

Portuguese Water Dog Foundation, Inc.



2012 SPRING UPDATE

MAF CO-SPONSORED RESEARCH PROGRESS REPORTS

D03CA-132: Gene Expression Profiling of Relapsed Lymphoma in Dogs

William C. Kisseberth, DVM, PhD, Dip. ACVIM (Oncology)
Oregon State University

FINAL UPDATE

Results: *Study Identifies Genes Associated with Lymphoma Relapse in Dogs*

Lymphoma is one of the most common and treatable cancers in dogs. More than 90 percent of dogs treated with chemotherapy go into remission. Unfortunately, most dogs relapse and eventually die of the disease.

The investigators compared gene-expression patterns of tumors before and after chemotherapy to determine changes that took place in the dogs that relapsed. They identified important candidate genes and different subtypes of lymphoma that will help in the development of new cancer treatments. These candidate genes must now be independently validated in another set of patient samples but have already contributed greatly to the understanding of genes associated with relapse and potential new therapeutic targets.♦

D08CA-050: Tyrosine Kinases in Canine Hemangiosarcoma

Stuart C. Helfand, DVM
Oregon State University

PROGRESS UPDATE: Hemangiosarcoma (HSA) remains one of the deadliest canine cancers, and dogs rarely live more than six months after diagnosis. New approaches are needed to improve the survival time of dogs afflicted with this devastating disease. Researchers from Oregon State University are expanding on prior Morris Animal Foundation-funded research into a novel class of drugs called tyrosine kinase inhibitors, which have the potential to control the growth of HSA cells. Tyrosine kinases are enzymes that function as cell-signaling messengers, and their increased activity is associated with uncontrolled HSA cell growth. To date, researchers have identified a tyrosine kinase-signaling protein that is abnormally active in HSA cells. Data indicate that signaling through this tyrosine kinase protein contributes to growth and proliferation of canine HSA. Researchers have also examined the effects of inhibiting tyrosine kinases in canine HSA. Working with canine HSA cell lines derived from tumors occurring in the heart, brain and beneath the skin, researchers found that inhibiting certain tyrosine kinases effectively suppressed growth of all these cell lines regardless of their origin. Additionally, when tyrosine kinase inhibitors were combined with standard-of-care HSA chemotherapeutic agents, the combined killing effect was significantly improved.

As a result of the marked suppression of HSA cell growth observed in the laboratory in response to tyrosine kinase inhibitors, researchers are hopeful that adding certain tyrosine kinase inhibitors as part of the treatment for dogs with HSA may increase survival time. Clinical evaluation in dogs with HSA will be necessary to validate the merits of this strategy. Hemangiosarcoma is a well-recognized problem in several dog breeds, including German Shepherds, Golden Retrievers, Great Danes, Boxers, English Setters, Pointers, **Portuguese Water Dogs**, Bernese Mountain Dogs, Flat-coated Retrievers and Skye Terriers. Gaining an understanding of abnormally functioning signaling proteins is providing new treatment options that will improve outcomes for dogs afflicted with this devastating disease.♦

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IN THIS ISSUE:

MAF PROGRESS REPORTS	1-2
AKC CHF PROGRESS REPORTS	2
IS HEMANGIOSARCOMA HEREDITARY? A CONVERSATION WITH DR. MODIANO	3
DONATION FORM	5
AKC CHF PROGRESS REPORTS (CONT)	6
HONOR ROLL OF DONORS	6-8

MAF CO-SPONSORED RESEARCH PROGRESS REPORTS (CONTINUED)

D10CA-002 Safety & Efficacy of a Novel Anthracycline, AD 198 in Dogs with Refractory Lymphoma

Alfred M. Legendre, DVM, MS, DACVIM
University of Tennessee

PROGRESS UPDATE: Lymphoma, a cancer of the lymphocytes (a type of white blood cell) that occurs commonly in dogs, is rarely cured because the cancer becomes resistant to chemotherapy. AD 198 is a new anthracycline drug that is similar to doxorubicin, which is used in chemotherapy. Though very effective, doxorubicin causes damage to the heart, which limits the total amount that can be safely given. AD 198 shows promise in treating lymphomas that are resistant to doxorubicin, and does not damage the heart. Researchers from the University of Tennessee are using an injectable formulation of AD 198 to determine the best dose for dogs with lymphoma. To date, they treated three dogs with resistant, end-stage lymphoma and saw a modest shrinking of lymph nodes in one dog. There were no observed major toxicities; however, in an independent study at another institution, researchers noted life threatening thrombocytopenia (a decrease of platelets in the blood) in a couple of dogs treated with AD198. Before enrolling and treating more patients, the researchers want to better understand why severe thrombocytopenia was observed in dogs treated at the other institution with doses well tolerated by other dogs. While awaiting this data, researchers will continue their laboratory tissue culture studies of cancer cells from dogs with chemotherapy-resistant lymphomas to determine how AD198 kills cancers cells. Information gained from this study will contribute to the ongoing search for an alternative treatment option for dogs suffering from chemotherapy resistant lymphoma.♦

