RESEARCH PROGRESS REPORT SUMMARY

Grant 02234-MOU: A Novel Approach for Prevention of Canine Hemangiosarcoma

Principal Investigator:	Jaime Modiano, VMD, PhD
Research Institution:	University of Minnesota
Grant Amount:	$432,000
Start Date: 3/1/2016	**End Date:** 2/29/2020
Progress Report:	Mid-Year 4

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Original Project Description:

Hemangiosarcoma, an aggressive form of cancer in dogs, is the cause of death for one out of every five Golden Retrievers in the United States. Portuguese Water Dogs and Boxers also have an especially high risk for this disease which is devastating for all dogs. Hemangiosarcoma is incurable partly because the cancer is detected at a very advanced stage when it is resistant to conventional therapies. Thus, an unconventional approach to improve outcomes for hemangiosarcoma patients will involve effective methods for early detection and for disease prevention. This project will pair two novel technologies consisting of a patented test to detect hemangiosarcoma cells in blood samples, and a treatment that attacks the cells that establish and maintain the disease. Three milestones will be met: first, will be to expand understanding of the performance and utility of the blood test for cancer in dogs with active disease; second will be to confirm the utility of the test to predict disease progression in treated dogs. And third will be to establish the performance of the test in the "early detection" setting (dogs at high risk without evidence of active cancer), and thus measure hemangiosarcoma prevention through eradication of the tumor initiating cells with the targeted, investigational drug. This project will create tools to guide further development, licensing and deployment of these paired technologies against cancer, specifically hemangiosarcoma, with an ultimate goal for disease prevention in all dogs.

Funding for the research is provided through the collaborative efforts and generosity of the American Boxer Charitable Foundation, Golden Retriever Foundation, and Portuguese Water Dog Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

Publications:

Abstracts and Posters

1. DePauw TA, Anderson KL, Graef AJ, Modiano JF. Early Detection for Hemangiosarcoma in Canines. (Poster). UMN Cancer Center GMOC Program Retreat, St. Paul, MN, June 1, 2016
2. DePauw TA, Anderson KL, Graef AJ, Modiano JF. Development of a Test to Detect Hemangiosarcoma Cells in Canine Blood. (Poster). Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 5, 2016
3. DePauw TA, Anderson KL, Graef AJ, Modiano JF. Development of a Test to Detect Hemangiosarcoma Cells in Canine Blood. (Poster). Masonic Cancer Center Research Symposium, Minneapolis, MN Nov. 2-3, 2016
4. DePauw TA, Anderson KL, Graef AJ, Kim JH, Modiano JF. Early detection and chemoprophylaxis for hemangiosarcoma in dogs. (Poster). First Annual University of Minnesota Center for Immunology and University of Chicago Department of Immunology Combined Retreat, Madison, WI, April 11-13, 2017
5. DePauw TA, Anderson KL, Graef AJ, Kim JH, Lewellen MJ, Winter A, Stuebner K, Modiano JF. Development of an Early Detection Test for Hemangiosarcoma in Dogs. (Poster). Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 4, 2017. Honorable Mention.
6. DePauw TA, Graef AJ, Dickerson EB, Henson MS, Borgatti A, Vallera DA, Cutter GR, Modiano JF. Circulating Tumor Cell Detection for Hemangiosarcoma Diagnosis. (Abstract and oral presentation). Veterinary Cancer Society Mid-Year Meeting, Anchorage, Alaska March 10-13, 2018
7. Park HH, DePauw TA, Modiano JF. Early-Detection of Canine Hemangiosarcoma in Blood Circulation through Adenovirus Transduction. (Poster). College of Veterinary Medicine Comparative Oncology Seminar, St. Paul, MN Aug. 9, 2018.
8. DePauw TA, Khammanivomg A, Graef AJ, Modiano JF. Circulating tumor cell detection for hemangiosarcoma diagnosis in dogs. (Poster). Connective Tissue Oncology Society Annual Meeting, Rome, Italy, Nov. 15, 2018.
9. DePauw TA, Graef AJ, Khammanivomg A, Modiano JF. Diagnosis for Hemangiosarcoma in Dogs using Circulating Tumor Cell Detection. (Poster). Masonic Cancer Center Research Symposium, Minneapolis, MN, April 10, 2019
10. DePauw TA, Modiano JF. Single Cell Sequencing on Circulating Tumor Associated Cells. (Poster). Masonic Cancer Center Genetic Mechanisms of Cancer Program Retreat, Chaska, MN, June 12, 2019

Presentations:

