RESEARCH PROGRESS REPORT SUMMARY

Grant 02806-MOU: Strategic Prevention of Canine Hemangiosarcoma: Lifetime Follow-Up

Principal Investigator: Jaime Modiano, VMD, PhD

Research Institution: University of Minnesota

Grant Amount: $269,238.00

Start Date: 8/1/2020 **End Date:** 1/31/2025

Progress Report: End-Year 4

Report Due: 7/31/2024 **Report Received:** 8/5/2024

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Original Project Description:

The Shine On project is designed to utilize complementary technologies to reduce the impact of hemangiosarcoma in companion dogs. This novel, potentially disruptive approach is the first of its kind where artificial intelligence applied to the results of a blood test will be used to assign dogs to a risk category for the development of hemangiosarcoma. The test, called the Shine On Suspicion (SOS) Test is designed to detect hemangiosarcoma at its earliest stages of development before it becomes a clinically-detectable disease. Dogs that are considered to be at high risk based on the SOS Test results will be eligible to receive the drug eBAT for strategic prevention; that is, to eliminate emergent hemangiosarcoma tumors before they form. eBAT is a rationally designed drug developed in the laboratory to attack the cells that initiate and maintain the cancer, as well as to make the environment inhospitable for their growth. For the initial phase of the Shine On project, investigators developed and refined the SOS Test and the artificial intelligence methods to assign dogs to specific diagnostic categories and started to establish the utility of the test in early detection in a group of 209 presumably healthy, pedigreed Golden Retrievers, Boxers, and Portuguese Water Dogs, 6 years of age or older. In this continuation phase of the Shine On project, this group of dogs that had the SOS Test will be followed for their lifetimes to identify any diagnosis of cancer or another chronic disease, the cause of death, and date of death. In addition, a subset of dogs determined to be at high risk using the SOS Test will receive eBAT in the setting of prevention and also followed over their lifetime to establish their outcomes. This project expects to develop firm proof of concept to support larger clinical trials, and eventual deployment of this approach to the veterinary community setting for all dogs at risk of developing hemangiosarcoma.

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

Publications:

1. DePauw TA, Khammanivong A, Schulte AJ, Winter AL, Lewellen M, Kim JH, Stuebner K, Vallera DA, Cutter GR, Borgatti A, Dickerson EB, Henson MS, Modiano JF. Identification of hemangiosarcoma-associated cells in liquid biopsies for early detection. Manuscript in preparation.

2. DePauw TA, Khammanivong A, Schulte AJ, Winter AL, Lewellen M, Kim JH, Stuebner K, Henson MS, Vallera DA, Dickerson EB, Borgatti A, Cutter GR, Modiano JF. Risk assignment for development of canine hemangiosarcoma through identification of hemangiosarcoma-associated cells in liquid biopsies. Manuscript in preparation.

3. Dicovitsky R, Schulte AJ, Schappa JT, Park-Lang H, Todhunter D, Taras E Lewellen M, Winter AL, Stuebner K, Pracht S, Chehadeh A, Bergsrud K, Schumacher R, Cutter GR, Weigel BJ, Borgatti A, Vallera DA, Modiano JF. Preclinical safety assessment of the novel epidermal growth factor and urokinase bispecific ligand targeted toxin, eBAT. Manuscript in preparation.

4. Li T, Khammanivong A, DePauw TA, Schulte AJ, Modiano JF. Liquid biopsy testing to monitor remission and anticipate relapse of canine hemangiosarcoma. Manuscript in preparation.

5. Sarver AL, Makielski KM, DePauw TA, Schulte AJ, Modiano JF. (2022). Increased risk of cancer in dogs and humans: a consequence of recent extension of lifespan beyond evolutionarily determined limitations? (Perspective). Aging and Cancer, 3(1), 3-19 https://doi.org/10.1002/aac2.12046

6. Schulte AJ, Dicovitsky R, DePauw TA, Khammanivong A, Lewellen M, Burt LE, Vallera DA, Cutter GR, Winter AL, Stuebner KM, Chehadeh A, Pracht S, Borgatti A, Henson MS, Dickerson EB, Ober C, Anderson KL, Nell E, Sarver AL, Modiano JF. Risk assessment, early detection, and strategic prevention of naturally occurring cancers in companion dogs. Manuscript in preparation.