D09CA-405: Enrichment for Canine Cancer Stem Cells by In Vitro Manipulation and Chemotherapy

Aric M Frantz, CVM, ACCR
University of Minnesota

PROGRESS UPDATE: One of the main reasons why cancer therapies fail may be because of the existence of highly resistant cells in tumors called cancer stem cells. Researchers at the University of Minnesota are working to understand the genetics of cancer stem cells in three canine cancers: hemangiosarcoma (cancer of blood vessel-forming cells), osteosarcoma (bone cancer) and glioblastoma multiforme (brain tumors). To achieve their goals, the scientists developed methods to maintain these cells in the laboratory and used the most contemporary technology to study their molecular properties. Their results show for the first time that cancer stem cells exist in canine hemangiosarcoma and confirm the existence of these cells in osteosarcoma and glioblastoma. Further, their results suggest that cancer stem cells are not alike in every tumor, although they may share essential properties that allow for potential targeted therapies which could benefit a majority of patients with these diseases. This Fellowship Training Grant has provided valuable training and career development opportunities for a future cancer researcher.♦

AKC CHF CO-SPONSORED RESEARCH PROGRESS REPORTS

01131: Genetic Background and the Angiogenic Phenotype in Cancer

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

PROGRESS UPDATE: Certain dog breeds are prone to develop certain types of cancer; yet, there has been little progress to define genes or other factors that account for this risk. Our recent work on hemangiosarcoma was the first to demonstrate that a dog's genetic background, defined by "breed," can influence the profile of genes that are expressed by tumors. Among other important implications, this implies that certain breeds are diagnosed with specific cancers more frequently than others because of the behavior of tumors after they arise, and not simply because they arise more frequently. Specifically, this may apply to the observed predisposition for hemangiosarcoma seen in Golden Retrievers, German Shepherd Dogs, and **Portuguese Water Dogs**. Here, we continued to test this premise by evaluating genome-wide gene expression profiles in samples from dogs of various breeds. Our results suggest that, while there are subtle differences that are influenced or modulated differently in tumors from dogs of different breeds, these differences may disappear when tumors are considered in their context as "tissues" that include microenvironment constituents. Rather, there appear to be distinct subtypes of hemangiosarcoma (perhaps with different biological behavior and prognosis?), which might arise from different cells of origin, or more likely, which develop in response to adaptation of the hemangiosarcoma cells to environments that show different patterns of inflammation, angiogenesis, coagulation, and hypoxia, each of which alters not only the predominant or favored differentiation of the tumor cells themselves, but also the way they instruct microenvironment cells to create a favorable niche. This underscores the importance of looking at these tumors in their context as "new tissues" or "new growths" rather than at the cells in isolation as we work to develop more effective strategies for detection, diagnosis, and therapy.♦

01429: Mechanistic Relationship of IL-8 in Cell Proliferation & Survival of Canine Hemangiosarcoma

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

Progress Report: We reported on assessment of gene expression and protein accumulation for IL-8 and other inflammatory cytokines in cell lines and tissues using array-based data, quantitative real time RT-PCR, and ELISA in our mid-year report. Our ongoing work has expanded on the previously reported data, generating unexpected and paradoxical findings. Specifically, there is a direct correlation between IL-8 gene expression and protein in culture supernatants under conditions of normal growth. However, under conditions of cellular stress, cell lines derived from different tumors show unique and distinct responses in terms of IL-8 regulation. In some cells (including most cells cultured under conditions that enrich cancer stem cells), IL-8 gene expression increases dramatically (by >1 order of magnitude), but secretion of IL-8 actually is decreased. The reason for this is not clear at present and might involve greatly

*The Spring and Fall Updates are publications
of the Portuguese Water Dog Foundation, Inc.*

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The mission of the **Portuguese Water Dog Foundation**

is to generate significant
resources to fund research into
genetic and other canine diseases
that will improve the life
and health of all
Portuguese Water Dogs.

(Continued on page 6)

IS HEMANGIOSARCOMA HEREDITARY? BY DR. JAIME MODIANO VMD, PHD

NO - or at least not exactly. What I will try to explain in detail below is that some breeds (including PWDs) are at greater risk to develop hemangiosarcoma and this risk is most probably due to heritable traits. But hemangiosarcoma is not heritable in the sense that affected parents would pass it to progeny in a Mendelian context. The risk factors are going to be multifactorial. Some will probably be amenable to selection (and reduction of risk) and some may be firmly embedded in the breed (fixed traits).

