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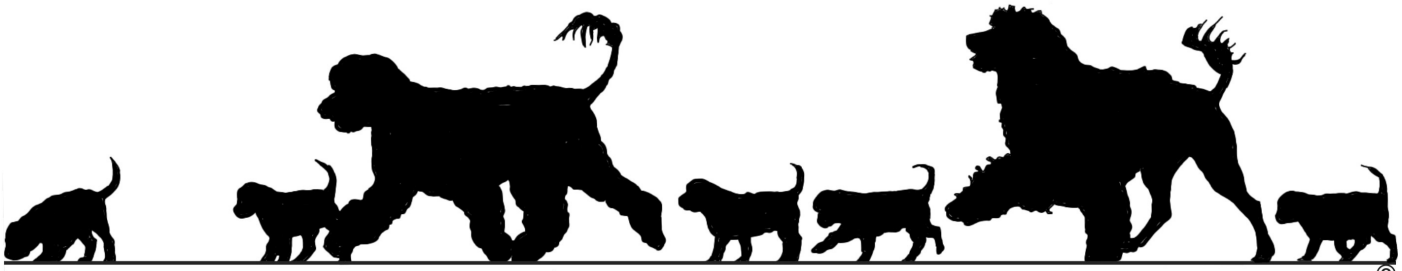

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We are dedicated to funding canine medical research focused on issues that affect the health and well-being of Portuguese Water Dogs everywhere.

Inside this issue

2016 Grants Funded

Veterinary Oncology Fellowship

Shirley Chu, DVM; University of Missouri

Project Abstract:

Lymphoma is one of the most common cancers in people and in dogs, and Diffuse Large B cell Lymphoma (DLBCL) is the most common aggressive lymphoma in these species. Dr. Chu's project is to further understand the effect of DNA methylation on cancer, using epigenetics, the study of potentially reversible changes to nuclear material that ultimately determine DNA expression. DNA methylation is the most permanent epigenetic mark and has been the most widely studied. DLBCL is the subject of this study to elucidate the first methylome in the canine species (specifically in Golden Retrievers).

MIRAseq (methylated CpG island recovery assay) is an enrichment technique that was used to collect genome wide DNA methylation informion. The methylomes will be analyzed to determine if a distinct fingerprint can be seen in DLBCL in Golden Retrievers, if this fingerprint models human DLBCL, and if a diagnostic panel can be produced for early diagnosis and aid in prognostication.

Other future projects to understand the genetic landscape of cancer in dogs include a parallel whole genome, exome and RNA–sequencing of DLBCL for the identification of actionable somatic mutations, biomarkers of minimal residual disease, sub-typing, tumor heterogeneity, structural variants and breed related susceptibility.

Co-sponsored with the AKC Canine Health Foundation

Capturing Tumor Cells in Canine Blood

Dr. Tracy Stokol, Ph.D.; Cornell University

Project Abstract:

This pilot study's aim is to develop a blood assay to count tumor cells circulating in a dog's blood. This technique has proven effective telling clinicians how aggressive a cancer is and provides information as to treatment and outcome for the patient. This assay is available for humans but currently not for our canine companions.

Just like their human owners, many dogs suffer from cancer, which is often malignant, spreading through the body via blood. Once tumors have spread, they usually result in a poor outcome, including death. The tumor cells in circulation (CTCs) can be counted in the blood of people with cancer using immunocapture devices. The number of CTCs in blood can tell the clinician how aggressive the tumor is, its potential to spread, and how long a patient might survive.

There is currently no such way of detecting CTCs in our canine companions. Development of an assay for counting CTCs in canine blood would be of tremendous benefit to our canine patients because, from a simple blood test, we could detect hidden tumors and gather information on tumor severity and the likelihood of spread or metastasis. The investigators will test a novel immuno-capture microdevice – the GEDI – for counting tumor cells in canine blood. This device can capture CTCs from blood in human patients with various cancers. This study will test its potential to do the same for dogs. In this pilot study, blood samples from healthy dogs will be manipulated to test the ability to count how many added tumor cells are captured by the GEDI device. If the GEDI does capture the tumor cells, the next step will be to determine if the device can capture CTCs from the blood of dogs that are known to have cancer, paving a path to early detection of cancer in dogs.

