



AMERICAN KENNEL CLUB  
**CANINE HEALTH  
FOUNDATION**  
PREVENT TREAT & CURE®

# The American Boxer Charitable Foundation's Impact on Canine Health

Peer Reviewed Scientific Publications and  
Presentations Resulting from Research  
Sponsored by the ABCF  
1999-2013

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## Oncology

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### Identification and Characterization of Genetic Mutations in Canine Mast Cell Tumors (0179)

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#### *Publications*

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AR-42, a novel HDAC inhibitor, exhibits biologic activity against malignant mast cell lines via down-regulation of constitutively activated Kit. Lin, Tzu-Yin; Fenger, Joelle; Murahari, Sridhar; et al. Blood. Volume: 115 Issue: 21 Pages: 4217-4225

Generation and characterization of novel canine malignant mast cell line CL1. Lin, Tzu-Yin; Thomas, Rachael; Tsai, Pei-Chien; et al. Veterinary Immunology and Immunopathology . Volume: 127 Issue: 1-2 Pages: 114-124 Published: JAN 15 2009

### Characterization of Receptor Tyrosine Kinase Dysfunction in Malignant Histiocytosis (191)

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#### *Publications*

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Evaluation of dysregulation of the receptor tyrosine kinases Kit, Flt3, and Met in histiocytic sarcomas of dogs. Zavodovskaya, R; Liao, AT; Jones, CLR; et al. American Journal of Veterinary Research. Volume: 67 Issue: 4 Pages: 633-641 Published: APR 2006

### Characterization and Modulation of Canine Mast Cell Derived Eicosanoids (0975)

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#### *Publications*

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Characterization and modulation of canine mast cell derived eicosanoids. Lin, Tzu-Yin; London, Cheryl A. Veterinary Immunology and Immunopathology . Volume: 135 Issue: 1-2 Pages: 118-127. MAY 15 2010

The Importance of the Mitotic Index as a Prognostic Factor for Survival of Canine Cutaneous Mast Cell Tumors: A Validation Study Response. Kass, Philip H.; Romansik, Erin M.; Reilly, Christopher M.; et al. Veterinary Pathology. Volume: 46 Issue: 2 Pages: 364-365 Published: MAR 2009

## Investigating the Role of STAT3 Activation in Canine Osteosarcoma (0976)

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### *Publications*

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Characterization of STAT3 activation and expression in canine and human osteosarcoma. Fossey, Stacey L.; Liao, Albert T.; McCleese, Jennifer K.; et al. BMC CANCER Volume: 9 Article Number: 81 Published: MAR 10 2009

The novel curcumin analog FLLL32 decreases STAT3 DNA binding activity and expression, and induces apoptosis in osteosarcoma cell lines. Fossey, Stacey L.; Bear, Misty D.; Lin, Jiayuh; et al. BMC CANCER Volume: 11 Article Number: 112 Published: MAR 28 2011

## Generation and Analysis of Canine Bone Marrow Derived Mast Cells (0678)

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### *Publications*

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A functional comparison of canine and murine bone marrow derived cultured mast cells. Lin, Tzu-Yin; London, Cheryl A. Veterinary Immunology and Immunopathology. Volume: 114 Issue: 3-4 Pages: 320-334 Published: DEC 15 2006

## Significance of Tumor Suppressor Genes in Canine Cancer (1626)

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Modiano JF, Ritt MG, Wojcieszyn J. (1999). The molecular basis of canine melanoma: Pathogenesis and trends in diagnosis and therapy. J Vet Intern Med 13, 163-174. PMID: 10357103

Ritt MG, Wojcieszyn J, Smith R, III, Mayor J, Barton CL, Modiano JF. (2000). Sustained nuclear localization of p21/Waf-1 upon growth arrest induced by contact inhibition. Cancer Lett, 158, 73-84. PMID: 10940512

Koenig A, Weeks BR, Wojcieszyn J, Modiano JF. (2001). Expression of S100a, vimentin, NSE, and Melan A/MART-1 in seven canine melanoma cell lines and twenty-nine retrospective cases of canine melanoma. Vet Pathol, 38, 427-435. PMID: 11467477

Dickerson EB, Fosmire S, Padilla ML, Modiano JF, Helfand SC. (2002). Potential to target dysregulated interleukin-2 receptor expression in canine lymphoid and hematopoietic malignancies. J Immunother, 25, 36-45. PMID: 11924909

Koenig A, Fosmire S, Bianco S, Wojcieszyn J, Modiano JF. (2002). Expression and significance of p53, Rb, p21/Waf-1, p16/Ink-4a, and PTEN tumor suppressors in canine melanoma. Vet Pathol, 39, 458-472. PMID: 12126149

Bianco SR, Sun J, Fosmire SP, Hance K, Padilla M, Ritt MG, Getzy D, Duke RC, Withrow S, Lana S, Matthiesen DT, Dow S, Bellgrau D, Cutter G, Helfand SC, Modiano JF. (2003). Enhancing anti-melanoma immune responses through apoptosis. *Cancer Gene Ther*, 10, 726-736. PMID: 12944992

Fosmire SP, Thomas R, Jubala CM, Wojcieszyn J, Valli VEO, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GR, Breen M, Modiano JF. (2007) Inactivation of the p16 cyclin-dependent kinase inhibitor in high-grade canine non-Hodgkin T-cell lymphoma. *Vet Pathol*, 44(4), 467-478. PMID: 17606508

### *Refereed Abstracts*

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Mayor J, Chitko-McKown CG, Modiano JF. (1998). Cloning of the canine WAF-1 gene. (Abstract). *Proc Annu Conf Vet Cancer Soc* 18:29.

Modiano JF, Wojcieszyn J, Avery AC, Thomas JS, Smith R, III. (1999). Advances in the diagnosis of leukemias in small animals. (Abstract). *Proc WAVLD Symposium* 9.

Helfand SC, Dickerson EB, Modiano JF, Padilla ML. (1999). The interleukin-2 receptor as a potential target in canine lymphoid malignancy. (Abstract). *Proc Annu Conf Vet Cancer Soc* 19.

Modiano JF, Fosmire S, Mayor J, Koenig A, Dickerson EB, Helfand SC, Weeks BR, Wojcieszyn J. (2000). Tumor suppressor genes in canine cancer. (Abstract). *Proc 27th Int Conf on Anim Gen (Canine Genetics)*.

Dickerson EB, Modiano JF, Helfand SC. (2000). Molecular characterization of the interleukin-2 receptor in canine lymphohematopoietic malignancy. (Abstract). *J Vet Intern Med* 14.

Koenig A, Wojcieszyn J, Weeks BR, Modiano JF. (2001). Expression of S100a, vimentin, NSE, and Melan A/MART-1 in seven canine melanoma cell lines and twenty-nine retrospective cases of canine melanoma. (Abstract). *Proc Genes Dogs and Cancer* 1:49.

Bianco SR, Hance K, Fosmire S, Koenig A, Withrow SJ, Matthiessen D, Ritt MG, Getzy DM, Duke RC, Bellgrau D, Cutter GR, Wojcieszyn J, Modiano JF. (2001) Induction of melanoma cell apoptosis by Fas ligand. (Abstract). *Proc Genes Dogs and Cancer* 1:53.

Modiano JF. (2001). Canine cancer genetics. (Abstract). *Proc ACVIM Forum*, 19:441-443.

Modiano JF. (2001). Loss of tumor suppressor gene expression in canine cancer: sporadic or heritable lesions? (Abstract). *Proc Genes Dogs and Cancer* 1:21.

Support from this CHF grant was acknowledged in the following presentations:

“The Role of Tumor Suppressor Genes in Melanoma: a Canine Model of Spontaneous Disease.” Presented for: the Department of Animal Science and the Comprehensive Cancer Center, University of Vermont, Feb. 8, 1999, Burlington, VT; the Committee of Comparative Medicine and Pathology, University of Chicago, April 29, 1999, Chicago, IL; the Center for Cancer Causation and Prevention, AMC Cancer Research Center, May 10, 1999, Denver, CO; Department of Pathology, Colorado State University, Oct. 8, 1999, Fort Collins, CO; and at Aspectos Moleculares de la Enfermedad con Tonos Tecnologicos (Molecular Aspects of Disease with Technological Overtones), October 21 - 22, 1999, Universidad Nacional de Asuncion, Asuncion, Paraguay.

“Hematopoietic Growth Factors in Health and Disease.” 17th Annual ACVIM Forum, June 10 - 15, 1999, Chicago, IL.

“Use of the CellDyn 3500 to Predict Blast Cell Lineage in Peripheral Blood of Dogs and Cats with Leukemia or Leukemic Lymphoma.” Gordon Research Conference on Comparative Hematopoiesis, August 8 - 13, 1999, Tilton School, Tilton, NH.