7. Dicovitsky R, Schulte AJ, Schappa JT, Lang HP, Todhunter D, Taras E Lewellen M, Winter AL, Stuebner K, Pracht S, Chehadeh A, Bergsrud K, Schumacher R, Cutter GR, Weigel BJ, Modiano JF, Borgatti A, Vallera DA. Preclinical safety assessment of the novel epidermal growth factor and urokinase bispecific ligand targeted toxin, eBAT.

8. DePauw TA, Schulte AJ, Khammanivong A, Dicovitsky R, Lewellen M, Stuebner KM, Winter AL, Burt LE, Bergsrud K, Pracht S, Ober C, Anderson KL, Nell E, Sarver AL, Kim JH, Henson MS, Dickerson EB, Borgatti A, Vallera DA, Cutter GR, Modiano JF. Impact of Breed (Ancestry) and Age in Cancer Risk Assessment and Interception in a Prospective Cohort of Companion Dogs: A Feasibility Study. Manuscript in preparation.

9. DePauw TA, Schulte AJ, Khammanivong A, Lewellen M, Stuebner KM, Luethke R, Winter AL, Burt LE, Bergsrud K, Pracht S, Sarver AL, Kim JH, Henson MS, Dickerson EB, Borgatti A, Spector LG, Vallera DA, Cutter GR, Modiano JF. Lifespan and cancer risk differences in boxers golden retrievers and Portuguese Water Dogs: a prospective cohort study. Manuscript in preparation.

Presentations:

1- DePauw TA, Khammanivong A, Modiano JF. (2020). Machine Learning for Early Detection of Hemangiosarcoma. Annual Meeting of the Veterinary Cancer Society, Oct. 15-17, 2020 (Conference was conducted virtually due to COVID-19). Abstract was selected for an oral platform presentation by Ms. Taylor DePauw

2- Modiano JF, DePauw TA, Khammanivong A, Schulte AJ, Winter AL, Kim JH, Stuebner K, Fahrenkrug AM, Vallera DA, Borgatti A, Dickerson EB, Henson MS. (2020). Early detection for strategic prevention of a terminal canine cancer: A model to reduce the impact of cancer in our society. (Abstract 4592). Proceedings of the Annual Meeting of the American Association for Cancer Research (Conference was conducted virtually due to COVID-19)

3- DePauw T, Khammanivong A, Lewellen M, Schulte A, Kim JH, Winter AL, Bergsrud K, Chehade A, Pracht S, Stuebner KM, Daniel J, Wolf-Ringwall A, Husbands B, Henson MS, Dickerson EB, Cutter GR, Vallera DA, Borgatti A, Modiano JF. (2021). The Shine On Program for Early Detection and Prevention of Canine Hemangiosarcoma. Proceedings of the Annual Meeting of the Veterinary Cancer Society

4- Modiano JF. (2021). Cellular Origin and Molecular Vulnerabilities of Canine Hemangiosarcoma – the Next Chapter in Treatment and Prevention (oral platform presentation in the hemangiosarcoma session chaired by Dr. Modiano). Annual Meeting of the Veterinary Cancer Society, Nov. 4-7, 2021 (Conference was conducted virtually due to COVID-19)

5- Modiano JF. (2021). Changing Our Approach to Cancer: Why Cancer Happens and How Early Detection and Strategic Prevention Will Help Us Defeat It (in-person presentation). Fetch DVM360 Conference. December 4, 2021, San Diego, CA 2021

6- Modiano JF. (2021). Changing the Face of Cancer through Effective Prevention. Fetch DVM360 Conference. December 5, 2021, San Diego, CA 2021

7- Modiano JF. (2021). Early Detection and Strategic Prevention of Canine Hemangiosarcoma: An Update on the Shine-On Project (live webinar). A free University of Minnesota/Animal Cancer Care and Research Program Webinar, November 9, 2021 (virtual lecture)

