



RESEARCH PROGRESS REPORT SUMMARY

Grant 01660: Identifying the Genes That Confer Risk for Osteosarcoma

Principal Investigator: Carlos Alvarez, PhD
Research Institution: The Research Institute at Nationwide Children's Hospital
Grant Amount: \$120,000.00
Start Date: 1/1/2012 **End Date:** 12/31/2019
Progress Report: End-Year 7
Report Due: 12/31/2018 **Report Received:** 1/2/2019

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Original Project Description:

Osteosarcoma (OSA) is the most common cancer of the bone in both dogs and humans. A prime candidate for investigation of the genetic component of OSA is the Greyhound, which has the highest risk of OSA of any breed. However, despite significant effort, classical genetic approaches have not identified any Greyhound variant that accounts for most OSA cases in that breed. Dr. Alvarez proposes that Greyhound OSA variants have been directly or indirectly selected for in racing performance, consistent with the vastly elevated incidence in racing vs. show Greyhounds. If this is true and all racers carried an OSA mutation on both chromosomes, then this could not be detected using classical approaches (which require different genetic markers to distinguish cases v. controls). Here Dr. Alvarez proposes an innovative genetic approach that is impervious to the limitations described above, and enables genome-wide discovery of Greyhound variation with large effects on OSA risk. Such findings would lead to rapid development of therapies and clinical trials in dogs, and translation to human medicine.

Publications:

Zapata, I., Moraes, L. E., Fiala, E. M., Zaldivar-Lopez, S., Couto, C. G., Rowell, J. L., Alvarez, C. E. Risk-modeling of dog osteosarcoma genome scans shows individuals with Mendelian-level polygenic risk are common. Revision under review.

Zaldívar-López, S., Rowell, J. L., Fiala, E. M., Zapata, I., Couto, C. G., & Alvarez, C. E. (2017). Comparative genomics of canine hemoglobin genes reveals primacy of beta subunit delta in adult carnivores. *BMC Genomics*, 18(1). <https://doi.org/10.1186/s12864-017-3513-0>



Clemente-Vicario, F., Alvarez, C. E. Rowell, J. L., Roy, S., London, C. A., Kisseberth, W. C., Lorch, G. (2015) Human Genetic Relevance and Potent Antitumor Activity of Heat Shock Protein 90 Inhibition in Canine Lung Adenocarcinoma Cell Lines, PLoS One, 10(11):e0142007. <http://doi:10.1371/journal.pone.0142007>. PMID: 26560147

Lutful Kabir, F. M., Alvarez, C. E., & Bird, R. C. (2015). Canine Mammary Carcinomas: A Comparative Analysis of Altered Gene Expression. *Veterinary Sciences*, 3(1). <https://doi.org/10.3390/vetsci3010001>

Alvarez, C. E. (2014) Naturally occurring cancers in dogs: insights for translational genetics and medicine, *ILAR Journal* 55(1):16-45. doi: 10.1093/ilar/ilu010. PMID: 24936028.

Presentations:

Alvarez, C.E., The Ohio State University: Animal Sciences 3105: Domestication, Form, and Function of the Dog, lecture titled Genetics of dog behavior & domestication, Jan. 25, 2018.

Alvarez, C.E., Scottish Deerhound Club of America National Specialty, "Genetics of canine osteosarcoma risk & implications for Scottish Deerhounds", May 16, 2018

Presenter, Cancer Drug Development: Predictability of Animal Experiments symposium (and participant in associated book project: *Methods and Principles in Medicinal Chemistry* series, Wiley-VCH), Collegium Helveticum, 8006 Zurich, Switzerland, Alternative animal models of disease: the unique strengths of the dog, March 12-14, 2014.

Swiss Tropical and Public Health Institute and University of Basel, Basel, Switzerland, Using dog genetics to identify the "missing heritability" of common diseases, March 14, 2014.

The Ohio State University VME 6540 Structure & Function of Cells (Cell Biology), Lecture on canine genetics & genomics (Fall term 2014)

Report to Grant Sponsor from Investigator:

We have conducted a small-scale genomewide association study of osteosarcoma risk in Greyhounds and are currently increasing the number of subjects in the study to improve the discovery rate and overall confidence. We successfully validated genetic mapping of osteosarcoma risk previously published by others and identified at least one risk allele that is common across dog breeds. In addition, we mapped four new candidate loci that will undergo further validation studies. The next issue is how to accelerate the use of this information for development of new therapies and genetic testing for clinical or breeding purposes. To that end, we conducted studies to measure the genetic risk



of dog osteosarcoma variations and re-annotated those known genome regions for gene content. In these ways, we have prioritized a subset of known variations because they have large contributions to risk and ranked the candidate genes according to genome location and biological relevance. We have new support from the Scottish Deerhound Club of America and are creating an osteosarcoma case-control cohort to expand our genetic studies to include a closely-related sighthound.