicine” and “Comparative Cancer Imaging and Metabolism in Osteosarcoma: A Translational Approach to Benefit Dogs and Children” Belo Horizonte, MG, Brazil; May 2-3, 2019.
• ACVIM Advanced Continuing Education for Veterinarians: “Molecular Imaging of Veterinary Cancer Patients” Las Vegas, NV; April 30, 2019.
• Ohio State University/James Comprehensive Cancer Center Grand Rounds: “The Comparative Approach to Cancer Drug Development: Integration of Canine Models” February 1, 2019; Columbus, OH.

Presented by Dr. John Rossmeisl

Center for Cancer Research Colloquium, February 20, 2019; Comparative Oncology Assessment of a Novel Apoptosis-Directed Theranostic Strategy for Meningioma
Report to Grant Sponsor from Investigator:

To date, we have been successful in enrolling and completing the treatment of 3 pet dogs with meningioma, which marks a 50% estimated completion (we plan on recruiting a total of 6 dogs). From the initial 3 dogs completing the clinical trial, we can make several preliminary statements regarding the tolerability and activity of this novel combination of oral drugs for managing canine meningioma. First, the combination of PAC-1 and hydroxyurea is safe and does not cause any unacceptable toxicity to typical body parts including the bone marrow and gastrointestinal tract. This is an important finding because whenever 2 new drugs are combined, it is necessary to ensure that drugs do not interact with one another to produce more severe side effects. Second, given that PAC-1 can penetrate the brain, we were uncertain if PAC-1 would cause worsening of neurologic status in dogs with preexisting brain diseases (meningioma). Based upon our preliminary findings from this study, we are much more confident that PAC-1 is safe to use in dogs with brain cancer, and these findings are similar to what is observed in human beings with the most aggressive form of brain cancer (glioblastoma multiforme) who also are being treated with PAC-1 combined with another chemotherapeutic agent (temozolomide). Last, the ability of PAC-1 + hydroxyurea to dramatically shrink meningioma tumor sizes is limited to date, and we have not observed any of the 3 dogs to have good tumor shrinkage, at best 2 of these dogs had stable disease (meaning that their tumors remained within 20% increase/decrease in size from pre-treatment levels). These findings are different than what we have observed with PAC-1 combined with temozolomide in dogs with meningioma, whereby we have seen some dogs have their tumor shrink dramatically (50%) following therapy. One difference between the current protocol (PAC-1 + hydroxyurea) versus our prior research with PAC-1 + temozolomide in dogs with meningioma is the duration of therapy. For the current protocol, we are treating dogs with 28-days with investigational combination, while in our prior work with PAC-1 + temozolomide, pet dogs were treated for twice as long (56 days).

The ongoing research supported by CHF continues to be highlighted at several meetings, within the United States and Internationally (Brazil and Spain) that emphasize the importance of comparative oncology for advancing shared veterinary and human health disorders, such as brain cancer.