Co-sponsored with the AKC Canine Health Foundation, Grant Number: 02237-A

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Final AKC CHF Reports

Disrupting the Differentiation of Cancer Stem Cells to Prevent the Spread of Hemangiosarcoma

Dr. Jaime F Modiano, VMD, PhD
University of Minnesota

Original Project Description:

Hemangiosarcoma is a rapidly fatal disease. The lifetime risk is alarmingly high for some breeds like Golden Retrievers (~20% will die of this disease) and Portuguese Water Dogs (~15% will die of this disease). Furthermore, the risk of hemangiosarcoma is not limited to a single breed. In fact so many dogs are at risk to develop hemangiosarcoma that 40 Breed Clubs designated it as a research priority for 2012. Despite considerable efforts to find effective treatments, the outcome for dogs with hemangiosarcoma has changed very little over the past 30 years. We believe this is because our understanding of this disease is still rudimentary, but that is changing. Recent evidence suggests hemangiosarcoma conforms to the "cancer stem cell" model, where a defined subset of cells is responsible for initiating and maintaining the tumor. These cells are resistant to conventional therapies and they also are very adaptable, being able to survive in a variety of niches. In the case of hemangiosarcoma, the cancer stem cells also retain or acquire the potential to differentiate along several different lineages. For this project, we will use this property against the tumor by modulating factors that support the self-renewal of the stem cell compartment and by inducing their terminal differentiation along alternate pathways that have reduced malignant potential. We propose that disrupting the interactions between hemangiosarcoma cancer stem cells and their microenvironment will enhance the sensitivity of these cells to conventional and targeted therapies and improve the outcomes of dogs with this disease.

Grant Objectives:

1. Define the role of CXCL12 (stromal derived factor-1 or SDF-1) and interleukin-8 (IL-8) in maintaining hemangiosarcoma self renewal and multipotency in vitro

2. Determine the potential to direct hemangiosarcoma differentiation in vivo by genetic or pharmacologic alteration of CXCL12 and IL-8 chemokine signals

3. Determine the potential to delay metastasis of hemangiosarcoma in vivo by pharmacologic alteration of inflammation and peroxisome proliferator activated receptor (PPAR) agonists.Co-sponsored with the Morris Animal Foundation, Grant Number: D16CA-056

Report to Grant Sponsor from Investigator:

We completed progress to achieve the aims. Our results confirm and extend the notions that interactions between the tumor and its local environment regulate hemangiosarcoma progression. Yet, variability in cells within tumors can reduce the predictability of hemangiosarcoma behavior, and possibly contribute to therapy resistance. For example, hemangiosarcomas respond to the degradation of their supporting matrix by recruiting inflammatory cells and blood vessels. But the magnitude of this effect is variable among different hemangiosarcomas, which requires us to consider that these tumors might adapt efficiently to very different micro-environments. The hemangiosarcoma microenvironment also tends to be rich in a molecule called CXCL12, which is used as a means of communication between the tumor cells and the normal supporting cells. Only some of the tumor cells have the receptors that transmit the signals from CXCL12. These cells help to support the tumor, and also can be efficient mediators of metastasis. But in their absence, other mechanisms might perform these functions. Attenuating inflammation and modulating the metabolic activity of the cells shows modest effects on hemangiosarcoma cell growth, but neither approach is completely effective to eliminate the tumor. This suggests that blocking specific pathways might have positive therapeutic effects in selected patients, but managing this disease will require combining strategies that lower the capacity of cells to simply switch their behavior to use alternate pathways to survive and thrive.

Health Implications of Early Spay/Neuter on Canine Health

Dr. Benjamin L Hart, DVM, PhD
University of California, Davis

Original Project Description:

This project extends our just-completed ACORN grant with Golden Retrievers, where we found that spay or neuter was related to a significant increase in risk in five diseases of concern: hip dysplasia; cranial cruciate ligament tear; lymphosarcoma; hemangiosarcoma; and mast cell tumor. Importantly, the disease risk was dependent upon whether the dogs were female or male and whether the spay or neuter was performed early (before one year of age) or

later. Mammary cancer occurred so infrequently that it could not be analyzed.