8- Modiano JF. (2021). How We Can Change the Cancer Landscape (in-person presentation). Fetch DVM360 Conference. December 5, 2021, San Diego, CA 2021

9- Modiano JF. (2021). One Pathologist's Dream: Detecting Cancer Before It Starts and Killing It Before It Forms (virtual, live seminar). Department of Laboratory Medicine and Pathology Grand Rounds, University of Minnesota School of Medicine, December 2, 2021, Minneapolis, MN

10- Modiano JF. (2021). What Is New, Exciting, and Encouraging in Canine Hemangiosarcoma? (In-person presentation) Fetch DVM360 Conference. December 5, 2021, San Diego, CA 2021

11- Borgatti A, Dickerson EB, Modiano JF, Diehl K. (2022). New Thoughts on Hemangiosarcoma in Dogs (pre-recorded podcast). Fresh Scoop Podcast (#52), Morris Animal Foundation, December 20, 2022

12- Li T, Khammanivong A, DePauw T, Schulte A, Modiano J. (2022). Monitoring Hemangiosarcoma Treatment Success with A Peripheral Blood Test (in-person poster presentation). National Veterinary Summer Scholars Symposium, August 4-6, 2022, Minneapolis, MN

13- Modiano JF, Schulte AJ, DePauw TA, Khammanivong A, Kim JH, Sarver AL, Cutter GR, Lindquist E, Makielski KM. (2022). Identification and characterization of the cancer permissive environment in companion dogs (in-person poster presentation and invited oral platform presentation). Inaugural AACR Aging and Cancer Meeting, November 17-20, 2022, San Diego, CA
14- Modiano JF. (2022). Burn Down the Mission – Creating an Inhospitable Environment to Improve Cancer Outcomes. RAR Seminar Series, University of Minnesota, September 30, 2022, Minneapolis, MN
15- Modiano JF. (2022). Comparative Oncology: Challenges and Opportunities for the Coming Decade. Oncology Breakout Session (in-person seminar). National Veterinary Summer Scholars' Symposium, August 5, 2022, St. Paul, MN
16- Modiano JF. (2022). Demystifying Cancer: Why cancer happens and what we can do about it (virtual live lecture). American Association of University Women Seminar Series, February 7, 2022
17- Modiano JF. (2022). Principles of Cancer Immunotherapy (virtual recorded lecture). The Science of Veterinary Oncology Lecture Series, American College of Veterinary Internal Medicine, an Online Resource, 2022
18- Modiano JF. (2022). Reducing the Impact of Cancer on our Society through Risk Assessment and Strategic Prevention (virtual live seminar). Australia and New Zealand College of Veterinary Scientists Science Week 2022, June 25, 2022, The Star, Broadbeach, Queensland, Australia
19- Modiano JF. (2022). Risk Assessment for Cancer - Find It Before It's there, Kill it Before It Forms (virtual live seminar). Department of Veterinary Clinical Sciences Grand Rounds, University of Minnesota College of Veterinary Medicine, September 22, 2022, St. Paul, MN
20- Modiano JF. (2022). Taming Canine Hemangiosarcoma: New, Exciting, and Encouraging Developments in Our Ability to Manage a Dreadful Cancer (virtual live seminar). Australia and New Zealand College of Veterinary Scientists Science Week 2022, June 25, 2022, The Star, Broadbeach, Queensland, Australia
21- Modiano JF. (2022). The Apparent Cancer Epidemic: Why is cancer so common in dogs and humans? (Virtual live lecture). Minnesota Dog Breeders Association Annual Meeting, February 6, 2022
22- Modiano JF. (2022). The Minnesota Solution to Cancer: Find It Before It Starts; Kill It Before It Forms (virtual live seminar). Hormel Institute Seminar Series, March 2, 2022, Austin, MN
23- Modiano JF. (2022). Two+ Decades of Progress on Canine Hemangiosarcoma (virtual live presentation, also available on Youtube as Ottertalk #25). Otterhound Club of America Ottertalk, November 1, 2022
24- Modiano JF. (2022). What is Hemangiosarcoma Anyway? (Virtual live presentation) UC Davis Veterinary Student Rounds, December 18, 2022
25- Modiano JF. (2022). Why Cancer Happens: A Story of Success and Unintended Consequences (virtual live seminar). Australia and New Zealand College of Veterinary Scientists Science Week 2022, June 25, 2022, The Star, Broadbeach, Queensland, Australia