The NCI definition of a familial (heritable) cancer is a cancer that occurs in families more often than would be expected by chance. These cancers often occur at an early age, and may indicate the presence of a gene mutation that increases the risk of cancer. They may also be a sign of shared environmental or lifestyle factors.

If we take hemangiosarcoma as a tumor in general - including the counterpart we see in mice and in humans (angiosarcoma), it is far more common in dogs than in any other species. That means that developmentally, dogs have greater risk than other animals to develop this tumor. It also could mean that dogs (as a species) are exposed to environmental factors that predispose to this condition.

Here, I will take a moment to dispel a common misconception that toys, food, food bowls, and other items we use for enrichment are responsible for this disease. Myth #1 - "my dog got hemangiosarcoma because I fed it from a plastic bowl" (or let it play with Nylabones, or rubber balls, or tennis balls, etc.). In humans, angiosarcoma is a very rare disease, but it was recognized that occupational exposure to vinyl chloride (who cleaned reactors used in the manufacture of PVC) led to increased risk of hemangiosarcoma of the liver. This had a very long latency (on average, about 2 decades between history of last exposure and diagnosis). Many people (and a few websites) mistakenly interpret this as "rubber and plastic products cause hemangiosarcoma". Finished PVC products are not the same as the monomeric vinyl chloride and despite new concerns about the softening materials, there is no evidence to support a link between plastic or vinyl or rubber products and cancer in dogs or people.

So, why do dogs get hemangiosarcoma so frequently, and is it really more common in certain breeds? The answer to the first question is "we do not know". Dogs and people develop cancer at about the same rate (lifetime risk on the order of 1 in 2 to 1 in 3), which probably says something about our shared environment. Staying with this subject, this is as good as any place to discuss life expectancy and diseases of ageing. Life expectancy for primordial humans was probably on the order of 20-30 years, with significant infant and adolescent mortality. Industrialization and social evolution provided shelter, and eventually hygiene and medical care. So humans in the developed world now have life expectancy of 80 years or longer. Recent estimates are that babies born in the U.S. in 2010 have a 50% probability to see their 100th birthday. Similarly, dogs in the wild have a life expectancy of 4-6 years, but domestic dogs have a life expectancy that is about twice as long. By preventing death from other causes, humans and dogs become more susceptible to chronic diseases associated with ageing, the most prominent being heart disease (in humans), cancer, arthritis, and in our society, diseases associated with obesity. So, a major factor in the perceived "cancer epidemic" is simply longevity. More people and dogs reaching older ages increases the number of people who are likely to develop cancer. Why is that? Because cancer is a disease that arises from mutations. More days alive means more cell divisions to maintain our bodies which means more chances to accumulate mutations.

Some environmental mutagens accelerate this (tobacco products, for example), but the most significant "mutagen" is the normal error rate in the process of normal DNA replication. There is no escaping the risk of cancer with ageing, although some factors that contribute to this risk might be reduced. Figuring out which factors can be reduced and how is an area of vigorous investigation called "cancer prevention research". A consistent finding is that lean body mass has a protective effect against cancer (for reasons unknown, although many hypotheses are being tested). This seems to be true in mice, monkeys, dogs, etc. and is probably the simplest thing people can do to reduce cancer risk (notice the word is "reduce" and not "eliminate"). Another relatively "easy" answer for humans is to avoid behaviors that increase risk (tobacco use, tanning beds, etc.). Dogs engage in "risky" behavior if they are allowed to roam in areas where transmissible venereal tumor is endemic (Southern Border States). So, practices that prevent roaming will not only protect dogs from getting "hit by the mail truck", but also from unnecessary fighting, injury, and even TVT. In female dogs, spaying before the first heat is protective against mammary cancer. The risk of mammary cancer in dogs that are spayed before their first heat is virtually 0, compared to about 10% (1 in 10) for intact bitches or females spayed after several heat cycles. There is some tantalizing data suggesting that green leafy vegetables or cruciferous vegetables may reduce the incidence of some cancers in dogs. Introducing such vegetables into the diet has no down side if the dogs will eat them.

But I digress... Back to hemangiosarcoma. Generally, sarcomas of all types are relatively common in dogs and very rare in humans. Sarcomas are tumors that arise from connective tissues (the "glue" that holds tissues together). People more commonly develop carcinomas (tumors that arise from the glandular and lining cells in tissues). We can only surmise that this species difference is genetic (developmentally determined), anatomic, or both. It is unlikely to be related to factors such as diet, as there are no subgroups with different exposures that defy this trend. It is estimated that hemangiosarcomas account for 5-10% of all tumors in dogs (compared to lymphoma, for example, which accounts for about 20% of all tumors, or mast cell cancer, which may account for an even higher percentage). By comparison, angiosarcoma accounts for about 0.01% of all tumors in humans!