“Genetics of Canine Cancer.” 1999 National Parent Club Health Conference, American Kennel Club, October 15 - 17, 1999, St. Louis, MO.

“Genes as Windows to Effective Treatment and Prevention of Canine Osteosarcoma.” BCOA National Meeting. May 25, 2000, Portland, OR.

“Tumor Suppressor Genes in Canine Cancer.” Advances in Canine Genetics, International Society for Animal Genetics, July 22, 2000, Minneapolis, MN (cancelled).

“Advances in Canine Cancer Research: Genetics of Canine Cancer, New Treatment Approaches, and The Research Partnership.” GRCA National Meeting. October 1, 2000, St. Louis, MO.

“Loss of Tumor Suppressor Gene Expression in Canine Cancer: Sporadic or Heritable Lesions?” Genes Dogs and Cancer, May 21-22, 2001, Keystone, CO.

“Canine Cancer Genetics.” 19th Annual ACVIM Forum, May 23-26, 2001, Denver, CO.

“Current Research in Cancer Genetics.” 2001 National Parent Club Health Conference, American Kennel Club, October 19 - 21, 2001, St. Louis, MO.



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- Thomas, R., Bridge, W., Benke, K., Breen, M (2003). Isolation and chromosomal assignment of canine genomic BAC clones representing 25 cancer related canine genes. *Cytogenetic and Genome Research* 102, 249-253
- Thomas R, Fiegler H, Ostrander EA, Galibert F, Carter NP, Breen M (2003). A canine cancer-gene microarray for CGH analysis of tumors. *Cytogenetics and Genome Research* 102, 254- 260
- Thomas R, Smith KC, Ostrander EA, Galibert F, Breen M (2003). Chromosome aberrations in canine multicentric lymphomas detected with comparative genomic hybridization and a panel of single locus probes. *British Journal of Cancer* 89, 1530-1537
- Fosmire SP, Dickerson EB, Scott A, Bianco SR, Pettengil M, Meylemans H, Padilla M, Frazer-Abel AA, Akhtar N, Getzy DM, Wojcieszyn J, Breen M, Helfand SC, Modiano JF (2004). Canine malignant hemangiosarcoma as a model of primitive angiogenic endothelium. *Laboratory Investigation* 84, 562- 572
- Jubala CM, Wojcieszyn J, Valli, VEO, Getzy DM, Modiano JF. Expression of CD20 in canine non- Hodgkin's B cell lymphomas (2005). *Veterinary Pathology* 42, 468-476
- Modiano JF, Breen M, Burnett RC, Parker HG, Inusah S, Thomas R, Avery PR, Lindblad-Toh K, Ostrander EA, Cutter G, Avery AC (2005). Distinct prevalence of B-cell and T-cell lymphoproliferative diseases among dog breeds indicates heritable risk. *Cancer Research* 65, 5654-5661
- Dickerson EB, Thomas R, Fosmire SP, Lamerato-Kozicki AR, Scott A, Bianco SR, Wojcieszyn J, Breen M, Helfand SC, Modiano JF (2005). Mutations of PTEN in canine hemangiosarcoma. *Veterinary Pathology* 42, 618-632
- Thomas R, Scott A, Langford C, Fosmire SP, Jubala CM, Lorentzen TD, Hitte C, Karlsson EK, Kirkness E, Ostrander EA, Galibert F, Lindblad-Toh K, Modiano JF, Breen M (2005). Construction of a 2Mb resolution BAC-microarray for CGH analysis of canine tumors. *Genome Research* 15, 1831-1837
- Lindblad-Toh K, Wade CM, Mikkelsen TS, Karlsson EK, Jaffe DB, Kamal M, Clamp M, Chang JL, Kulbokas EJ 3rd, Zody MC, Mauceli E, Xie X, Breen M, et al and Lander ES (2005). Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* 438, 803-819
- Modiano JF, Breen M, Lana SE, Ehrhart N, Fosmire SP, Thomas R, Jubala CM, Lamerato-Kozicki AR, Ehrhart EJ, Schaack J, Duke RC, Cutter GC, Bellgrau D. (2006). Naturally occurring translational models for development of cancer gene therapy. *Gene Ther Mol Biol*, 10, 31-40.
- Khanna C, Lindblad-Toh K, Vail D, London C, Bergman P, Barber L, Breen M, Kitchell B, McNeil E, Modiano JF, Niemi S, Comstock K, Ostrander E, Westmoreland S, Withrow S. (2006) Dogs, cancer, translation and genomics: a novel comparative opportunity (Correspondence). *Nat Biotech*, 24 (9), 1065-1066. PMID: 16964204

Modiano JF, Breen M, Valli VEO, Wojcieszyn JW, Cuter GR. (2007) Predictive value of p16 or Rb inactivation in a model of naturally occurring canine non-Hodgkin lymphoma (Letter). *Leukemia*, 21, 184-187. PMID: 16990767

Fosmire SP, Thomas R, Jubala CM, Wojcieszyn J, Valli VEO, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GR, Breen M, Modiano JF. (2007) Inactivation of the p16 cyclin-dependent kinase inhibitor in high-grade canine non-Hodgkin T-cell lymphoma. *Vet Pathol*, 44(4), 467-478. PMID: 17606508

Breen M and Modiano JF. (2008) Evolutionarily conserved cytogenetic changes in hematologic malignancies of dogs and humans – Man and his best friend share more than companionship. *Chromosome Res*, 16(1), 145-154. PMID: 18293109

### *Book Chapters*

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Modiano JF, Breen M, London CA, Avery AC. Breed Specific Canine Lymphoproliferative Diseases. Chapter 22 pp. 439-450. In *The Dog and its Genome*. Ostrander EA, Giger U, Lindblad-Toh K, eds. Cold Spring Harbor Press: Cold Spring Harbor, 2005

Modiano JF, and Breen M. Genetic Factors in Cancer Etiology. In *Small Animal Clinical Oncology*, 4th edition. Withrow SJ and Vail DM, eds. Elsevier: New York, 2005.

Breen M, and Thomas R. Karyotype and Chromosomal Organization. Chapter 10 pp. 159-178. In *The Dog and its Genome*. Ostrander EA, Giger U, Lindblad-Toh K, eds. Cold Spring Harbor Press: Cold Spring Harbor, 2005.

Thomas R, Breen M, and Modiano JF. Cancer Genetics. In *Small Animal Oncology*. Henry C, ed. Elsevier: New York, 2006.

### *Abstracts and Scientific Presentations and Other Presentations That Included Data from This Work and Acknowledged the Support of CHF*

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M. Breen. Canine Myeloid Neoplasms and Cytogenetics. 56th Annual Meeting of the American College of Veterinary Pathologists, Dec 7th 2005. INVITED SPEAKER

J. F. Modiano. Canine Cancers to Model Disease Susceptibility and Outcomes. The Jaqua Foundation Symposium in Memory of Dr. Samuel Pollock at Michigan State University, November 16, 2005, East Lansing, MI, INVITED SPEAKER

J. F. Modiano. Genetic Impact of Disease Risk: Understanding Prevention and Treatment. 2005 National Parent Club Health Conference, American Kennel Club, October 22 - 24, 2005, St. Louis, MO, INVITED SPEAKER

M. Breen . Chromosomes and Cancer. 2005 National Parent Club Health Conference, American Kennel Club, October 22 - 24, 2005, St. Louis, MO, INVITED SPEAKER

J. F. Modiano. "Genetics of Canine Cancer. 2005 Tufts Canine & Feline Breeding and Genetics Conference, Sept. 29- Oct. 1, 2005, Sturbridge, MA, INVITED SPEAKER

M. Breen "Dogs, Genes, Chromosomes and Cancer". Golden Retriever Club of America National, Gettysburg, September 30th 2005. INVITED SPEAKER

J. F. Modiano. Evolution and Genetic Susceptibility for Blood Cancers. Front Range Blood Malignancies and Tumor Immunology Group, September 28, 2005, Denver, CO, INVITED SPEAKER

J. F. Modiano. Naturally Occurring Translational Models for Development of Cancer Therapy. University of Colorado Cancer Center Symposium, September 20, 2005, Denver, CO, INVITED SPEAKER

J. F. Modiano. Naturally Occurring Translational Models for Development of Cancer Therapy. International Conference on Emerging Technologies in Drug and Gene Based Therapeutics, September 3-10, Hersonissos, Crete, Greece, INVITED SPEAKER

Modiano JF, Duke RC, Bellgrau D (2005). Naturally occurring translational models for development of cancer therapy. Proceedings Int Conf Emerging Technol Drug Gene Based Ther 8, 49 (abstract #32)