Because breeds differ in vulnerability to joint disorders and risks of various cancers, we propose to expand this approach, on a breed-by-breed basis, to additional popular breeds and analyze all important joint disorders and cancers in each breed. We propose to include n this phase Labrador Retrievers, German Shepherd Dogs and Dachshunds. Upon negotiation with CHF, we will include 1-2 additional breeds, such as Rottweilers, Chihuahuas, Standard Poodles or Miniature Poodles.

We now know the numbers of subjects needed for each breed and the minimum number of disease cases needed to perform statistical analyses. For the breeds mentioned above, our database has sufficient subjects. The expected results will be of immediate benefit to caregivers of the breeds wishing to reduce the likelihood of various devastating diseases.

Grant Objectives:

To develop a generalized understanding of the impact of early spay and neuter on disease risk in dogs.

Report to Grant Sponsor from Investigator:

The long-term goal of this project is to evaluate the breed-specific effects of neutering (both sexes) at different ages on joint disorders (hip dysplasia, cranial cruciate ligament tear and elbow dysplasia) and some cancers (lymphosarcoma, hemangiosarcoma, mast cell tumor).

The effects of neutering at various ages were also examined in females with regard to mammary cancer, urinary incontinence and pyometra.

Labrador Retriever (1,500 cases: males–272 neutered, 536 intact; females–347 neutered, 345 intact)

The major finding was a significant 2-fold increase in one or more joint disorders with neutering in the first year in both males and females above the 5 percent level of intact dogs. The occurrence of the cancers followed was low (3-4%) and not affected by neutering.

German Shepherd Dog (1,170 cases)

The paper is under review. Early neutering significantly increased the incidence of one or more joint disorders and the occurrence of the cancers followed was low and not affected by neutering.

Small-dog Breeds
Chihuahua (831 cases)
Yorkshire Terrier (553 cases)
Shih Tzu (322 cases)

These breeds lacked joint disorders associated with neutering at any age above the low incidence of intact dogs. The occurrence of one or more cancers was low in both intact and neutered dogs.

Long-dog breeds
Dachshund (548 cases)
Corgis (191 cases)

Joint disorders in these breeds were not associated with neutering at any age above the low incidence of intact dogs. The occurrence of one or more cancers was low in both intact and neutered dogs. In male and female Dachshunds the occurrence of intervertebral disc disorders was high in intact dogs and not increased by neutering.

Rottweiler (696 cases)

Males and females showed an increase above intacts in one or more joint disorders with early neutering. The incidence of one or more of the cancers was not increased in either gender by neutering at any age.

Boxer (645 cases)

There was no increase in joint disorders associated with neutering at any age above the low incidence in intact dogs. Intact males had a fairly high incidence of cancers, which was increased in one of the neuter periods. Intact females had a fairly high incidence of cancers, not increased by neutering.

Doberman Pinscher (295 cases)

In males, there was no increase in one or more joint disorders associated with neutering above the low level in intact males. In females, however, there was an elevated incidence of joint disorders in an early neuter period, compared to none in intact females. In both sexes, the occurrence of cancers was less than the low level in intact dogs and not markedly affected by neutering.

Bulldog (471 cases)

The moderate occurrence of one or more joint disorders in intacts appeared not to be increased with neutering in males and females. For cancers, there was no evident increase in occurrence associated with neutering above the moderate level of intact male and female dogs.

CHF Progress Reports

Grant 01787: Clinical Advancement of a Cancer Vaccine in Dogs

Dr. Nicola J Mason, BVetMed, PhD
University of Pennsylvania

Original Project Description:

Canine lymphoma is the most common hematopoeitic cancer in dogs with an estimated annual incidence of 30/100,000. Chemotherapy induces remission in 75-85% of patients; however, the majority relapse with drug-resistant lymphoma within 8-10 months of diagnosis and most dogs die of their disease shortly thereafter. Cell-based vaccine strategies that stimulate anti-tumor immunity have shown promise in the treatment of many different cancer types including non- Hodgkin's lymphoma (NHL) in humans. We have used a cell-based vaccine to induce anti tumor immunity in dogs with NHL. This vaccine given three times after successful induction chemotherapy significantly prolonged overall survival. However, in the majority of dogs the vaccine did not prevent relapse but significantly prolonged second remission duration induced by rescue chemotherapy when compared to unvaccinated controls. These findings suggest that the lymphoma vaccine stimulated anti-tumor immunity but that this was insufficient to prevent relapse and only upon immunological boosting (through a poorly defined but previously recognized chemotherapy effect) could prolonged cancer free survival be realized.