The observation that certain breeds develop certain tumors more frequently was initially made in the 1960's. To my knowledge, Dorn was the first to report this in his studies of cancer incidence in Contra Costa County in California, but it is possible that there are earlier reports or which I am not aware. Dorn's observations sparked tremendous interest and there was a wonderful NCI monograph published in 1980 by Priester and McKay that combed through the Veterinary Medical Database compiled initially from 15 veterinary schools and later from >20 veterinary schools, of all cases seen at their teaching hospitals. To place hemangiosarcoma as defined in this study in perspective, the database had >1300 cases of lymphoma (entered between 1964 and 1977), and only 165 cases of hemangiosarcoma. When hemangiosarcoma was evaluated by itself, breeds with the highest risk (2-3 times greater than the average for all dogs) included: Boxers, Great Danes, German Shepherd Dogs, English Setters, Golden Retrievers, Pointers and German Shorthaired Pointers. It is worth noting that some of the breeds that seem to be at high risk today were not represented by large numbers of dogs in the U.S. in the 1960's and 1970's.

Because the studies excluded geographic differences, age, sex, and other demographics as causal in this association, the logical assumption was that these breeds had "genetic factors" (more accurately referred to as "heritable traits") that made their risk to develop hemangiosarcoma higher. Along with "high risk" breeds, there also were "low risk" breeds, which interestingly were mostly small and toy breeds.

(continued on page 4)

IS HEMANGIOSARCOMA HEREDITARY? BY DR. JAIME MODIANO (CONT'D)

(continued from page 3)

This database is still an incredible resource, but it was not maintained in the same manner past the mid-1980's, so the information included may not be completely timely. More recent information comes from a number of Breed Health Surveys. These surveys have a wealth of interesting data, but they must be interpreted with some caution due to the inherent problems of survey studies (reporting bias, recall bias, etc.) Probably most Portuguese Water Dog owners are familiar with Margaret Slater's report from 2005-2006. The PWD health survey data showed almost 50% of PWDs included that died prior to 2005 had died from cancer (consistent with the known lifetime risk of cancer for dogs as mentioned above), but almost 1/3 of cancer deaths were attributed to hemangiosarcoma (which is higher than the expected ~10% of tumors). To place this in context, the Golden Retriever Health Survey from 1999-2000 showed that almost 20% of all deaths in Golden Retrievers could be attributed to hemangiosarcoma (and another ~12% to lymphoma), whereas for PWDs, about 15% of all deaths were attributable to hemangiosarcoma and only ~6% to lymphoma. Still relatively high numbers, though.

What is it then that makes PWDs (or Golden Retrievers, or German Shepherd Dogs) more susceptible, and are relatives of affected dogs at higher risk? The answer to what makes PWDs more susceptible is "we don't know". We are actively asking this question in our research, and this is where a plea for samples may resonate. We can only get answers if we can study material from dogs that get this disease. Paperwork, clinical lab results, radiographs, etc. will not help. We need physical samples submitted as described on our website. Nothing less will do and there are no other easy ways to answer this question.

Until we can get an answer to the first question, we cannot specifically answer the second question. Without a baseline for information, we have to go with the assumption that the risk is approximately the same across all members of the breed. This may turn out to be an incorrect assumption, but there is nothing we know or nothing we have observed that tells us we should go in another direction at this time.

So, when we talk about risk, each dog is independent from any other dog. If two littermates (or four littermates or eight littermates) develop this cancer, it does not necessarily imply that the breeding was a "high risk" breeding. If the cancers occur in adult dogs or in older dogs, then those dogs need to be considered in the context of the whole population (at least their whole generation) and more than likely they will be in the realm of the ~15% that were "expected" to develop hemangiosarcoma. In a litter of 7 dogs, if one were to develop hemangiosarcoma, the rest would not be "protected" by the 1 in 15 occurrence in the litter. Risk does not work that way. If you wish, imagine two individuals flipping coins at the same time. Both will get ~50% heads and 50% tails, but what individual #1 gets in a toss does not influence what individual #2 gets on the same or subsequent toss (just like the result of one toss by any individual does not influence or predict the result of the next toss. Every toss is a 50/50 chance of heads or tails). The same is true for cancer risk and dogs.

Now, if a litter had multiple animals that developed a rare cancer at a very young age, that would trigger a high level of suspicion that there may be a heritable component related to the breeding or one of the parents. That is not the case for hemangiosarcoma in PWDs (median age at diagnosis is about 10, just like we see for most other breeds).