J. F. Modiano. Cancer Pathogenesis and Immunotherapy from Mouse to Man - where does DOG Fit? Merck-Merial Scholars Conference, July 28-31, 2005, Athens, GA, INVITED SPEAKER

Jubala CM, Wojcieszyn J, Valli, VEO, Getzy DM, Fosmire SP, Coffey D, Bellgrau D, Modiano JF. Expression of CD20 in normal canine B cells and in canine non-Hodgkin's lymphoma. UCHSC Integrated Department of Immunology Retreat, Vail, CO, Sept. 29 - Oct. 1, 2004

Breen. M. Canine Cytogenetics – Resources and Applications. Idexx. Maine, Nov. 2004. INVITED SPEAKER

Matthew Breen, Rachael Thomas, Allyson Scott, Ruth Hudson, Christophe Hitte, Travis Lorentzen, Francis Galibert, Elaine A. Ostrander. Generation and Application of a 2Mb Cytogenetic BAC Map of the Canine Genome. Advances in Canine and Feline Genomics. Utrecht. 2nd International Conference Oct 2004. INVITED SPEAKER

Rachael Thomas, Allyson Scott, Ruth Hudson, Cordelia Langford, Christophe Hitte, Travis Lorentzen, Francis Galibert, Elaine Ostrander, Matthew Breen. Development of molecular cytogenetic and genomic microarray resources for the study of canine tumors. Advances in Canine and Feline Genomics. Utrecht. 2nd International Conference Oct 2004. INVITED SPEAKER

Matthew Breen. The Canine Genome – Paws for thought. NCSU Biotechnology Center, NCSU, Nov. 2004. INVITED SPEAKER.

J. F. Modiano and M. Breen. (2004). Mechanisms of Canine Lymphomagenesis. Keynote address, Oncovet III, October 22-24, 2004, Sao Paulo, Brazil. INVITED SPEAKER

Breen, M. Dogs, Canine Cancer – Questions in Search of Answers. Golden Retriever Foundation – "Brunch with Betty White". INVITED SPEAKER – SPECIAL GUEST, Beverly Hills, California, Oct 2004.

J. F. Modiano. (2004). Advances in Canine Lymphoma and Hemangiosarcoma. Annual Meeting of the American Boxer Club, May 4-5, 2004, Cincinnati, OH. KEYNOTE PRESENTATION

J. F. Modiano. (2004). Cancer Genetics - Implications for Prevention, Diagnosis, and Therapy. Canine Winter Symposium, Buckhorn Valley Kennel Club and Mile High Golden Retriever Club, January 24, 2004, Fort Collins, CO. INVITED SPEAKER

J. F. Modiano. (2003). Lessons Learned from Liquid Tumors in Dogs. Animal Cancer Center Seminar Series, Colorado State University, November 17, 2003, Fort Collins, CO. INVITED SPEAKER

J. F. Modiano. (2003). Advances in Biology, Diagnosis and Treatment of Canine Cancer. Rottweiler National Specialty Health Seminar. April 20, 2003, Greeley, CO. KEYNOTE PRESENTATION

J. F. Modiano. (2003). Spontaneous Canine Models of Cancer for Development of Immunotherapy. Section of Medical Oncology, Department of Medicine Basic Science Conference, University of Colorado Health Sciences Center, January 28, 2003, Denver, CO. INVITED SPEAKER

J. F. Modiano. (2003). Canine Lymphoma. Montana Veterinary Medical Association Annual Winter Meeting, January 16-17, 2003, Bozeman, MT. INVITED SPEAKER

R. Thomas, H. Fiegler, E. A. Ostrander, F. Galibert, N. P. Carter and M. Breen (2003). Development and Application of a Canine Cancer-Gene Microarray for CGH Analysis of Canine Tumors. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3011.0903

J. F. Modiano, S. P. Fosmire, S. R. Bianco, R. Thomas, M. Breen, D. M. Getzy, J. Wojcieszyn and S. C. Helfand (2003). Differential Phosphorylation of Rb in Canine B and T Cell Lymphomas. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3036.0903

E. B. Dickerson, S. P. Fosmire, R. Thomas, A. Scott, S. R. Bianco, J. Wojcieszyn, M. J. Pettengill, M. Breen, S. C. Helfand and J. F. Modiano (2003). Anomalies of PTEN in Canine Malignant Endothelial Tumors. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3031.0903

J.F. Modiano, S.P. Fosmire, M. Breen (2003). Inactivation of Rb Tumor Suppressor Pathway in Canine Cancers. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3027.0903, INVITED SPEAKER

M. Breen, R. Thomas, S.C. Faircloth, J. A. Mahoney, M.J. Pettengill, A. Scott, S. Thomson, R. Hudson, S.R. Bianco, S.P. Fosmire, M.G. Ritt and J.F. Modiano (2003). Molecular Cytogenetics of Canine Lymphoma and Leukemia. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3021.0903, INVITED SPEAKER

F. Lingaas, K. Comstock, E. F. Kirkness, A. Sørensen, T. Aarskaug, C. Hitte, M. L. Nickerson, L. Moe, L. S. Schmidt, R. Thomas, M. Breen, F. Galibert, B. Zbar and E. A. Ostrander. (2003). A Mutation in a Canine Gene is Associated with Hereditary Multifocal Renal Cystadenocarcinoma and Nodular Dermatofibrosis in the

German Shepherd Dog. In: Genes, Dogs and Cancer: 3rd Annual Canine Cancer Conference - 2003, Modiano J. F. (Ed.) International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), 2003; P3012.0903

Breen, M. et al. (2003) Development of an ordered genomic microarray for comparative genomic hybridization analysis of canine cancer. 13th North American Colloquium on Animal Cytogenetics & Gene Mapping, Louisville, KY. July 2003

Thomas, R., Smith, K.C., Ostrander, E.A., Galibert, F., Breen, M. (2003). Chromosome Aberrations in Canine Multicentric Lymphomas Detected with Comparative Genomic Hybridisation and a Panel of Single Locus Probes. 13th North American Colloquium on Animal Cytogenetics & Gene Mapping, Louisville, KY. July 2003

Modiano, J.F., Fosmire, S.P., Bianco, S.R., Breen, M., Thomas, R., Getzy, D.M., Wojcieszyn, Helfand, S.C. (2003). Inactivation of the p16/Rb pathways in canine lymphoma. Keystone Symposia: Molecular Targets of Cancer Therapy (E1). Banff, Alberta, Canada March 19-24, 2003

Breen, M. (2003). Cellular Genomics – Dog FISH and CHIPs. State of the art presentation, 21st ACVIM Forum, Oncology Specialist Group, Charlotte, North Carolina. STATE OF THE ART PRESENTATION

Modiano, J.F., Fosmire, S.P., Bianco, S.R., Breen, M., Thomas, R., Getzy, D.M. (2002). Heritable and sporadic genetic lesions of canine lymphoma: A preliminary assessment of abnormalities in the p16/Rb pathways. UCHSC Integrated Department of Immunology Retreat, Copper Mountain, Colorado. Sept 11-13 2002.

Breen, M. (2002). Cellular Genomics. Application to Veterinary Health. American College of Veterinary Pathologists. New Orleans, Dec 2002 KEYNOTE PRESENTATION

Breen, M. (2002) Cellular Genomics: Canine Genome Mapping and Cancer. Dept. of Genetics, NCSU Fall Seminar Series. Nov 2002. INVITED SPEAKER

Breen, M. (2002) Canine Molecular Cytogenetics. Development of Higher Resolution Resources for Studies of Canine Cancer. Cleveland, Sept. 2002 INVITED SPEAKER

## Heritable and Sporadic Genetic Lesions in Canine Lymphoma (615A)

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### Publications

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Modiano JF, Breen M, Valli VEO, Wojcieszyn JW, Cuter GR. (2007) Predictive value of p16 or Rb inactivation in a model of naturally occurring canine non-Hodgkin lymphoma (Letter). *Leukemia*, 21, 184-187.

Fosmire SP, Thomas R, Jubala CM, Wojcieszyn J, Valli VEO, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GR, Breen M, Modiano JF. (2007) Inactivation of the p16 cyclin-dependent kinase inhibitor in high-grade canine non-Hodgkin T-cell lymphoma. *Vet Pathol*, 44(4), 467-478.

Breen M and Modiano JF. (2008) Evolutionarily conserved cytogenetic changes in hematologic malignancies of dogs and humans – Man and his best friend share more than companionship. *Chromosome Res*, 16(1), 145-154.

Breen M and Modiano JF. (2008) Shared pathogenesis of human and canine tumors - an inextricable link between cancer and evolution. *Cancer Therapy*, 6, 239-246 (Review).

