



RESEARCH PROGRESS REPORT SUMMARY

Grant 03032-MOU: Early Detection of Canine Osteosarcoma

Principal Investigator: Jaime Modiano, VMD, PhD

Research Institution: University of Minnesota

Grant Amount: \$497,469.60

Start Date: 4/1/2022 **End Date:** 9/30/2025

Progress Report: Mid-Year 3

Report Due: 9/30/2024

Original Project Description:

Funding for the research is provided through the collaborative efforts and generosity of the Golden Retriever Foundation®, Great Dane Club of America Charitable Trust, Irish Setter Club of America Foundation, Irish Wolfhound Foundation and Irish Wolfhound Club of America, Leonberger Health Foundation International, Rottweiler Health Foundation, and the AKC Canine Health Foundation, which will oversee grant administration and scientific progress.

Primary bone cancers (called osteosarcomas) affect more than 8,000 dogs, and possibly as many as 50,000 dogs per year in the United States. Although the risk for bone cancer is greatest in large and giant breeds, it is a health concern for many breeds. The impact of the problem is highlighted by the fact that osteosarcoma accounts for up to 10-20% mortality in some breeds. While osteosarcoma is treatable, only 30-40% of dogs that receive the standard of care survive one year or longer, and fewer than 20% are alive at two years. In addition, some dogs suffer significant treatment-related morbidity. Thus better strategies to manage this cancer are needed. Given the current understanding that size and longevity are two major factors associated with osteosarcoma risk, and the challenges of treating this disease once it is established, investigators have focused efforts on developing tests that allow detection of osteosarcoma at or near its origin. Early detection, in turn, will enable the deployment of strategic prevention in dogs at high risk. This project will place special emphasis on Irish Wolfhounds, Rottweilers, Great Danes, Golden Retrievers, Irish Setters, and Leonbergers, without neglecting other breeds (or mixed breed dogs) at risk. The central goal is to develop a blood test for early detection of osteosarcoma as the initial step in the implementation of the long-term strategy of early detection and targeted prevention. Success in this effort will be foundational to implement the test in clinical practice and to provide access to prevention. Investigators propose that this approach—combining early detection and targeted prevention—is a novel and potentially transformative strategy to address the unmet health

need for dogs at risk of bone cancer. This project may also add to the proof-of-concept that will enable using this type of approach to reduce the impact of cancer in humans.

Publications: None to date.

Presentations:

1. Makielski, K. (2022). Development of a Canine Osteosarcoma Early Detection Test: The COED Study. Presented at the inaugural ACVIM Research Colloquium & Networking Event, June 24, 2022, Austin, TX.

2. Makielski KM. (2022). Molecular Signatures of Disease Behavior. Masonic Cancer Center Seminar Series, December 20, 2022, Minneapolis, MN.

3. 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), May 27, 2023, Alicante, Spain.

4. Modiano JF. (2023). A Liquid Biopsy Platform for Novel Exosome-Based Cancer Diagnostics and Its Applications in Medicine and Veterinary Medicine. Annual Meeting of the European Society of Veterinary Oncology (ESVONC), May 27, 2023, Alicante, Spain.

5. Makielski KM, Modiano JF. (2023). Assessment of biological aging and cancer risk using liquid biopsies. ACVIM 2023, June 15-17, 2023, Philadelphia, PA.

6. Makielski KM, Khammanivong A, Labe CH, Schulte AJ, Kreager LE, Rendahl AK, Cutter GR, Spector LG, Weigel BJ, Modiano JF. (2023). Identification of serum exosomal gene signatures associated with prognosis in pediatric osteosarcoma. FACTOR Osteosarcoma Conference 2023, June 22-24, 2023, Atlanta GA.

7. Labé CH, Wojtysiak M, Lewellen M, Winter AL, Reid K, Myers E, Modiano JF, Makielski, KM. (2023). Investigation of exosome concentration as a potential biomarker for canine cancer. This work was presented at the National Veterinary Scholars Symposium on August 3-5, 2023, in San Juan,

PR, at the University of Minnesota Comparative Oncology and Immunology Seminar Series on August 9, 2023, and at the Masonic Cancer Center Research Symposium on October 30, 2023, in Minneapolis, MN

8. Wojtysiak M, Labé CH, Lewellen M, Myers E, Winter AL, Reid K, Modiano JF, Makielski, KM. (2023). Comparison of plasma preparations to optimize exosome enrichment for early detection of canine osteosarcoma. This work was presented at the National Veterinary Scholars Symposium on August 3-5, 2023, in San Juan, PR, at the University of Minnesota Comparative Oncology and Immunology Seminar Series on August 9, 2023, and at the Masonic Cancer Center Research Symposium on October 30, 2023, in Minneapolis, MN

9. Modiano JF. (2023). "Modifying the Cancer Permissive Environment for Strategic Cancer Prevention." Mari Lowe Seminar Series, University of Pennsylvania, November 30, 2023, Philadelphia, PA.