National Professional Presentations

- "Progress in Treatment and Prevention of Canine Hemangiosarcoma: From the Lab to the Clinic and Back Again." Baker Institute Seminar Series, Cornell University, March 15, 2016, Ithaca, NY

- “The Role of Companion Animals in Development of Innovative Strategies for Cancer Treatment and Prevention.” UC Davis Center for Comparative Medicine Seminar Series, April 5, 2016, Davis, CA
- “Comparative Approaches to Cancer Research: Deconvoluting our Evolutionary Legacy.” Bio-Techne Seminar Series, May 5, 2016, Minneapolis, MN
- “Swimming Against the Current: A Turning Point in the Battle Against Hemangiosarcoma.” Keynote Address, 2016 ICCI Cancer Research Symposium, Ontario Veterinary College, May 17, 2016, Guelph, ON, Canada
- *“Where the Future Lies: Innovations in Cancer Treatment and Prevention.” Keynote Address, 3rd World Veterinary Cancer Congress (WVCC), May 25-29 (May 29), 2016, Foz do Iguaçu, Brazil
- "Clinical and Translational Cancer Research in Companion Animals at the University of Minnesota." Boston Scientific Invited Seminar, Sept. 11, 2017, Arden Hills, MN
- *"Biomarkers, Biotherapeutics, and Other Discoveries at the Boundary of Spontaneous and Experimental Disease in Animals." Annual Meeting of the American College of Veterinary Pathologists, November 7, 2017, Vancouver, BC, Canada
- "Accelerating to the Future: Companion Animals as Keystones in Innovation for Cancer Prevention and Treatment." Inaugural Penn Vet Cancer Symposium, December 1, 2017, Philadelphia, PA
- “Advances in Diagnosis and Management of Canine Hemangiosarcoma.” State of the Art (SOTA) Presentation (Specialty Symposium), ACVIM Forum, June 13, 2018, Seattle, WA
- “Dogs, Kids, and Elephants - How We Answered Peto's Paradox and Developed Next-Generation Solutions for Cancer Prevention.” Penn Vet: Advancing Research and Medical Synergies, VMD PhD 50th Anniversary Symposium, March 22, 2019

Local Professional Presentations

- “Dogs and the Development of Cancer Immuno-Prevention,” Pediatric Epidemiology Training Seminar Series, University of Minnesota, August 1, 2016, Minneapolis, MN
- “Turning the Tables: Using the Hallmarks of Cancer to Develop Effective Strategies for Immunoprevention.” Department of Veterinary Clinical Sciences Grand Rounds, University of Minnesota College of Veterinary Medicine, September 15, 2016, St. Paul, MN
- “Discovery and Applications of Cell-Free Nucleic Acid Markers of Cancer using Comparative Approaches.” Masonic Cancer Center, University of Minnesota Seminar Series, January 10, 2017, Minneapolis, MN
- “eBAT: A Safe and Effective EGF-Targeted Angiotoxin for Cancer Developed Using a Comparative, Multispecies Approach.” Masonic Cancer Center - CETI Immunotherapy Mini Symposium, October 13, 2017, Minneapolis, MN
- “Rational Prevention Strategies to Overcome Cancer Risk and the Evolutionary Constraints on Lifespan.” Comparative Oncology and Immunology Seminar Series, Animal Cancer Care and Research Program, University of Minnesota, May 9, 2019, St. Paul, MN
- “Disrupting the Inevitability of Cancer.” Masonic Cancer Center Genetic Mechanisms of Cancer Program Retreat, Minnesota Landscape Arboretum, June 12, 2019, Chaska, MN