Ito D, O'Brien TD, Modiano JF. (2010). Exclusion of cytoplasmic fragments in flow cytometric analysis of lymph node samples from dogs with lymphoma using membrane-permeable violet laser-excitable DNA-binding fluorescent dye (DyeCycle Violet). *Vet Clin Path*, 39(4), 494-498. PMID: PMC3065654

Ito D, Endicott MM, Jubala CM, Helm KM, Burnett RC, Husbands BD, Borgatti A, Henson MS, Burgess KE, Bell JS, Kisseberth WC, Valli VE, Cutter GR, Avery AC, Hahn KA, O'Brien TD, Modiano JF. (2011). A lymphoid progenitor population in canine non-Hodgkin lymphoma. *J Vet Intern Med*, 25(4), 890-896. PMID: 21777289

Frantz AM, Sarver AL, Ito D, Phang TL, Karimpour-Fard A, Scott MC, Valli VEO, Lindblad-Toh K, Burgess, KE, Husbands BD, Henson MS, Borgatti A, Kisseberth WC, Hunter LE, Breen M, O'Brien TD, Modiano JF. (2013). Molecular profiling reveals prognostically significant subtypes of canine lymphoma. *Vet Pathol* 50(4), 693-703. PMID: 23125145

### Refereed Abstracts

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Jubala CM, Fosmire SP, Thomas R, Wojcieszyn JW, Valli VEO, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GC, Breen M, Modiano JF. (2006) Inactivation of the Rb pathway in naturally occurring high-grade canine non-Hodgkin lymphoma. *Proceedings Genes Dogs Cancer* 4-4:10

Jubala CM, Fosmire SP, Thomas R, Wojcieszyn JW, Valli VEO, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GC, Breen M, Modiano JF. (2006) Inactivation of the Rb pathway in naturally occurring high-grade canine non-Hodgkin lymphoma. *Proceedings Biosymposia Signaling Transduction Modulators in Cancer Therapy* 34 (abstract P-11)

Ito D, Frantz AM, Endicott M, Jubala CM, Helm KM, Hahn KA, Husbands B, Borgatti A, Henson MS, O'Brien TD, Modiano JF (2009). Characterization of putative lymphoma-initiating (cancer stem) cells in canine lymphoma. *Proceedings Genes Dogs Cancer* 5

Ito D, O'Brien TD, Modiano JF (2009). Characterization of putative lymphoma-initiating (cancer stem) cells in canine lymphoma. Proceedings of the American Association for Cancer Research (abstract 3751)

Modiano JF and Breen M. Hematopoetic Cancer - an Inevitable Inheritance of Mammalian Evolution. Proceedings of the 17th Annu ECVIM Forum, 2007

Modiano JF and Breen M. Heritable and Sporadic Factors in the Pathogenesis of Canine Leukemias. Proceedings of the 17th Annu ECVIM Forum, 2007

Modiano JF. Uncovering heritable influences on dog cancer. Proceedings of the 27th Annu ACVIM Forum, 2009

### *Invited Research Seminars*

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"Dogs, Cancer, and Evolution: a Contemporary Voyage of Discovery with the Beagle." Invited Seminar for the "Comparative Models of Disease" Symposium sponsored by the American Association of Veterinary Immunologists at the 94th Annual Meeting of the American Association of Immunology, May 21, 2007, Miami, FL

"Hematopoetic Cancer - an Inevitable Inheritance of Mammalian Evolution." Keynote Address, Meeting of the European Societies for Veterinary Oncology and Clinical Pathology and the European College of Veterinary Internal Medicine, September 13-15, 2007, Budapest, Hungary

"Heritable and Sporadic Factors in the Pathogenesis of Canine Leukemias." State of the Art Lecture, Meeting of the European Societies for Veterinary Oncology and Clinical Pathology and the European College of Veterinary Internal Medicine, September 13-15, 2007, Budapest, Hungary

"ARF, SNF & Other Reasons Dogs Get Cancer." University of Minnesota Cancer Center, Genetic Mechanisms of Cancer Program Seminar Series, September 27, 2007, Minneapolis, MN

"The Beagle Revisited - New Lessons about Cancer and Evolution." Department of Laboratory Medicine and Pathology Grand Rounds, University of Minnesota School of Medicine, October 31, 2007, Minneapolis, MN

"Taking a Bite out of Cancer – How Dogs can Help Inform Cancer Biology and Treatment." University of Minnesota Cancer Epidemiology Interest Group, January 18, 2008, Minneapolis, MN

"The Beagle Revisited - New Lessons about Cancer and Evolution." Keynote Address, Penn Vet Student Research Day, University of Pennsylvania School of Veterinary Medicine, March 20, 2008, Philadelphia, PA

"The Influence of Heritable Factors on Cancer Phenotypes." Thielen Tribute Symposium, University of California, Davis, May 31, 2008, Davis, CA

"Cancer Genetics - the View down the Road to Effective Prevention and Treatment." AKC Canine Health Foundation Breeders Symposium, October 14, 2006, Denver, CO

“Ten Years of Cancer Research for Canine Health in Partnership with the Rottweiler Health Foundation.” Rottweiler National Specialty Health Seminar, May 24, 2008, Lake Elmo, MN

“The Comparative Oncology Program at the University of Minnesota.” University of Minnesota Adult Curiosity Camp – All Creatures Great and Small, July 17, 2008, St. Paul, MN

“Shared Pathogenesis of Human and Canine Tumors - an Inextricable Link between Cancer and Evolution.” Genetic Epidemiology and Risk Assessment (GERA) & Hematologic Malignancies Programs, Mayo Clinic Cancer Center, October 24, 2008, Rochester, MN

## Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma (947b)

### Publications and Scientific Presentations

Thomas R, Wang HJ, Tsai P-C, Langford C, Fosmire SP, Jubala CM, Getzy DM, Cutter GR, Modiano JF, Breen M. (2009). Influence of genetic background on tumor karyotypes: evidence for breed-associated cytogenetic aberrations in canine appendicular osteosarcoma. *Chromosome Res*, 17(3):365-377 (Epub 2009 Apr 1 PMID: 19337847)

Thayanithy V, Sarver A, Kartha R, Li L, Angstadt AY, Breen M, Steer C, Modiano JF, Subramanian S. (2012). Perturbation of 14q32 miRNAs-cMYC gene network in osteosarcoma. *Bone* 50, 171-181. PMID: 22037351.

Scott MC, Sarver AL, Gavin KJ, Thayanithy V, Getzy DM, Newman RA, Cutter GR, Lindblad-Toh K, Kisseberth WC, Hunter LE, Subramanian S, Breen M, Modiano JF. (2011). Molecular subtypes of osteosarcoma identified by reducing tumor heterogeneity through an interspecies comparative approach. *Bone*, 49, 356-367. PMID: PMC3143255

Angstadt AY, Motsinger-Reif A, Thomas R, Kisseberth WC, Couto GC, Duval DL, Nielsen DM, Modiano JF, Breen M. (2011). Characterization of canine osteosarcoma by array comparative genomic hybridization and RT-qPCR: signatures of genomic imbalance in canine osteosarcoma parallel the human counterpart. *Genes Chromosomes Cancer*, 50(11), 859-874. PMID: 21837709

Thayanithy V, Park CW, Sarver A, Kartha R, Korpela DM, Graef A, Steer C, Modiano JF, Subramanian S. (2012). Combinatorial treatment of DNA and chromatin-modifying drugs cause cell death in human and canine osteosarcoma cell lines. *PLoS ONE*, 7(9), e43720. PMID: PMC3434163

Angstadt AY, Thayanithy V, Subramanian S, Modiano JF, and Breen M. (2012). A genome-wide approach to comparative oncology: High-resolution oligonucleotide aCGH of canine and human OS pinpoints shared microaberrations. *Cancer Genet*, 205(11), 572-587. PMID: 23137772

Sarver AL, Thayanithy V, Scott MC, Cleaton AM, Hogendoorn PCW, Modiano JF, Subramanian S. (2013). MicroRNAs at 14q32 locus have prognostic significance in osteosarcoma. *Orphanet J Rare Dis*, 8(1), 7. PMID: 23311495

Karlsson E, Sigurdsson S, Ivansson E, Thomas R, Elvers I, Wright J, Howald C, Tonomura N, Perloski M, Swofford R, Biagi T, Fryc S, Anderson N, Courtay-Cahen C, Youell L, Ricketts S, Mandlebaum S, Rivera P, von Euler H, Kisseberth W, London CA, Lander ES, Couto G, Comstock K, Starkey M, Modiano JF, Breen M,



Lindblad-Toh K. (2013). Genome-wide analyses implicate 33 loci in heritable dog osteosarcoma, including regulatory variants near CDKN2A/B. *Genome Biol*, 14, R132. PMID: 24330828