I will throw in a small nugget about treatment of visceral hemangiosarcoma (not hemangiosarcoma of the skin, which is a different disease and is generally more benign) - the ONLY thing that we know works at all is the standard of care - removing the primary tumor and following the surgery with chemotherapy. The principal goals to remove the tumor are to eliminate the major mass and source of tumor cells (especially when gross metastasis is not evident) and to reduce the chance of a lethal bleeding episode. The goal of chemotherapy is to delay recurrence from microscopic spread, which exists in virtually every dog diagnosed with hemangiosarcoma. Surgery alone has benefit (simply by reducing the probability of an impending lethal bleeding episode) and some dogs can be cured with surgery alone (probably those where the tumor has uncharacteristically remained confined to one site). About 10-15% of dogs that are treated will do remarkably well, surviving >1 year and potentially much longer (long enough to die from something else). About 35% of dogs will survive >4-6 months but will fail to reach the 1-year anniversary. And about 50% of dogs will die within 4-6 months of diagnosis. This is a bad disease...

Chemotherapy can be used alone in certain circumstances, when temporary palliation is desirable and surgery cannot be done (most of the time this is in tumors of the heart that are considered inoperable). Metronomic chemotherapy (lower doses administered more frequently) may be equally effective to conventional chemotherapy, but does not appear to be better. Which to choose is a matter of convenience (frequency), how well dogs tolerate the medications (side effects), and other individual factors or preferences. New experimental therapies have not yet shown efficacy. A number of isolated reports exist, but none have held up in larger studies. Several new drugs are under investigation, but participation in clinical trials should be an informed decision with clear understanding that a clinical trial is an experiment.

There is a report from the 1980's that suggested immunotherapy would be effective to treat hemangiosarcoma. The compound used then has recently become available again, and so will probably be put to the test in new studies. Other immune approaches have not shown better results than the standard of care, but there are many reasons to continue investigating this treatment modality.

Many (most or all) products marketed on the internet and elsewhere that are supposed to "boost the immune system" and/or to cure this disease have not been shown to be effective in controlled clinical studies. Buyer beware. There are far too many predatory people with profit motive that prey on desperate owners. They also like to "blame" practitioners of veterinary medicine for being hostile to their products (there is no hostility, just skepticism when proof is provided as anecdotes or testimonials instead of as data). I also should warn that many new "tests" being marketed by reputable diagnostic labs are not especially useful, except in very specific circumstances, so I encourage owners to ask "why are we doing the test?" and "what is the benefit?" (How do positive or negative results help us?) and inquire about options, just like they would when it comes to treatment. The final decision on how to approach a diagnosis and how to treat should be guided by educated assessment of all options and not by coercion or by blind faith.

I hope this helps answer the question. I realize I may have rambled and it may not make a lot of sense on first read, but I wanted to be as thorough as possible.

Thanks again for all your support. I can tell you that our work is generating incredibly exciting data that will undoubtedly help us understand progression and treatment for the disease. We still need to get our hands around how to tackle the issue of heritability.♦

(Editor's note: We wish to sincerely thank Dr. Jaime Modiano for sharing his time and vast knowledge on hemangiosarcoma with the PWD!)

DONATION FORM



The Portuguese Water Dog Foundation, Inc.
P.O. Box 203
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Tel 610-707-2589

The Portuguese Water Dog Foundation, Inc. needs your help and support to fund research to improve the quality of life and health of our Portuguese Water Dogs. Your **tax-deductible** donation, **in any amount**, would be greatly appreciated. In addition to personal donations, a donation may be made in memory or honor of a friend or loved one, whether human or canine. Donors' names will be kept anonymous upon request.

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- Dr. J.D. Northway in memory of Ann Northway, Cassie & Splash
- In honor of the members & friends of the Nutmeg Portuguese Water Dog Club who purchased the 2012 calendar with the profit earmarked for cancer research
- Paulsen Family Foundation
- Geri Zuckerman

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- The Portuguese Water Dog Club of America in memory of Pat Qvigstad

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- Gwen Anderson
- The Colorado Portuguese Water Dog Club is offering this donation to the Portuguese Water Dog Foundation in honor of the following beloved companions who crossed the Rainbow Bridge in 2011:
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"Onyx" - Valkyrie's Black Onyx CDX NA NAJ RN CGC TDIA Loved by Ilse de Granda
"Galli" - Bayswater Galileo of Sundance Loved by Dr. Hill & Bettie Hastings
- John & Susan Cucura
- Diva Fund in memory of Cutwater's Dark and Divine Diva (AKA Diva)
- Amanda Ford as a Thank You to all those who contributed to & purchased the "Nauti Dogs of the Pacific Northwest Calendar"
- Fred & Susan Forman in memory of Cypress Bays Aviator Magellan
- Verne Foster
- Alan & Margeaux Frank in honor of Buffy Nicolas
- Pat Kolvek in memory of Chessie & her sister Allie, & to help stop cancerous tumors in our dogs
- Lily & Colin McCullough in memory of Stella & in honor of Sadie, Callie & Sophie
- Michael & Linda McLean
- John Northway & Lisa Grote in memory of Ann Northway, Splash & Cassie as well as in honor of J.D. Northway and Polly
- Portuguese Water Dog Club of Northern California
- Dr. Mark & Jill Roudebush
- Stan & Milarie Rude in memory of BIS CH Fox Isle Wind Point's Keeper, AOM -- Jesse
- Donna Shalala & The Cheka Fund at The Miami Foundation
- Gloria & Mike Sullivan
- Elaine & Mark Suter in memory of CH Olympia Do Vale Negro
- Jennifer Walsh in memory of "Splash" Pratt