Continuing Education and Outreach

- "Cancer Therapy for Companion Animals." Spring 2016 Mini Medical School, Academic Health Center, University of Minnesota, March 28, 2016, Minneapolis MN
- "Changing the Face of Cancer through Effective Prevention." Featured Speaker for the Golden Retriever 2016 National Specialty, October 5, 2016, Placerville, CA
- "Progress in Cancer Treatment and Prevention: an Update from the Animal Cancer Care and Research Program, University of Minnesota." Minnesota Purebred Dog Breeders Association, February 4, 2017, Minneapolis, MN
- "Canine Cancer and What We Can Do About It." Educational Seminar, Vizsla Club of America 2017 National Specialty, May 4, 2017, Del Mar, CA
- "Update on Hemangiosarcoma Research." Health Seminar, American Boxer Club, 2017 National Specialty, May 10, 2017, Indianapolis, IN
- "Canine Cancer and What We Can Do About It." Educational Seminar, National Amateur Retriever Championship, June 16, 2017, Eau Claire, WI
- "2017 Portuguese Water Dog National Specialty Health Seminar. Hemangiosarcoma Update: Reducing the Impact of Cancer through Effective Prevention." Portuguese Water Dog 2017 National Specialty, September 14, 2017, Warwick, RI
- "Studying Cancer in Dogs as a Path Towards a World Where We No Longer Fear Cancer - A Contemporary Update on Canine Hemangiosarcoma." By Borgatti A, Fahrenkrug AM, Modiano JF. Published in The Alpenhorn (The Official Publication of the Bernese Mountain Dog Club of America), Fall 2017, pp. 64-68
- "Studying Cancer in Dogs as a Path Towards a World Where We No Longer Fear Cancer - A New Strategy Raises Hope for Hemangiosarcoma." By Borgatti A, Fahrenkrug AM, Modiano JF. Published in The Alpenhorn (The Official Publication of the Bernese Mountain Dog Club of America), Winter 2018
- "Progress in Cancer Treatment and Prevention: an Update from the Animal Cancer Care and Research Program, University of Minnesota." Norwegian Elkhound Association of America National Specialty Health Seminar, May 9, 2018, Purina Farms, St Louis, MO
- "Progress in Cancer Treatment and Prevention: an Update from the Animal Cancer Care and Research Program, University of Minnesota." Dachshund Club of America National Specialty Health Seminar, May 24, 2018, Purina Farms, St Louis, MO
- "Two Decades of Advances in Canine Hemangiosarcoma: The Light at the End of the Tunnel is Getting Brighter, and It's Not a Train." 2019 AKC Canine Health Foundation National Parent Club Canine Health Conference, August 10, 2019, St Louis, MO

Report to Grant Sponsor from Investigator:

The hypothesis of our project was that identifying dogs at risk for the earliest signs of hemangiosarcoma, and using the drug eBAT (called BEAT in the original proposal) to target the

cancer-stem cell compartment in these dogs, would create an effective means for prophylaxis. We proposed two aims and three milestones. The aims were that (1) our test could detect hemangiosarcoma cells in the circulation prior to the onset of grossly detectable disease, and (2) that eBAT would be safe to eliminate the incipient cancer cells. The milestones were to (1) confirm the sensitivity and specificity of the test in dogs with active disease and expand its predictive value; (2) confirm the utility of the test to monitor relapse; and (3) establish the performance parameters of the test in the "early detection" setting (dogs at risk without gross disease) and the potential to prevent hemangiosarcoma by eradicating the cancer stem cells using eBAT.

We have refined and improved the detection test, so we are confident that it can achieve clinically useful metrics for diagnosis. Our current estimates for sensitivity (can we find the disease if it is present?) and specificity (is it really the disease if the test calls it as such?) are close to 90% and 95%, respectively. We have evidence that the hemangiosarcoma-associated cells change over time in dogs receiving treatment. The dogs participating in this part of the study (prediction of relapse) are still being followed up and the results through the end of 2019 will be reported in the next and final progress report. In terms of early detection, it appears that about 50% of dogs at or over the age of 10 years have some pathology that can be detected by our test. This is consistent with the "textbook" expectation of 50% of dogs over 10 probably dying from cancer.

In the case of dogs that enrolled in phase-3 (early detection) and had a known outcome of death or tumor diagnosis, our test so far indicated the presence of an abnormality in 19 of 21 (91%). While we cannot yet say that the test matched the outcome in all these dogs, it does tell us that the use of the screening test to trigger more thorough diagnostic testing would benefit a large proportion of dogs. On the other hand, 98 of 99 (99%) dogs that were called "unaffected" by the test, and where at least six months had elapsed since the testing, had not developed disease in the interim time since the test was done.

As far as establishing the efficacy of eBAT as a tool for prevention, there is a very high bar for proof. Experiments done in parallel to this project (with funding outside AKC CHF) suggest that eBAT can delay or prevent development of hemangiosarcoma or the associated terminal hemorrhage caused by hemangiosarcoma in mice harboring canine hemangiosarcoma tumors. These are not perfect models and the results are still preliminary. Nonetheless, combined with the remarkable safety of eBAT, they provide support to continue testing dogs at risk, and to eventually be able to formally test the hypothesis that fewer dogs in the population receiving eBAT prevention would develop hemangiosarcoma than in the population that did not receive it.

Regardless of the final result, we have introduced significant innovation in this trial that will be of interest to the biomedical and translational communities, and we remain excited to provide support for additional large-scale trials for early cancer detection in companion dogs.