### *Refereed Abstracts*

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Murahari S, Jalkanen AL, Kulp SK, Chen C-S, Jubala CM, Fosmire SP, Modiano JF, Fossey SL, London CA, Kisseberth WC (2008). OSU-HDAC42, a novel histone deacetylase inhibitor with potent antitumor effects on human and canine osteosarcoma cells. *Proceedings of the American Association for Cancer Research* (abstract 2445)

Young AC, Thomas R, Tsai P-C, Kisseberth W, Subramanian S, Modiano JF, Breen M (2009). Heritable and breed specific genetic abnormalities in canine osteosarcoma. *Proceedings Genes Dogs Cancer 5*

Gavin K, Sarver A, Scott M, Vijjeswarapu M, Getzy DM, Newman RA, Cutter GR, Hunter LE, Kisseberth WC, Breen M, Modiano JF (2009). Expression profile of cancer-related genes associated with poor clinical outcome in canine osteosarcoma. *Proceedings Genes Dogs Cancer 5*

Lindblad-Toh K, Karlsson E, Tonomura N, Barber L, Burgess K, Breen M, Modiano J, McNiel E, Ostrander E, London C, Comstock K, Azuma C. (2009). Mapping genetic risk factors for osteosarcoma and hemangiosarcoma. *Proceedings Genes Dogs Cancer 5*

Gavin K, Sarver A, Scott M, Vijjeswarapu M, Getzy DM, Newman RA, Cutter GR, Hunter LE, Kisseberth WC, Breen M, Modiano JF (2009). Outcome-associated molecular signatures in osteosarcoma. *ACVIM Late Breaking Abstracts*

Scott M, Gavin K, Sarver A, Vijjeswarapu M, Getzy DM, Newman RA, Cutter GR, Hunter LE, Kisseberth WC, Breen M, Modiano JF. Expression profile of cancer-related genes associated with favorable clinical outcome in canine osteosarcoma. *Proceedings UMN CVM Research Days, St. Paul, MN March 25, 2009*

Scott M, Duckett M, Martinez H, Wong D, Iverson B, Modiano J, Nuñez R (2010). Ambient temperature stabilization of RNA derived from feline and canine tumor cells for use in gene expression assays. *Proceedings of the Plant and Animal Genetics Symposium 2010*

Scott1 M, Duckett M, Modiano J, Yang C, Martinez H, Iverson B, Nuñez R. (2010). Ambient temperature stabilization of feline and canine tumor cell RNA for use in gene expression assays. *GenVault Technical Application Note for GenTegra™*

## *Invited Research Seminars*

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“Comparative Assessment of the Prevalence, Etiology, and Natural History of Cancer in Dogs and Humans.” Inaugural Skippy Frank Translational Medicine Meeting, Jan 15-17, 2009, Palo Alto, CA

“Going to the Dogs.” Developmental Origins of Cancer, a Minnesota Futures Symposium, February 29 – March 1, 2009, Minneapolis, MN

“Everything I wanted to Know about Cancer, I Learned from My Dog.” 40th Anniversary VMSTP Reunion, March 19-20, 2009, Philadelphia, PA

“Heritable Traits in Sporadic Cancers: How Old Dogs Teach People New Tricks.” Oregon State University College of Veterinary Medicine Guest Speaker Series, March 31, 2009, Corvallis, OR

“Uncovering Heritable Influences on Dog Cancer.” 27th Annu ACVIM Forum, June 2-6, 2009, Montreal, Quebec, Canada

“Taking a Bite out of Cancer –Dogs and Comparative Oncology Inform the Biology, Heritability and Treatment of Cancer.” Ontario Veterinary College Research Seminar Series, September 18, 2009, Guelph, Ontario, Canada

“Naturally Occurring Animal Models of Cancer.” Animal Models of Human Disease. A Life Science Alley and Veterinary Clinical Sciences Symposium, November 11, 2009, St. Paul, MN

“Tracking a Killer – How Dogs can Help Find Cures for Cancer.” Department of Veterinary Clinical Sciences Grand Rounds, University of Minnesota College of Veterinary Medicine, September 24, 2009, St. Paul, MN

“From Research to Treatment - University of Minnesota Animal Cancer Care and Research Program: Leadership in the Battle Against Cancer.” Bearded Collie Club of America National Specialty Health Seminar, October 7, 2009, Minneapolis, MN

“University of Minnesota Animal Cancer Care and Research Program and Masonic Cancer Center Comparative Oncology.” Annual Meeting of the Van Sloun Foundation, University of Minnesota Arboretum, November 7, 2009, Chaska, MN

“Heritable Traits and Cancer.” Bernese Mountain Dog Club of the Greater Twin Cities Health Seminar, Stone Mountain Pet Lodge, Blaine, MN

“Everything You Want to Know about Cancer.” Keeshond National Specialty Health Seminar, Olympia Resort, May 27, 2010, Oconomowoc, WI

### *Publications*

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Scott M, Duckett M, Modiano J, Yang C, Martinez H, Iverson B, Nuñez R. (2010). Ambient temperature stabilization of feline and canine tumor cell RNA for use in gene expression assays. GenVault Technical Application Note for GenTegra™. <http://www.genvault.com/downloads/case-studies-and-applicationnotes/ambient-temperature-stabilization-app-note.pdf>

Schappa JT, Frantz AM, Gorden BH, Dickerson, EB, Vallera DA, Modiano JF. (2013). Hemangiosarcoma and its cancer stem cell subpopulation are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors. *Int J Cancer*, 133(8), 1936-1944. PMID: 23553371

Koopmeiners JS, Modiano JF. (2014). Extending the TITE CRM to multiple outcomes with application to a phase 1 clinical trial in canine hemangiosarcoma. *Clin Trials*, 11(1), 38-48. PMID: 24082004

Gorden BH, Kim JH, Sarver AL, Frantz A, Breen M, Lindblad-Toh K, O'Brien TD, Sharkey LC, Modiano JF, Dickerson EB. (2014). Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization. *Am J Pathol*, 2014 Feb 10. pii: S0002-9440(14)00030-3. doi: 10.1016/j.ajpath.2013.12.025. [Epub ahead of print]. PMID: 24525151

Kim JH, Frantz AM, Anderson KL, Graef AJ, Scott MC, Robinson SR, Sharkey LC, O'Brien TD, Dickerson EB, Modiano JF. (2014). Interleukin-8 promotes canine hemangiosarcoma growth by regulating the tumor microenvironment. *Exp Cell Res*, 2014 Feb 25. pii: S0014-4827(14)00083-4. doi: 10.1016/j.yexcr.2014.02.020. [Epub ahead of print]. PMID: 24582862

Thomas R, Borst L, Rotroff D, Motsinger-Reif A, Lindblad-Toh K, Modiano JF, Breen M. (2014). Genomic profiling reveals extensive heterogeneity in somatic DNA copy number aberrations of canine hemangiosarcoma. *Chromosome Res*, 2014 Mar 6. [Epub ahead of print]. PMID: 24599718

Borgatti A, Duckett MM, Spangler C, Modiano JF. (2014). Binding of VEGF-A to canine cancer cells with preferential expression of VEGFR1. *Veterinary World*, 7(1), 1-6

### *Manuscripts Submitted*

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Tonomura N, Thomas R, Karlsson E, Megquier K, Turner-Maier J, Sarver AL, Frantz AM, Ito D, Elvers I, Mauceli E, Arendt M, Howald C, Perloski M, Swofford R, Kim JH, Barber L, Burgess K, Lander E, Azuma C, Modiano JF, Breen M, Lindblad-Toh K. Genome-wide association study identifies shared risk loci common to two malignancies in golden retrievers.

## *Graduate Thesis*

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Aric M. Frantz (DVM/PhD Candidate - Comparative Molecular Biosciences, University of Minnesota). PhD Thesis, "Comparative and Molecular Approaches to Improve Identification, Classification, and Therapeutic Options in Cancer" successfully defended on Aug. 28, 2012.

## *Manuscripts in Preparation*

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Frantz AM, Sarver AL, Gorden BH, Lewellen M, O'Brien TD, Modiano JF . Conserved transcriptional drivers of tumorigenicity identified through uniform culture of ontogenetically distinct cancers of the dog.