10. Modiano JF. (2023). "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"), SLOVET (Sociedad Latinoamericana de Oncología Veterinaria) Virtual Meeting (Mexico), January 20, 2024

11. Makielski KM & Modiano JF. (2024). "Liquid biopsies for cancer detection: Are we pawsitive we know what we are doing?" Minnesota Veterinary Medical Association 2024 Annual Meeting, February 8, 2024, Minneapolis, MN.

12. Makielski KM & Modiano JF. (2024). "Liquid Biopsies in Veterinary Medicine." Minnesota Association of Veterinary Technicians 2024 Convention, February 9, 2024, Minneapolis, MN.

13. Makielski KM, Khammanivong A, Labe C, Wojtysiak M, Myers E, Leon A, Lewellen M, Winter A, Reid K, Rendahl AK, Cutter GR, Spector LG, Weigel BJ, Modiano JF. Canine osteosarcoma early detection: The COED study – identification of exosomal gene signatures associated with osteosarcoma development in otherwise healthy at-risk dogs. World Veterinary Cancer Congress 2024, March 22, 2024, Tokyo, JP.

14. Modiano JF. "Updates on the COED Project." Irish Wolfhound National Specialty, May 21, 2024, Eureka, MO.

15. Wojtysiak MM, Chehadeh A, Pracht S, Winter A, Reid K, Bolle R, Feiock C, Magstadt J, Labe CH, Gordon-Evans W, Modiano JF, Makielski KM. Characterization of canine extracellular vesicles in conditions leading to bone remodeling. 2024 National Veterinary Scholars Symposium, August 7-9, 2024, St. Paul, MN.

16. Magstadt JM, Labe CH, Wojtysiak M, Duval K, Khammanivong A, Mills LJ, Winter A, Feiock C, Reid K,

Lewellen M, Spector LG, Weigel BJ, Modiano JF, Makielski KM. Plasma exosome concentrations in healthy dogs and dogs with osteosarcoma. American Association for Cancer Research (AACR): Advances in Pediatric Cancer Research, September 5-8, 2024, Toronto, CA.

17. Labe CH, Wojtysiak M, Khammanivong A, Lewellen M, Magstadt J, Myers E, Winter A, Reid K, Feiock C, Borgatti A, Weigel BJ, Spector LG, Vallera D, Rendahl AK, Cutter G, Modiano JF, Makielski KM. Differences in plasma exosome concentrations in healthy dogs and dogs with cancer in the Canine Osteosarcoma Early Detection (COED) study. Veterinary Cancer Society, October 17-19, 2024, Orlando, FL (accepted for poster presentation).

18. Makielski KM. "Updates on the COED Project." Great Dane Club of America National Specialty, November 21, 2024, Kalahari Resort, Wisconsin Dells, WI.

19. Makielski KM, Magstadt JM, Labe CH, Khammanivong A, Wojtysiak M, Duval K, Lewellen M, Winter A, Reid K, Chehadeh A, Buettner M, Feiock C, Rendahl AK, Cutter G, Spector LG, Weigel BJ, Modiano JF. Dogs with cancer have higher plasma exosome concentrations compared with healthy dogs in the Canine Osteosarcoma Early Detection (COED) study. American Association for Cancer Research (AACR): Liquid Biopsy from Discovery to Clinical Implementation, November 13-16, 2024, San Diego, CA (Accepted for poster presentation).