Boatswain \$100-\$249

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- Aspencoves Glory Days in memory of Pat Qvigstad
- Cammi Avery in memory of Boomer Avery & Joaquin Conger
- Steve & Karen Begin in memory of Myrtle Rimmer
- Deb Bender in memory of Pat Qvigstad
- Deb Bender in memory of CH Deewal Oreo Speedwagon Aries, "OREO"



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Looking for reasons (or excuses) to support the PWD Foundation and health research throughout the year? You can show your support and at the same time acknowledge a human or PWD friend or family member. Send a donation to honor that friend or a memorial donation in the memory of a departed friend. The PWD Foundation will send a card embossed with our logo acknowledging your generosity to the person or family you designate. ♦

AKC CHF CO-SPONSORED RESEARCH PROGRESS REPORTS *(Continued)*

increased utilization, reduced turnover of mRNA without enhanced translation, increased turnover of IL-8 protein, blocked protein secretion under these conditions, or even intracellular utilization (binding to IL-8 receptors within intracellular compartments). In other cells, both IL-8 gene expression and protein synthesis are reduced. Moreover, addition of exogenous IL-8 to hemangiosarcoma cells at physiologic levels (i.e., within the range measured in culture supernatant) leads to growth arrest of hemangiosarcoma cells, and blocking the interaction of endogenous IL-8 (made by the cells) and the IL-8 receptor using neutralizing antibodies increases growth of hemangiosarcoma cells. We have further uncovered a relationship between the stem cell signaling factor, Slug (Snail-2), and IL-8. The importance of Slug in maintenance of the stress-phenotype is of great interest, as this protein is intimately involved in generation of cancer stem cells in other models, and modulation of IL-8 may be a consequence of Slug activity. The importance of Slug in maintaining vital hemangiosarcoma cell growth and survival, as well as generation of cancer stem cells, and the role of IL-8 to induce cell cycle arrest vs. cell death will be areas of emphasis for the second year of this project. ♦

Boatswain \$100-\$249(cont'd)

- Leon Benson & Family in memory of CH Magico Sobressair dos Pinhos "Sophie"
- Leon Benson & Family in memory of UGRACH UKC/AKC CH Deewal Oreo Speedwagon Aries, RN, CD, OA, OAJ, TDIA, BROM, CPE3, HeartDog "Oreo"
- Karen Berggren in honor of the PWD PSG
- Benita Bottom-Svitchan & Tag Along PWDs wishing a Happy 1st Birthday to Addy, Alfie, Charlie, Holly, Luna, Maji, Puck and Sab
- Benita Bottom-Svitchan Siena, Savoy & Sabato for friends in memory of Ivana, Allie & KoKo
- Lance & Deonne Boxer
- Lucia Dudley in memory of Rosie
- Barbara Floch, Cosmos Reg. in honor of the PWD PSG
- Barbara Floch, Cosmos Reg. in memory of Pinehaven Casablanca, Bogey
- Fred & Susan Forman in honor of the PWD PSG
- Friends of Sarah Kahn & Bean in memory of Bean - HIT CH Fairwind's Ponto Branco Cafe VCD2 UD MX MXJ NAP CWDX PROM
- Fay Gallus / Richard Sweet in memory of our dogs (PWD)
- Vicki & Ken Goldberg in honor of Blue, Maggie, & Indy
- Monica Hadrian & Stephen Lawroski in memory of Mambo
- Kimberly Hanson in honor of the PWD PSG
- Angela Harding in honor of The Rain City "Coffee" Litter
- Pat Hogan in honor of Dr. Richard Bennett
- Susan Hopkins & Chulsa Kennels in honor of the PWD PSG
- Mr. & Mrs. Joseph A. Horgan in memory of Ronan, our #1 PWD
- Scott & Liz Kantor in memory of Moses Kantor
- Krauss Family in memory of Zephyr and Sam
- Haven & Alan Lane in loving memory of our Tejo Seago
- Dr. K Michael & Linda Laughlin
- Arthur & Roberta Levin in memory of our beloved PWD Bissa Levin
- Cindy & Jeff Lewis in honor of Dauber & thanks to the WSU Vet Teaching Hospital Oncology Department
- Lou Ann & Bob Lindquist in memory of Teddy Bear
- Warren Lloyd in honor of the PWD PSG
- Thomas & Linda Majcher
- Pam Marshall
- Pam Marshall, Marty Smith & Pete Yurka
- Mary Ann & Brian McGunigle
- Heather, Rob & Berit Morrissey in honor of Rockmere's Isabella Do Mar "Bella"
- Sanford Morse in memory of Gus
- Barb & Don Niemann in memory of Ron Holden
- Kathie Peightal in memory of "Doc" Sunnyhill Kryptonite at RM
- Mike & Kristi Portugue in memory of Neptune
- Susan & Win Priem
- Nancy Reinisch in honor of Jodi Whetzel & Aspencove's Maji
- Marilyn Rimmer
- Candice Rosen
- Sue & Steve Rosenstein in memory of CH Sunnyhill Gabriella of Noreast (Gabby)
- Stan & Milarie Rude in memory of Molukie
- Stan & Milarie Rude in memory of CH Blu Water Fleur Delacour, AKA, DellaDo
- Robert & Virginia Santoli in memory of Dexter, Maggie & Gidget
- Marge & Charles Schreiber in memory of Mildred Reinert
- Lynne Schwartz-Rivendell Kennel in memory of Susan McMahon
- Joan Sennett & Dick Tewes in memory of our beloved Schooner
- Jim & Phyllis Stanton in memory of Augusto (Gus) 3/18/97 - 12/20/10
- Susan Straight & Elona Meyer in memory of Margo & Harry
- Cory and Anne Tinker in honor of the PWD PSG
- Anne & Dennis Wentz in honor of Chessie
- Lisa Wiley in honor of the PWD PSG