## *Refereed Abstracts*

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Scott M, Duckett M, Martinez H, Wong D, Iverson B, Modiano J, Nuñez R (2010). Ambient temperature stabilization of RNA derived from feline and canine tumor cells for use in gene expression assays. Proceedings of the Plant and Animal Genetics Symposium 2010

Frantz A, Sahli N, Dickerson E, O'Brien TD, Modiano JF. (2010). Ontogenetically distinct cancers of the dog form sphere cultures in a shared culture condition. Points of Pride Proceedings (Sept. 29, UMN CVM Research Symposium), St. Paul, MN

Schappa J, Frantz A, Vallera DA, Modiano J. (2010). Epidermal growth factor and urokinase target therapeutic toxins to ontogenetically distinct tumor cells expressing cognate receptors. Points of Pride Proceedings (Sept. 29, UMN CVM Research Symposium), St. Paul, MN

Korpela D, Kassie F, Scott M, Duckett M, Modiano J. (2010). Nicotinic receptor activation in metastatic canine hemangiosarcoma. Points of Pride Proceedings (Sept. 29, UMN CVM Research Symposium), St. Paul, MN

Schappa JT, Frantz AM, Gorden BH, Vallera DA, Dickerson EB, Modiano JF. (2011). Sensitivity of canine hemangiosarcoma stem cells to a ligand targeted toxin containing epidermal growth factor and urokinase. Proceedings Keystone Symp: Stem Cells, Cancer, and Metastasis C4

Frantz AM, Gorden BH, Dickerson EB, O'Brien TD, Modiano JF. (2011). Shared properties of tumor-initiating cells defined by sphere-forming culture of ontogenetically distinct cancers Proceedings Keystone Symp: Stem Cells, Cancer, and Metastasis C4

Gorden BH, Frantz AM, Ito D, Modiano JF, Dickerson EB. (2011). Identification of a cancer stem cell-like population in canine hemangiosarcoma. Proceedings Keystone Symp: Stem Cells, Cancer, and Metastasis C4

Schappa JT, Frantz A, Gorden B, Vallera DA, Modiano JF, Dickerson E. Sensitivity of canine hemangiosarcoma to a ligand targeted toxin containing epidermal growth factor and urokinase. Proceedings Masonic Cancer Center Research Symposium, Minneapolis, MN May 18, 2011

Frantz AM, Gorden BH, Dickerson EB, O'Brien TD, Modiano JF. Ontogenetically distinct cancers of the dog form sphere cultures in a shared culture condition. Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 19, 2011 - This poster won First Prize in the Graduate Student Category

Ouzoonian LB, Gorden BH, Modiano JF, Dickerson EB. Inhibition of receptor tyrosine kinases in canine hemangiosarcoma. Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 19, 2011

Frantz AM, Sarver AL, Dickerson EB, O'Brien TD, Modiano JF (2012). Cancer stem cells from three ontogenetically distinct canine tumors have shared patterns of gene expression. Proceedings of the 2nd World Veterinary Cancer Congress

Modiano JF, Sarver AL, Scott MC, Frantz AM, Kim JH, Ito D, Graef AJ, Hwang TH, Dickerson EB, Sharkey LC, O'Brien TD, Breen M, Lindblad-Toh K, and Kisseberth WC (2012). Heritable traits influence cell-intrinsic behavior of sporadic canine cancers. Proceedings of the 2nd World Veterinary Cancer Congress

Frantz AM, Gorden BH, Dickerson EB, O'Brien TD, Modiano JF. Shared gene expression signatures of tumor-initiating cells from ontogenetically distinct cancers. Proceedings Masonic Cancer Center Research Symposium, Minneapolis, MN May 30, 2012

Modiano JF, Dickerson EB. (2012). Not Your Father's Hemangiosarcoma: Insights from Genetic and Functional Studies. Proceedings 2012 ACVIM Forum

Schappa JT, Frantz AM, Gorden BH, Dickerson EB, Vallera DA, Modiano JF. Hemangiosarcoma and its cancer stem cell sub-population are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors. Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 10, 2012 - This poster won First Prize in the Post-Doctoral Fellows Category

Merrill E, Schappa J, Scott M, Gorden B, Anderson K, Vallera D, Modiano J. Mechanisms of cancer targeting through the epidermal growth factor receptor. Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 10, 2012

Graef AJ, Kim JH, Modiano JF, Dickerson EB. Inhibition of CXCR4 in canine hemangiosarcoma. Points of Pride Proceedings (UMN CVM Research Symposium), St. Paul, MN Oct. 10, 2012

Merrill E, Schappa J, Scott M, Gorden B, Anderson K, Vallera D, Modiano J (2012). Mechanisms of cancer targeting through the epidermal growth factor receptor. Proceedings of the 2012 Meril NIH National Veterinary Scholars Symposium

Schappa JT, Frantz AM, Gorden BH, Dickerson EB, Vallera DA, Modiano JF (2012). Sensitivity of chemoresistant canine hemangiosarcoma and its cancer stem cell sub-population to a ligand-targeted toxin containing epidermal growth factor and urokinase. Proceedings of the First Meeting of the São Paulo Advanced School of Comparative Oncology

Tonomura N, Thomas R, Karlsson E, Megquier K, Turner-Maier J, Sarver AL, Frantz AM, Ito D, Elvers I, Mauceli E, Arendt M, Howald C, Perloski M, Swofford R, Kim JH, Barber L, Burgess K, Lander E, Azuma C, Modiano JF, Breen M, Lindblad-Toh K (2013). Genome-wide association study identifies shared risk loci

common to two malignancies in golden retrievers. Proceedings of the European Society of Veterinary Oncology

Elvers I, Tonomura N, Turner-Maier J, Modiano J, Breen M, Lindblad-Toh K (2013). Searching for causative mutations in canine lymphoma and hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Tonomura N, Thomas R, Karlsson E, Megquier K, Turner-Maier J, Sarver AL, Frantz AM, Ito D, Elvers I, Mauceli E, Arendt M, Howald C, Perloski M, Swofford R, Kim JH, Barber L, Burgess K, Lander E, Azuma C, Modiano JF, Breen M, Lindblad-Toh K (2013). Interaction between the immune system and malignant cells is indicated to play a common role in tumorigenesis for two malignancies in golden retrievers. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Graef AJ, Kim JH, Sarver AL, Frantz AM, O'Brien TD, Sharkey LC, Dickerson EB, Modiano JF (2013). Gene expression profiling reveals a role of CXCR4/7 in canine hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Kim JH, Sarver AL, Frantz AM, Scott MC, Graef AJ, Tonomura N, Elvers I, Thomas R, Lewellen M, Dickerson EB, Breen M, Lindblad-Toh K, Modiano JF (2013). Germ-line risk factors are associated with upregulation of genes mediating cell cycle arrest and stem cell activity in canine hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Thomas R, Borst L, Lindblad-Toh K, Modiano JF, Breen M (2013). Characterization of generalized and breed-associated DNA copy number aberrations in canine hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

### *Presentations (Invited)*

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“Comparative Oncology Sarcoma Projects.” Sarcoma Program Retreat, Masonic Cancer Center, University of Minnesota, March 17, 2010, Minneapolis, MN

“Heritable Traits and Cancer.” Bernese Mountain Dog Club of the Greater Twin Cities Health Seminar, March 20, 2010, Stone Mountain Pet Lodge, Blaine, MN

“Hemangiosarcoma – Who Art Thou?” Stem Cell Institute Research Conference, University of Minnesota, April 21, 2010, Minneapolis, MN

“Everything You Want to Know about Cancer.” Keeshond National Specialty Health Seminar, Olympia Resort, May 27, 2010, Oconomowoc, WI

“Integrative Molecular Approaches to Cancer.” ASVCP Education Symposium: Comparative Oncology, Concurrent Annual Meeting of the ACVP and ASVCP. The American College of Veterinary Pathologists, 61st Annual Meeting. The American Society for Veterinary Clinical Pathology, 45th Annual Meeting. Baltimore, MD, October 31, 2010.

“Molecular Approaches to Cancer: from the Lab to the Clinic and Back.” Leonberger National Specialty Health Seminar, April 14, 2011, Warwick, RI.

“Recent Progress in Molecular Genetics of Cancer and Challenges Ahead.” 2011 National Parent Club Health Conference, American Kennel Club, August 12 - 14, 2011, St. Louis, MO

“Molecular Genetic Tools in Cancer Diagnosis and Treatment: Recent Advances and Challenges Ahead.” 5th Tufts Canine & Feline Breeding and Genetics Conference, Sept. 16-17, 2011 Boston, MA

“Recent Advances in Canine Hemangiosarcoma.” Bouvier des Flandres National Specialty Health Seminar, October 5, 2011, St. Louis, MO.