Grant Objectives:

To optimize our cell-based vaccine approach to induce functional, long lasting tumor-specific immune responses that aim to prevent relapse and prolong survival in dogs with non-Hodgkin's lymphoma.

Report to Grant Sponsor from Investigator:

The goal of this proposal is to build on our previous work developing a cell-based vaccine that aims to stimulate potent tumor-specific immune cells (known as T cells) that will kill lymphoma cancer cells. Our previous work has shown that white blood cells known as B cells found in the peripheral blood can be activated and grown outside of the body using special "feeder cells" that express an important molecule known as CD40L. The stimulated B cells (known as CD40-B cells) can be loaded with genetic material (RNA) that

has been extracted from the patient's tumor. When re-injected back into the patient, the CD40-B cells are able to present the tumor material to the body's immune system and stimulate an anti-tumor immune response. We have previously shown in a phase I clinical trial that this approach has produced promising results with respect to prolonging overall survival in dogs with lymphoma. Since then we have been working to further improve this vaccine in two important ways: firstly we aimed to generate a more robust system that induces greater B cell proliferation and produces B cells that have improved capacity to stimulate the patient's T cells against the cancerous cells; and secondly to generate a more user-friendly system of B cell activation and expansion that would only require basic laboratory equipment to make these vaccines for canine patients.

Our work has focused on optimizing the feeder cells that are used to stimulate B cells from the patient's blood. Our proposed clinical trial involves repeat vaccination of dogs with lymphoma (rather than just 3 initial vaccines as per our first, phase I trial). Thus generation of a robust system that allows for optimal B cell activation and expansion aims to supply more B cells that can be cryopreserved for repeat vaccinations.

Current methods of generating the CD40-B vaccine from lymphoma patients are labor intensive and require specialized laboratory equipment that is not available in most facilities. Therefore, we have explored ways to enable use of these feeder cells without the need for special equipment. To this end, we have developed protocols that utilize KTCD40L cells that have previously been irradiated (using a Cs-137 irradiator) and cryopreserved. This eliminates the need for irradiation and maintaining a fresh stock of KTCD40L cells and provides a more off-the-shelf product that could be used by standard laboratories to stimulate canine PBMCs.

We have performed several experiments to evaluate whether these pre-irradiated, cryopreserved feeder cells can effectively expand canine B cells. We have found that canine B cell expansion using thawed, previously irradiated KTcCD40L feeder cells is possible however it is sub-optimal when compared to freshly irradiated feeder cells. However, the moderate drop in B cell expansion efficacy is off-set by the easy of use and potential for commercialization enabling any facility with standard laboratory to equipment to generate autologous CD40-B cells.

We have re-opened our clinical trial and have since enrolled 13 dogs following optimization of our B cell culture system.

Grant 01828: Mapping of Genetic Risk Factors for Canine Hip Dysplasia

Dr. Antti Iivanainen, DVM, PhD
University of Helsinki and the Folkhälsan Institute of Genetics

Original Project Description:

Canine hip dysplasia (HD) is common a developmental disorder of the hip joint affecting many breeds and severely suppressing the quality of life. As the disease has several genetic risk elements and is additionally influenced by environmental factors like feed and exercise, it is of paramount importance that the genetic association studies are conducted using adequately sized cohorts of genotyped diseased and healthy animals. This proposal involves two research groups (Finland and France) engaged in the genetics of HD in German Shepherd, Golden retriever and Labrador retriever breeds. HD is a polygenic disease and requires large enough sample sizes (>300-400 dogs) so that contributing genetic loci can reliably discovered.

This proposal aims to genotype 288 dogs in German Shepherds increasing the total number of studied dogs in this breed over 400. By doing this, we expect to increase the power of the association studies so that all major genetic risk factors can be uncovered with a high statistical significance. The loci identified in German Shepherds will be followed up in the other breeds. The identification of genetic risk elements allows developing genetic tests that can be used in breeding programs to control the disease incidence as well as further studies regarding the possible role diet and exercise in the HD development.