26- Dicovitsky, R (2022). Shine-On Prevention of Canine Hemangiosarcoma: Lifetime Follow-up (virtual live seminar). Department of Veterinary Clinical Sciences Grand Rounds, University of Minnesota College of Veterinary Medicine February 24, 2022, Minneapolis, MN
27- Kappenman I, Spielman R, Modiano J, Schulte A. (2023). Optimizing flow cytometry antibody panel for the Shine On Suspicion project protocol. National Veterinary Scholars Symposium, San Juan, PR, August 3-5, 2023
28- Modiano JF. (2023). Applications of Liquid Biopsies in Veterinary Medicine. Scheduled 3 in-person lecture hours to be delivered at the Annual Meeting of the European Society of Veterinary Oncology, on May 27, 2023, Alicante, Spain.
29- Modiano JF. (2023). Defining the Cancer Permissive Environment and Its Applications in Early Detection, Risk Assessment, and Strategic Prevention of Cancer. Annual Meeting of the European Society of Veterinary Oncology (ESVONC), Alicante, Spain, May 27, 2023
30- Modiano JF. (2023). Liquid Biopsies in Diagnostic Pathology: A Brief History and Current and Future Applications. Keynote Address: Annual Meeting of the European Society of Veterinary Oncology (ESVONC), Alicante, Spain, May 27, 2023
31- Spielman R, Kappenman I, Modiano J, Schulte A. (2023). Optimizing lysis of canine red blood cells for flow cytometry. National Veterinary Scholars Symposium, San Juan, PR, August 3-5, 2023
32- Modiano JF, Dickerson EB, Borgatti A. (2023). What Do We Really Know About Canine Hemangiosarcoma?" Veterinary Cancer Society Oncology Connections, May 9, 2023
33- Modiano JF. (2023). Liquid Biopsies in Diagnostic Pathology: A Brief History and Current and Future Applications. Keynote Address: Annual Meeting of the European Society of Veterinary Oncology (ESVONC), Alicante, Spain, May 27, 2023
34- Modiano JF. (2023). Defining the Cancer Permissive Environment and Its Applications in Early Detection, Risk Assessment, and Strategic Prevention of Cancer. Annual Meeting of the European Society of Veterinary Oncology (ESVONC), Alicante, Spain, May 27, 2023
35- Kappenman I, Spielman R, Modiano J, Schulte A. (2023). Optimizing flow cytometry antibody panel for the Shine On Suspicion project protocol. National Veterinary Scholars Symposium, San Juan, PR, August 3-5, 2023
36- Spielman R, Kappenman I, Modiano J, Schulte A. (2023). Optimizing lysis of canine red blood cells for flow cytometry. National Veterinary Scholars Symposium, San Juan, PR, August 3-5, 2023
37- Schulte AJ, DePauw TA, Khammanivong A, Winter AL, Stuebner K, Kappenman I, Spielman R, Burt LE, Lewellen M, Borgatti A, Feiock C, Dicovitsky R, Henson MS, Dickerson EB, Chehadeh A, Pracht S, Bergsrud K, Reid K, Espejo-Freire A, Murugan P, Linden MA, Cutter GR, Weigel BJ, Sarver AL, Vallera DA, Modiano JF. (2023). Optimization and translation of a flow cytometry protocol for cancer risk prediction in dogs. Masonic Cancer Center Research Symposium, October 30, 2023, Minneapolis, MN
38- Modiano JF. (2024). "Cambiando Nuestro Enfoque del Cáncer: Porqué Ocurre el Cáncer y Como la Detección Temprana y la Prevención Estratégica Nos Ayudarán a Derrotarlo" (Changing Our Approach to Cancer: Why Cancer Happens and How Early Detection and Strategic Prevention