“Cancer and Evolution: What is the Solution?” Keynote Address, University of Iowa Molecular and Cellular Biology Graduate Program Retreat, September 30, 2011, Iowa City, IA

“Recent Progress in Molecular Genetics of Cancer and Challenges Ahead.” AKC Canine Health Foundation Breeders Symposium, November 5, 2011, St. Paul, MN

“The Tumor Cell and its Microenvironment – Insights into Tumor Evolution and Tumor Heterogeneity.” Cancer Biology Fall Seminar Series at Cornell University, November 1, 2011, Ithaca, NY

“Insights from Genetic and Functional Studies of Hemangiosarcoma.” 30th Annual ACVIM Forum, June 1, 2012, New Orleans, LA

“The Future is Now: Advances in Canine Cancer Care and Research.” Havanese National Specialty Health Seminar, July 10, 2012, Bloomington, MN

“From Bench to Cageside – An Update of Clinical Translation in Oncology at the U of M.” Comparative Oncology Seminar Series, University of Minnesota, September 13, 2012, St. Paul, MN

“The Animal Cancer Care and Research Program at the University of Minnesota and Advances in Our Understanding of Canine Hemangiosarcoma.” Portuguese Water Dog National Specialty Health Seminar, October 2, 2012, Lake Geneva, WI

“Companion Animals as Models of Naturally Occurring Cancers.” Arizona Society of Pathologists 2012 Fall Conference, November 10, 2012, Mayo Clinic, Scottsdale, AZ

“Persistence versus Stubbornness: How We Can Learn from Failure to Achieve Therapeutic Success in Cancer.” Annual Meeting of the American Animal Hospital Association, March 14-17, 2013, Phoenix, AZ

## Gastrointestinal Disease

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### Mucosal Gene Expression Profiles in Canine Inflammatory Bowel Disease (0945)

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#### *Publications*

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Inflammatory bowel disease in veterinary medicine. *Front Biosci (Elite Ed)*. 2012 Jan 1;4:1404-19. Jergens AE, Simpson KW.

### Granulomatous Colitis In Boxer Dogs: Genetic Analysis of Disease and Functional Analysis of Bacterial Killing (1445)

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#### *Publications*

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Pitfalls and progress in the diagnosis and management of canine inflammatory bowel disease. *Vet Clin North Am Small Anim Pract*. 2011 Mar;41(2):381-98. Simpson KW, Jergens AE.

Granulomatous colitis of boxer dogs. *Vet Clin North Am Small Anim Pract*. 2011. Mar(2)433-445 Craven M, Mansfield CS, Simpson KW.

## Musculoskeletal Conditions and Disease

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### Phenotypic Characterization and Mapping Genes Associated with Canine Degenerative Myelopathy in the Boxer Dog (821)/Phenotypic Characterization of Peripheral Nerve Disease in Degenerative Myelopathy Dogs (1212)/Determination of Outcome Measures for Clinical Progression and Morphometric Studies of Spinal Cord Disease in Degenerative Myelopathy Dogs (1213)

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#### *Publications*

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Breed Distribution of SOD1 Alleles Previously Associated with Canine Degenerative Myelopathy *Journal of Veterinary Internal Medicine*. 2014. 92:531-541. R. Zeng, J.R. Coates, G.C. Johnson, L. Hansen, T. Awano, A. Kolicheski, E. Ivansson, M. Perloski, K. Lindblad-Toh, D.P. O'Brien, J. Guo, M.L. Katz, and G.S. Johnson

Characterization of Thoracic Motor and Sensory Neurons and Spinal Nerve Roots in Canine Degenerative Myelopathy, a Potential Disease Model of Amyotrophic Lateral Sclerosis. *Journal of Neuroscience Research*. 2014. 28:515-521 Morgan, Brandie R.; Coates, Joan R.; Johnson, Gayle C.; Shelton, G. Diane; Katz, Martin L.



NIH Grant 5R21NS078242-02

PI / Project Leader: COATES, JOAN RIPLEY

Title: THERAPEUTIC DEVELOPMENT FOR AMYOTROPHIC LATERAL SCLEROSIS IN A CANINE MODEL

Awardee Organization: UNIVERSITY OF MISSOURI-COLUMBIA

Abstract Text:

DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is characterized by loss of motor neurons resulting in stiffness, slowing of movement, and severe muscle wasting and weakness. Patients die in 3-5 years secondary to failure of respiratory muscles. There are no effective therapies for ALS. The discovery of superoxide dismutase (SOD1) mutations as causative for a proportion of the inherited forms of ALS led to the generation of rodent SOD1 mutation models in the hope that these animal models would provide new therapeutics. Although the rodent ALS models have provided many advantages for the study ALS and therapeutics, such animal models have failed to accurately predict therapeutic responses in ALS patients. However, clinical similarities between the inherited SOD1-related ALS and the more prevalent ALS with no SOD1 mutation, and recent findings of SOD1 aggregates in tissues of sporadic ALS patients, suggest that further study of SOD1 still is relevant to all ALS. Canine degenerative myelopathy (DM) is an inherited, progressive adult-onset neurodegenerative disease that has many similarities to human ALS and potentially serves as an important novel model for therapy development. Recently, we found that an E40K missense mutation in SOD1 underlies most cases of canine DM. Similarities between the canine and human nervous systems and homogeneity of the DM phenotype will facilitate translation of therapies into ALS patients. A promising therapeutic strategy using antisense oligonucleotides (ASOs) that target SOD1 mRNA to suppress SOD1 protein was recently demonstrated in a rodent ALS model. The SOD1 ASO decreased amounts of SOD1 in neurons and slowed disease progression. Studies of canine DM, with its spontaneous SOD1 mutation, may yield data more relevant to human ALS and help advance SOD1 ASO clinical trials in ALS patients. Guided by supportive preliminary data, studies will be conducted to achieve the following Specific Aims: 1) Evaluate the safety and pharmacokinetics of intrathecal delivery of a SOD1 ASO in normal dogs to develop an optimized protocol for therapy in DM. Acquisition of such data in normal dogs is critical for the development of this novel treatment approach before instituting a pilot study in privately owned DM-affected dogs. A study of ASO therapy in canine DM as a disease model for ALS is significant, because it should facilitate the translation of a therapeutic approach from laboratory to clinic. 2) Evaluate the safety and preliminary therapeutic effects of intrathecally administered SOD1 ASO in DM-affected dogs. If canine DM is to serve as an effective disease model by which to evaluate ALS therapies, we must demonstrate therapeutic efficacy through a comparative approach using objective measures of disease progression that are shared across species. MUNE is expected to serve as an ideal biomarker for therapeutic translation in DM-affected dogs because the technique is also performed in ALS patients. The proposed research is innovative because it focuses on a promising therapeutic approach in a naturally-occurring canine disease that is analogous to human ALS.

## Reproductive Conditions and Disease

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### Whole Genome Association Analyses for Cryptorchidism in Dogs (1248)

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#### *Publication*

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A genome-wide association study for canine cryptorchidism in Siberian Huskies. J Anim Breed Genet. 2013 Nov 2; epub 1-8. Zhao X, Onteru S, Saatchi M, Garrick D, Rothschild M.

## Regenerative Medicine

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### Tissue Regeneration Using Canine Mesenchymal Stem Cells: Effects of Donor Characteristics and ex vivo Expansion on Cell Pluripotency (0971)

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#### *Publications*

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Effects of donor characteristics and ex vivo expansion on canine mesenchymal stem cell properties: implications for MSC-based therapies. Cell Transplant. 2012 21(10):2189-200. Epub 2012 Apr 2. Volk SW, Wang Y, Hankenson KD.

Translating stem cell therapies: the role of companion animals in regenerative medicine. Wound Repair Regen. 2013 May-Jun;21(3):382-94. Epub 2013 Apr 29. Volk SW, Theoret C.

### Isolation and Characterization of Canine Induced Pluripotential Stem Cells (iPS) (1272)

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#### *Publications*

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Growth requirements and chromosomal instability of induced pluripotent stem cells generated from adult canine fibroblasts. Koh S, Thomas R, Tsai S, Bischoff S, Lim JH, Breen M, Olby NJ, Piedrahita JA. Stem Cells Dev. 2013 Mar 15;22(6):951-63. doi: 10.1089/scd.2012.0393. Epub 2012 Nov 28.

## Cardiology

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### Inheritance Patterns and Molecular Genetic Analysis of Doberman Pinschers and Boxer Dogs with Familial Dilated Cardiomyopathy (0021)

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#### *Publications*

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Meurs KM, Spier AW, Miller MW, Lehmkuhl LB, Towbin JA. Familial ventricular dysrhythmias in Boxer dogs. *J Vet Intern Med*, 13, 1999, 437-439.

Spier AW, Meurs KM, Coover DD, Lehmkuhl LB, O'Grady MR, Freeman LM, Burghes AH, Towbin JA. Western blot analysis of myocardial dystrophin,  $\alpha$ -sarcoglycan and  $\beta$ -dystroglycan in dogs with idiopathic dilated cardiomyopathy. *Am J Vet Res*, 62, 2001, 67-71.

Meurs KM, Magnon AL, Spier AW, Miller MW, Lehmkuhl LB, Towbin JA. Evaluation of the cardiac actin gene in Doberman pinschers with dilated cardiomyopathy. *Am J Vet Res*, 62, 2001, 33-36.