Grant Objectives:

1. To establish an accurately phenotyped primary study cohort for genetic studies. We aim to sample at least 300 cases and 300 controls.

2. To perform a GWAS for 144 cases and 144 controls using canine high density SNP arrays.

3. To replicate the associated loci in independent multinational cohorts of dogs in different breeds.

Report to Grant Sponsor from Investigator:

The overall objective of our study is to perform a genome wide association study (GWAS) of canine hip dysplasia (CHD) in German Shepherds using a large sample cohort (200 cases and 200 controls). CHD is a common problem in many breeds. The dysplasia phenotype is graded from radiographs. In this study, we use the standards of Fédération Cynologique Internationale (FCI) ranging from A (healthy) to E (severely dysplastic). Each hip joint is graded individually.

As the disease progresses also the risk for hip joint arthrosis -- a painful and incurable condition -- increases. The identification of genetic risk factors would enable the development of genetic tests to aid the breeders in controlling the disease. Four hundred animals consisting of carefully matched pairs of healthy and affected individuals should provide enough power for the association study to uncover the major genetic risk factors for this degenerative disease.

At present, we have collected a study cohort of 1141 dogs including 411 cases and 730 controls. We have analyzed the association of CHD to a genome wide array of genetic markers using 526 dogs. The results indicate suggestive associations to ca. 30 markers on several chromosomes. Preliminary analyses suggest that CHD associates with some of the markers also in an independent cohort of 833 dogs from four breeds.

We are currently finalizing the analyses and preparing a manuscript on the results.

Grant 01889-G: Innovations in Prevention, Diagnosis, and Treatment of Cancer - Goldens Lead the Way

Dr. Jaime F Modiano, VMD, PhD
University of Minnesota

Original Project Description:

Lymphoma and hemangiosarcoma are major health problems in golden retrievers, causing both suffering and premature death. As part of our ongoing project, Discovery and Characterization of Heritable and Somatic Cancer Mutations in Golden Retrievers, we have identified several regions of the genome that contain genetic heritable risk factors for lymphoma and hemangiosarcoma in Golden Retrievers.

(Continued on page 8)

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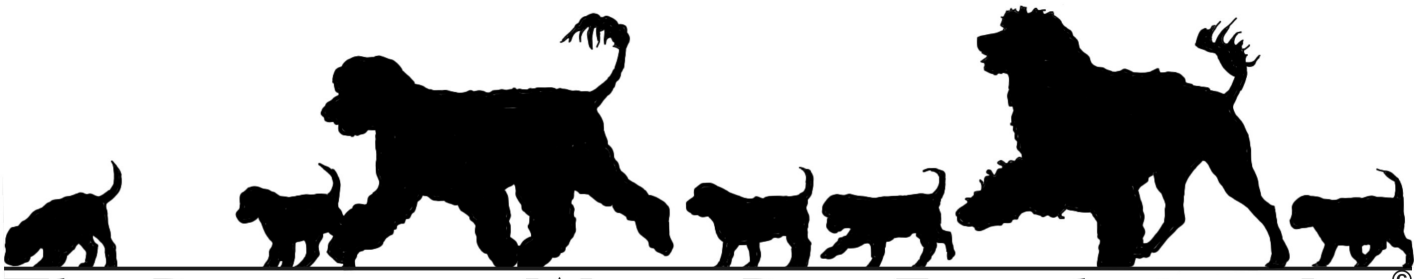

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Colorado PWD Club in memory of Colorado Club members who had a PWD cross the Rainbow Bridge in 2015

Vicki & Ken Goldberg – thank you to all the breeders fighting to keep this breed mentally balanced and healthy!!