Boatswain \$100-\$249(cont'd)

- Penny Yamamoto wishing a Happy one year Birthday to their wonderful puppies – Timbermist "Corzo" and Timbermist "Annie"
- Penny Yamamoto in memory of Pat Qvigstad
- Robert Yellowlees

Sailor \$50-\$99

- Mary Barbara & Michael B. Alexander
- Charley & Frank Arruda & Leala in memory of Revo & Dicey for D12CA-028 Research
- Leslie Wolfe Arista in memory of Ravi Kocher
- Deb Bender in memory of Deewal Oreo Speedwagon Aries, "OREO"
- Ann Benninger in honor of the PWD PSG
- Anthony & Judy Berry-Price in memory of Ron Holden
- Maxine Brainer in memory of Harley & Hannah Brainer
- David Buchheit (Aarion's) in honor of the PWD PSG
- Kenneth Buckwalter
- Kathy A. Bumiller - Sweetwater PWDs in memory of CH Della Do!! Thanks for letting me be a small piece in your life by finishing you to your championship & being my "Grand dog"
- Ann Camp in honor of the PWD PSG
- Linda Campbell & Linda Hinkle in honor of the PWD PSG
- Linda Carey in memory of "Gabby" – CH Sunnyhill Gabriella of Noreast
- David W. Carroll
- Bud & April Carter in memory of our beloved Gabbie
- Colorado Portuguese Water Dog Club in memory of Marilyn Bowen
- Jo-Ann Curnow in honor of the PWD PSG
- Bill & Judy DeSana
- Diamante PWDs, Jim & Kimberly Beach in honor of the PWD PSG
- Joyce & Doug Dreyer in memory of our beloved Murphy 2003-2011
- Roslyn Eskind in honor of the PWD PSG
- Amanda Ford in honor of the PWD PSG
- Jane & Stu Freeman in honor of the PWD PSG
- Therese Freeman in honor of Bombardier
- Melissa Furmanek in honor of the PWD PSG
- Peter Gardner & Patty Smith in honor of PWD "Atticus"
- Lisa Genovese wishing a Very Merry Christmas to Robert & Jeanne Genovese
- Amy Gilroy in memory of Ron Holden
- Betty Gray in memory of Stella Lou Bauman
- Dorothy Hankinson in honor of the PWD PSG
- Kimberly Hanson in memory of Oreo
- Laura Hardman in honor of the PWD PSG
- Chris Harris in honor of the PWD PSG
- Angela & Stan Harding, Rain City PWDs in honor of the PWD PSG
- Petro Haring – Sandstone PWD in honor of the PWD PSG
- Rita Hasel in honor of the PWD PSG
- Susan Heath in honor of the PWD PSG
- Pat Hogan in memory of Pat Qvigstad
- Pat Hogan in honor of the PWD PSG
- Hallie Howe in honor of the PWD PSG
- Linda & Krista Hunt, Kalista in memory of Kalista's Arkas Starboy loved & missed by Barb & Jerry Zeller
- Linda & Krista Hunt, Kalista in honor of the PWD PSG
- Beverly Ironside in memory of Max, Ghillie and Grace
- Bea Jennings in honor of the PWD PSG
- Mimi Karlsson in honor of the PWD PSG
- Karma Portuguese Water Dogs in honor of the PWD PSG
- Ralph & Karla Klumpp in memory of Abby
- Bobbe Kurtz wishing a Happy 13th Birthday to Starview's Sea Siren