### Evaluation of the Clinical Outcome of Asymptomatic Adult Boxers with Ventricular Arrhythmias Over a Four-Year Period (0091)

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#### *Publications*

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Ambulatory electrocardiographic evaluation of clinically normal adult Boxers. Stern, Joshua A.; Meurs, Kathryn M.; Spier, Alan W.; et al. *Journal of the American Veterinary Medical Association*. Volume: 236 Issue: 4 Pages: 430-433 Published: FEB 15 2010

Temporal Variability of Ventricular Arrhythmias in Boxer Dogs with Arrhythmogenic Right Ventricular Cardiomyopathy. Scansen, B. A.; Meurs, K. M.; Spier, A. W.; et al. *Journal of Veterinary Internal Medicine*. Volume: 23 Issue: 5 Pages: 1020-1024. Published: SEP-OCT 2009

Evaluation of serum cardiac troponin I concentration in Boxers with arrhythmogenic right ventricular cardiomyopathy. Baumwart, Ryan D.; Orvalho, Joao; Meurs, Kathryn M. *American Journal of Veterinary Research*. Volume: 68 Issue: 5 Pages: 524-528 Published: MAY 2007

Assessment of plasma brain natriuretic peptide concentration in Boxers with arrhythmogenic right ventricular cardiomyopathy. Baurwart, RD; Meurs, KM. *American Journal of Veterinary Research*. Volume: 66 Issue: 12 Pages: 2086-2089 Published: DEC 2005

Arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death in boxer dogs. Basso, C; Fox, PR; Meurs, KM; et al. Conference: ESC Congress 2004 Location: Munich, GERMANY Date: AUG 28-SEP 01, 2004 Sponsor(s): ESC. *European Heart Journal*. Volume: 25 Supplement: S Pages: 111-111 Published: AUG-SEP 2004

Evaluation of spontaneous variability in the frequency of ventricular arrhythmias in Boxers with arrhythmogenic right ventricular cardiomyopathy. Spier, AW; Meurs, KM. Conference: 18th Annual Forum of

the American-College-of-Veterinary-Internal-Medicine Location: SEATTLE, WA Date: MAY 25-29, 2000.  
Sponsor(s): Amer Coll Vet Internal Med. Journal of the American Journal of Veterinary Medicine. Volume:  
224 Issue: 4 Pages: 538-541 Published: FEB 15 2004

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## Molecular Analysis of Familial Ventricular Arrhythmias in the Boxer Dog (0156)

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Meurs KM, Lacombe VA, Dryburgh K, Fox PR, Reiser PR, Kittleson MD. Differential expression of the cardiac ryanodine receptor in normal and Arrhythmogenic right ventricular cardiomyopathy canine hearts. *Human Genetics*, 120, 2006,111-118.

Magnetic Resonance Imaging of Right Ventricular Morphology and Function in Boxer Dogs with Arrhythmogenic Right Ventricular Cardiomyopathy. Baumwart, R. D.; Meurs, K. M.; Raman, S. V. *Journal of Veterinary Internal Medicine*. Volume: 23 Issue: 2 Pages: 271-274 Published: MAR-APR 2009

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## The Assessment of Ejection Murmurs in the Boxer Dog (0169)

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### *Publications*

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Koplitz S, Meurs KM, Bonagura JD. Echocardiographic assessment of the left ventricular outflow tract in the boxer dog. *J Vet Intern Med*, 20, 2006, 904-911

Koplitz, SL, Meurs KM, Bonagura JD, Luis Fuentes V. Aortic velocity measurements in boxer dogs with soft cardiac murmurs. *J Am Vet Med Assoc*, 222, 2003, 770-774.

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## A Molecular Evaluation of Two Forms of Canine Cardiomyopathy (0440)

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### *Publications*

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Meurs KM, Fox PR, Spier AW, Koplitz S, Baumwart RD. A prospective pedigree and linkage analysis of familial dilated cardiomyopathy in the Doberman pinscher. *J Vet Intern Med*, 21,2007, 1016-1020.

An index of myocardial performance applied to the right ventricle of Boxers with arrhythmogenic right ventricular cardiomyopathy. Baumwart, Ryan D.; Meurs, Kathryn M. *American Journal of Veterinary Research*. Volume: 69 Issue: 8 Pages: 1029-1033 Published: AUG 2008

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## Identification of genetic modifiers that impact clinical expression of arrhythmogenic right ventricular cardiomyopathy in the Boxer dog (1753)

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### *Publications*

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In progress



## Publications Attributed To Alternate Funding Sources (Non-CHF)

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Dr. Meurs would like to thank Boxer owners for their time, commitment and participation in the following studies:

Association of Dilated Cardiomyopathy with the Striatin Mutation Genotype in Boxer Dogs. Meurs, K. M.; Stern, J. A.; Sisson, D. D.; et al. *Journal of Veterinary Internal Medicine*. Volume: 27 Issue: 6 Pages: 1437-1440. Published: NOV 2013 NCSU Funds

A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman pinscher. Meurs, Kathryn M.; Lahmers, Sunshine; Keene, Bruce W.; et al. *Human Genetics*. Volume: 131 Issue: 8 Pages: 1319-1325 Published: AUG 2012 (Funded by Ott Endowment)

Genome-wide association identifies a deletion in the 3' untranslated region of Striatin in a canine model of arrhythmogenic right ventricular cardiomyopathy. Meurs, Kathryn M.; Mauceli, Evan; Lahmers, Sunshine; et al. *Human Genetics*. Volume: 128 Issue: 3 Pages: 315-324 Published: SEP 2010 (Funded by Ott Endowment)

Plasma fatty acid concentrations in Boxers and Doberman Pinschers. Smith, Caren E.; Freeman, Lisa M.; Meurs, Kathryn M.; et al. Conference: 23rd Annual Forum of the American-College-of-Veterinary-Internal-Medicine Location: Baltimore, MD Date: JUN 01-04, 2005 *American Journal of Veterinary Research*. Volume: 69 Issue: 2 Pages: 195-198 Published: FEB 2008 (Tufts)

Desmosomal gene evaluation in Boxers with arrhythmogenic right ventricular cardiomyopathy. Meurs, Kathryn M.; Ederer, Martina M.; Stern, Joshua A. *American Journal of Veterinary Research*. Volume: 68 Issue: 12 Pages: 1338-1341 Published: DEC 2007 (Funded by Ott endowment)

Arrhythmogenic right ventricular cardiomyopathy in Boxer dogs is associated with Calstabin2 (FKBP12.6) deficiency. Oyama, MA; Reiken, S; Meurs, KM; et al. *Journal of Veterinary Internal Medicine*. Volume: 20 Issue: 3 Pages: 747-748 Published: MAY-JUN 2006

Clinical, echocardiographic, and electrocardiographic abnormalities in Boxers with cardiomyopathy and *Journal of the American Veterinary Medical Association*. Volume: 226 Issue: 7 Pages: 1102-1104 Published: APR 1 2005

Use of signal-averaged electrocardiography in the evaluation of arrhythmogenic right ventricular cardiomyopathy in Boxers. Spier, AW; Meurs, KM. Conference: 19th Annual Forum of the American-College-of-Veterinary-Internal-Medicine Location: DENVER, CO Date: MAY 23-26, 2001. Sponsor(s): Amer Coll Vet Internal Med. *Journal of the American Veterinary Medical Association* Volume: 225 Issue: 7 Pages: 1050-1055 Published: OCT 1 2004 (Ohio State Intramural)

Boxer dog cardiomyopathy: an update. Meurs, KM. *Veterinary Clinics of North America Small Animal Practice*. Volume: 34 Issue: 5 Pages: 1235-+ Published: SEP 2004 (review paper)

Assessment of heart rate variability in Boxers with arrhythmogenic right ventricular cardiomyopathy. Spier, AW; Meurs, KM. Conference: 20th Annual Forum of the American-College-of-Veterinary-Internal-Medicine Location: DALLAS, TX Date: MAY-JUN -, 2002. Sponsor(s): Amer Coll Vet Internal Med. Journal of the American Journal of Veterinary Medicine. Volume: 224 Issue: 4 Pages: 534-537 Published: FEB 15 2004 (OSU Intramural)

Correlation of QT dispersion with indices used to evaluate the severity of familial ventricular arrhythmias in Boxers. Spier, AW; Meurs, KM; Muir, WW; et al. American Journal of Veterinary Research. Volume: 62 Issue: 9 Pages: 1481-1485 Published: SEP 2001 (Not funded)

Comparison of in-hospital versus 24-hour ambulatory electrocardiography for detection of ventricular premature complexes in mature Boxers. Meurs, KM; Spier, AW; Wright, NA; et al. Journal of the American Journal of Veterinary Medicine. Volume: 218 Issue: 2 Pages: 222-224 Published: JAN 15 2001 (Not funded)