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John Mazurek & Sherry Sands in memory of John Azevedo for his love and contribution to our beloved Portuguese Water Dogs

Jere McInerney in thanks to Cathy Winkler for wonderful pups

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Sailor $50-$99

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Antranik & Eloise Barsamian in memory of John Azevedo

Glenn Bayard in memory of my Best Friend, Sam

Sandy Beard in memory of John Azevedo

Cindy Berube in honor of the PWD PSG

Janet Boyd in honor of the PWD PSG

David Buchheit in honor of the PWD PSG

Sandra Busse in honor of the PWD PSG

Joseph & Barbara Connolly

Bonnie B. Cooksey in honor of the breeders of my PWD, Dr. Virginia Brown and Marjorie Mann

Delmarva PWD Club

Chris & Steve Dostie in honor of CH DownEast Cruzin' The High Seas CD RA PAD AAD MX MXJ AWD

Rebecca Elon

Roslyn Eskind in honor of the PWD PSG

Roslyn Eskind in memory of Nina, loved by the Wolff family

Fran & Paul Fehling in memory of Daisy and Calvin

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Sailor $50-$99 (continued)

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Sarah Maas in honor of the PWD PSG

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Coleen Sanguinetti in memory of John J. Azevedo, Jr.

Donna Sessa-Carter

Darby Stacey in memory of Vidal "Andy" Andrade

Stacy, John & Tony Stahl

Susan Straight

Sterling Sugars, L.L.C. in memory of Vidaul "Andy" Andrade

Nancy Vener

Janet Warnsdorfer, Galaxy PWDs in memory of "Cisco" Galaxy's The Cisco Kid

Janis Watts in memory of Legado Guardacostas Schooner AWD

Elana Winsberg & Mike Barber in memory of our beloved Tinker and Marisol

Jerry & Kim Wolcoveick in memory of Alice Vicha and all her PWDs

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Sherry & Aaron Goren in honor of Miriam Goren on her special birthday

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John & Mary Catherine Katinas

George & Ruth Klopping in memory of John J. Azevedo, Jr.

Kristina de Leeuw

Richard Lulenski in memory of Riley (12 years 3 months)

Carol Mattingley & Ann Bowley, Windruff PWDs in memory of Naia

Elizabeth Gouveia Miner in memory of Maggie

Barbara & Donald Niemann in memory Jack & Yvonne McCredie's "Bingo"

Christine Parseghian

Ilene Perelman

Kristi & Michael Portugue in memory of "Lacee" from her Kalista "T" littermate, Hydro

Sidney Schuler in memory of Rocky

Linda Skora

Linda Smith

Nedra & Hugh Smith

Southern California PWD Club in memory of Maskey Heath

Southern California PWD Club in memory of La Familia's Saucy Lady

Southern California PWD Club in memory of "Taffy" CH Roseknoll's Saltwater Taffy RE OAP NJP THDN WWD SROM MAC1 MAC2

Southern California PWD Club in memory of "Kaci" Finisterra Wicked Little Angel CDX CGC WWD

Our Funding Strategy

The Foundation funds research projects which focus on diseases/conditions that will benefit Portuguese Water Dogs, primarily through the Canine Health Foundation (CHF) and Morris Animal Foundation (MAF).

We also have and will continue to fund health research projects specific to the Portuguese Water Dog. These dedicated Portuguese Water Dog research opportunities must go through a peer review process to ensure the quality and relevance of research, and to help maintain the objectivity and credibility of the funded project.

Our Process

Research funded through the CHF and MAF have established deadlines for researchers to submit their projects for review and acceptance. Typically these deadlines are in the Fall of each year. CHF and MAF provide a list of approved projects at the end of their review process.

The Foundation's selection process is to identify CHF and MAF projects that study diseases or conditions that are of concern to the Portuguese Water Dog community. Although some research being conducted may use other breeds — all dogs with that particular condition will benefit from the results. Our goal is to focus on the disease and how it applies to health concerns within the Portuguese Water Dog breed.