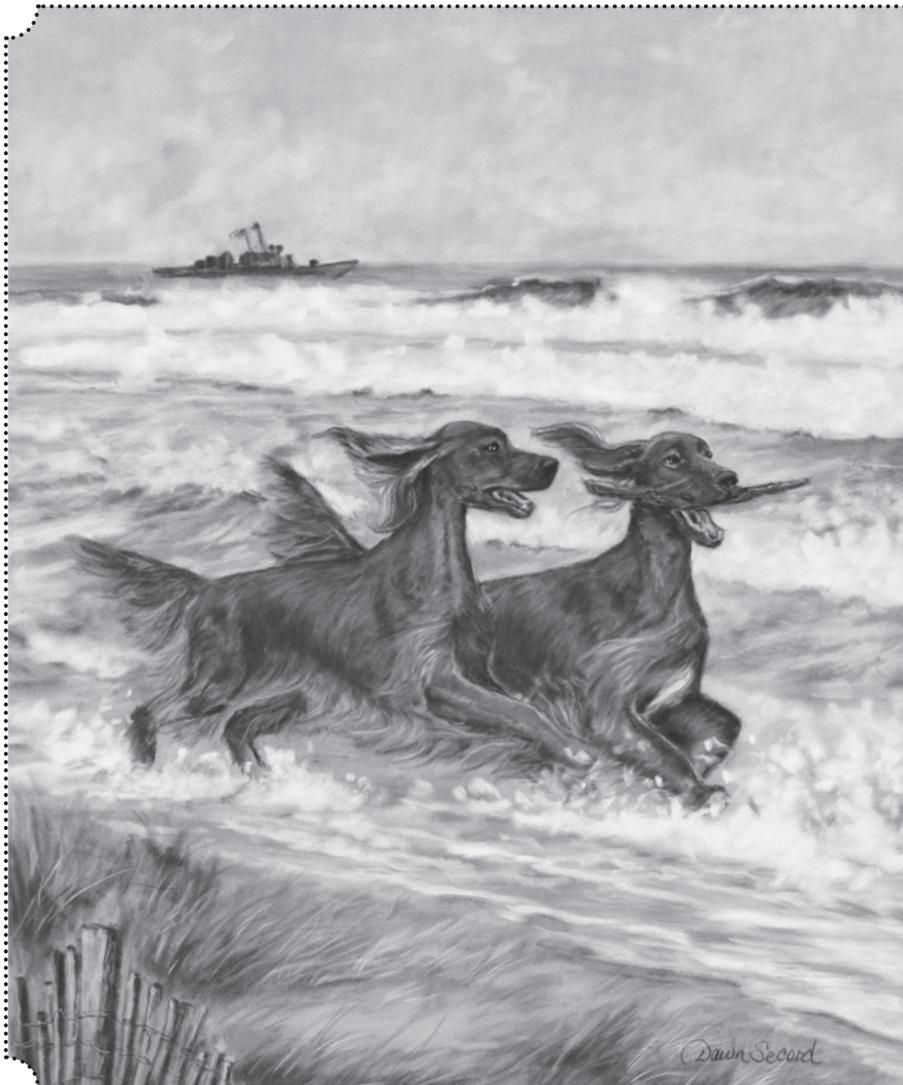
20. Makielski KM. Exosomes in Veterinary Medicine: Pioneering Advances and Breakthroughs in Diagnostics and Therapeutics. American College of Veterinary Internal Medicine (ACVIM) Forum 2025, June 19-21, 2025, Louisville, KY (Submitted for presentation, pending decision).

Report to Grant Sponsor from Investigator:

In this study, we aim to identify blood biomarkers that can be used to assign a probability of developing osteosarcoma to otherwise healthy dogs at risk for this disease. We had a large set of samples and also collected new samples for this project. The control (old and new) samples include healthy dogs and dogs with cancer. These samples are used to identify the patterns that are exclusively present in dogs with cancer, and specifically in dogs with bone cancer. The experimental group includes healthy dogs at risk for development of bone cancer. This risk is based on age (older than 4.5 years) and on size. Dogs from six breeds received preference in recruitment, although large dogs of other breeds and mixed breeding were also eligible to enroll. A gift from the Irish Wolfhound Foundation in advance of this project was instrumental in helping us to finalize the infrastructure. It also allowed us to pilot enrollment of 25 dogs to make sure the protocols were efficacious and reasonable. Recruitment for the experimental group was

launched at the end of August of 2022 and we began enrolling dogs and receiving samples, in random order, in October 2022. As of March 31st, 2024, we have completed enrollment and collected a total of 478 new samples for both parts of this project. We are following enrolled dogs for the duration of the project (and ideally for the lifetime of the dogs) and experiments and data analysis have begun with the goal of constructing the metrics of the test. Such a test for predicting the occurrence of bone cancer in dogs would be extremely valuable to veterinary medical community and dog owners world-wide. Our approach will use artificial intelligence technologies to describe patterns that are associated with the formation of these cancers.

We have also used this project as a training vehicle to engage young scientists and encourage them to pursue careers in canine health research. Courtney Labé, Meagan Wojtysiak, Emily Myers, and Abigail Leon are veterinary students who completed Summer Scholar projects or otherwise worked on the COED project in the lab and have continued work on this program as they progress through veterinary school. These students have each expressed an interest in continuing on a path that includes research, and specifically research that aims to improve the health and wellbeing of companion dogs, as a major component of their future careers.



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