Will Help Us Defeat It"), 3-hours of lecture at the SLOVET (Sociedad Latinoamericana de Oncologia Veterinaria) Virtual Meeting (Mexico), January 20, 2024

39- Makielski KM and Modiano JF. (2024). Liquid Biopsies for Cancer Detection: Are We Pawsitive We Know What We Are Doing? Annual Meeting of the Minnesota Veterinary Medical Association, Minneapolis, MN, February 8, 2024

40- Makielski KM and Modiano JF. (2024). Liquid Biopsies in Veterinary Medicine. Annual Meeting of the Minnesota Association of Veterinary Technicians, Minneapolis, MN, February 9, 2024

41- 41-Modiano J (2024). From Furry Friends to Fossil Giants: What We Can Learn by Studying Cancer across the History of Life on Earth." The Animal Health Education Series, University of Minnesota College of Veterinary Medicine, St. Paul, MN, February 6, 2024

42- Modiano JF. (2024). What Do We Really Know about Canine Hemangiosarcoma? Italian Society for Vet Oncology Hemangiosarcoma Symposium (virtual event), February 10, 2024

43- Modiano J. (2024). Early Detection, Risk Assessment and Strategic Prevention: A New Recipe to Manage Hemangiosarcoma and Other Life-Threatening Cancers. Italian Society for Vet Oncology Hemangiosarcoma Symposium (virtual event), February 10, 2024

44- Modiano JF, Schulte AJ, Dicovitsky R, DePauw TA, Khammanivong A, Lewellen M, Burt LE, Vallera DA, Cutter GR, Winter AL, Stuebner KM, Chehadeh A, Pracht S, Borgatti A, Henson MS, Dickerson EB, Ober C, Anderson KL, Nell E, Sarver AL. (2024). Risk assessment, early detection, and strategic prevention of naturally occurring cancers in companion dogs (Abstract 5176). Annual Meeting of the American Association for Cancer Research, San Diego, CA, April 5-10, 2024.

45- Modiano J. (2024). Evolution, Aging, and Cancer: How Dogs can Help Us Understand and Manage the Perceived Cancer Epidemic. Invited platform presentation for the Educational Session on Spontaneous Cancers of Companion Animals as Clinically Relevant Models for Advancing Human Oncology. Annual Meeting of the American Association for Cancer Research, San Diego, CA, April 6, 2024

Report to Grant Sponsor from Investigator:

The goal for this project is to develop a reliable, accessible, and actionable test to identify dogs at risk for hemangiosarcoma during the earliest stages of disease and to use a strategic, rationally designed approach to prevent its occurrence in these high-risk dogs before it becomes clinically detrimental and life-threatening. The study has two objectives. The first is to determine the most reasonable duration of an SOS test result. In other words, how long can a low-risk SOS test result be trusted and how much time might elapse between a high-risk SOS test result and the development of hemangiosarcoma. The second aim is to continue periodic testing for dogs previously enrolled in the Shine On study whose test result would have placed them in a high-risk category for development of hemangiosarcoma, and to provide eBAT as a strategy for prevention in up to 12 of these dogs.

To complete the first objective, we are conducting surveys to determine the health status of every dog enrolled in Shine On phase-3 (SO3, the early detection phase) at 6-month intervals. This effort will continue throughout the duration of the study.

To complete the second objective, we have finalized the analysis of the data from Shine On phase-1 (SO1) (used as the "training set" for SOS test) and applied those results to dogs from SO3 to select candidates for continued, periodic testing. We have enrolled more than 60 dogs into the Shine On continuation (SOC). Owners of dogs that have been assigned to the high-risk category have been provided information about available screening, and they have been given the opportunity to complete screening, and if eligible, to enroll in eBAT prevention. To date, we have screened 32 dogs and nine have been eligible for - and enrolled in eBAT prevention. We have expanded the eligibility and continue our efforts to test and recruit subjects for the study. The data from these experiments will be aggregated and analyzed as described in the proposal.

The project has also been extremely successful in training the next generation of researchers with specific interest in canine health.