"Shine On" Challenge Campaign Donors

1000+

The Portuguese Water Dog Club of the Twin Cities in memory of the PWDs we lost in 2015

$500-$999

Sue Hopkins

Delmarva PWD Club in special thanks to the Keystone PWD Club and the Nutmeg PWD Club for all their assistance at the 2014 PWDCA National Specialty

$250-$499

Chuck & Candi Bubert in memory of Lisa Humke

Delmarva PWD Club in special thanks to Cheryl Phillips and her late husband, Rick, for all their contributions

Nancy, Trevor & Lowell Sedlacek, Success PWDs in loving memory of CH Driftwood N Broek's Goldfish

$100-$249

Arnold & Sandra Brown in memory of our beloved "Sage" GCH CH Ebb Tide's Upcountry Titan AOM MX MXJ CD CGC WWD Therapy & R.E.A.D. Dog

Gail DesRoches

Nancy Kurkjian

Thomas & Linda Majcher in memory of Indy Majcher (1/26/2016) & Isa Ritchie (2/11/2016) playmates and friends

Donald Niemann

Ann Marie Reed

$50-$99

Phyllis Crane

Roslyn Eskind

Pamela Francis

Alan & Haven Lane

Kristi & Mike Portugue in memory of Neptune and Ocea, our first two PWDs. Loving & devoted companions, forever in our hearts.

Margaret Scoggin in memory of Vidual "Andy" Andrade

Barbara & Jim Whiteherse

Up to $49

Karen Kirby Ash, Saltydawg in memory of Saltydawg Grace Spitfire

Karen Kirby Ash, Saltydawg in memory of "Coal" Saltydawg Chip Off The Ole Dock

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Moby" Kalista Lands A Lunker CD BC TD RAE MX MXJ WWD for his MX!!

Linda K. & Krista K. Hunt, Kalista in memory of Kalista's Darlin Kelsey loved and missed by Janice Holth and family

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Beamer" CH Kalista's Ultra Black Magic Water RN NA for his NA title!!

Linda K. & Krista K. Hunt, Kalista in memory of "Lacee" Kalista's Take A Bow

Linda K. & Krista K. Hunt, Kalista in memory of "Hattie" Kalista's Howling Hattie

Linda K. & Krista K. Hunt, Kalista in honor of "Oliver" Kalista's Ready For Adventure CD RN AX AXJ NF AWD CGC for his AXJ!!

Linda K. & Krista K. Hunt, Kalista in honor of "Y" MACH2 Kalista's Now What BN RA MXG MJG NAP NJP MXF T2B CAA CWD for his MACH2!!

Linda K. & Krista K. Hunt, Kalista in honor of "Kuper" CH Kalista's Terceiro's AKC Championship!!

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Queixo" MACH3 Kalista's Just What The Dr. Ordered UD RAE MXG MJB2 MXF T2B CWDX SROM for her MACH3!!

Linda K. & Krista K. Hunt, Kalista in memory of "Bruno" Kalista's Force De Agua loved and missed by Doug and Stacy Ferderer and Family

Kristi & Mike Portugue in memory of Frances Silverman, longtime PWDCTC member, dog lover, and water training friend

Grant 01889-G: Innovations in Prevention, Diagnosis, and Treatment of Cancer - Goldens Lead the Way (continued from page 4)

We also identified additional somatic mutations in tumors that occur recurrently in both cancers, some of which are linked to duration of remission when treated with standard of care. Our results indicate that a few heritable genetic risk factors account for as much as 50% of the risk for these cancers. These findings offer the potential to develop tests and strategies for DNA tests that can predict risk for individual dogs, as well as to manage risk across the population as a whole. Indeed, both the inherited risk factors and tumor mutations point to pathways that have been implicated in the pathogenesis of LSA and HSA, and thus should inform the development of targeted therapies.

In this proposal we aim to find the precise mutations for the heritable genetic risk factors and to validate markers (mutations) used to determine risk at the heritable loci in a larger independent population of Golden Retrievers from the USA and from Europe in order to develop robust risk prediction tools and an accompanying DNA test. We will identify and characterize tumor mutations and study their relationship to the heritable risk factors, tumor pathogenetic mechanisms, and disease outcome.

Grant Objectives:

To determine whether newly identified risk loci harbor key genes or regulatory elements that contribute to and/or lower the threshold for initiation of lymphoma (LSA) and hemangiosarcoma (HSA), and furthermore, if they cooperate with acquired mutations that are necessary for clinical progression of these two diseases.

Report to Grant Sponsor from Investigator:

This project has completed the first thirty months. We have made new and exciting discoveries that will help us to understand mechanisms of tumor progression and response to therapy, and we have created the infrastructure to integrate clinical performance and outcome data with the molecular properties of the tumors and their microenvironment interactions.