Sailor \$50-\$99(cont'd)

- Janet Lancaster in honor of the PWD PSG
- Carol Rae & Andrew Lanza in honor of Belle
- Sandra Lappi in honor of the PWD PSG
- Karen & Randy Latham in memory of Chessie
- Candace Lawhorne in honor of Robel Wind at Rivergate & Kimlyn's Daydream
- Carol Mattingley & Ann Bowley in memory of Mildred Reinert
- Carol Mattingley & Ann Bowley in memory of Myrtle Rimmer
- Carol Mattingley & Charles Schreiber in memory of Pat Qvigstad
- Yvonne McCredie in memory of "Comet"
- Jane McEwen in honor of the PWD PSG
- Angela Miler in honor of the PWD PSG
- Mart Miller in memory of Legado Deusa de Ashbe RN AWD
- Barbara & Donald Niemann in honor of the PWD PSG
- Nightskye PWDs in honor of the PWD PSG
- Barbara Nugent in loving memory of Lili
- Jim and Deborah Nungesser in memory of Abby, Cooper and Potter
- From the members of the Nutmeg Portuguese Water Dog Club as a Thank You to Melinda Harvey
- From the members of the Nutmeg Portuguese Water Dog Club as a Thank You to Sheryl Shaker
- Leslie Osterhout in honor of the PWD PSG
- John and Diane Parks in memory of CH Anelakia I Lokelani
- Lisa Penfield in memory of KoKo Penfield
- Lisa Penfield in memory of Wrigley Penfield
- Phoenix Veterinary Hospital in memory of Ravi Kocher
- Cindy Probst in honor of the PWD PSG
- Janice Reilly in honor of the PWD PSG
- Marilyn Rimmer in honor of the PWD PSG
- Marilyn Rimmer in memory of Fenway
- Marilyn Rimmer in memory of Maise
- Marilyn Rimmer in memory of Seven
- Marilyn Rimmer in memory of G.D. Spradlin
- Barbara & John Rossi in memory of Jamie
- Jill Roudebush in honor of the PWD PSG
- Stan, Milarie & Mickey Rude in memory of Pat Qvigstad
- The Crew at Ruff Wave PWDs in honor of the PWD PSG
- Martha Ruskai in honor of the PWD PSG
- Julie Rust in honor of the PWD PSG
- Saltydawg PWDs, Jim & Karen Ash in memory of Saltydawg As Time Goes By, Bruin
- Saltydawg PWDs, Jim & Karen Ash in memory of Turbo
- Saltydawg PWDs, Jim & Karen Ash in honor of the PWD PSG
- Santa Clara Dog Training Club in memory of Ron Holden
- Virginia Santoli in honor of the PWD PSG
- Sandy Saybolt in honor of the PWD PSG
- Seadancer PWDs in honor of the PWD PSG
- Heather Shilo in honor of the PWD PSG
- Cindy & Ezra Simon in memory of our beloved "Cisco" Aka: Menino Francisco Da Praia
- Kami Smith & Gene Boyd in memory of Molly Brown
- Southern California Portuguese Water Dog Club in memory of: CH DeSagres Star CDX RE AX AXJ CWDX GROM - Carlotta CH Anelakia I Lokelani - Ivy Legado Deusa de Ashbe RN AWD - Sadie
- Kathleen Souza in honor of the PWD PSG
- Barb Stanek in honor of the PWD PSG
- Elaine & Mark Suter in honor of the PWD PSG
- Kim & Becky Suthers in memory of Peppermint

Sailor \$50-\$99(cont'd)

- Drewsar PWD, Mari, Sara and Herb Szauerzopf in honor of the PWD PSG
- Tabitha Thompson in honor of the PWD PSG
- Troy & MaryBeth Turner in honor of the PWD PSG
- Denise Wallentinson in memory of Stephanie Yee & Koko
- Mrs. Ra Walmsley in honor of the PWD PSG
- Janis Watts in memory of Legado Deusa de Ashbe RN AWD
- Marvin Weinberger
- Judy Weinstein in memory of Turnabout Triple Sec VCD3 MX MXJ TDX UD WWD "Tripp"
- Margaret White congratulating all the Deercase PWDs who titled in 2011
- Sue Wilcox-Hall in honor of the PWD PSG
- Sian Wilstrup in honor of the PWD PSG
- Jerry & Kim Wolcoveick in memory of Alice Vicha and all the Norvic's PWDs
- Theresa Zorad in honor of the PWD PSG

DECK HAND up to \$49

- Anonymous
- Carol & Warren Cooke in memory of Allie
- Carol & Warren Cooke in memory of Beau
- Ragmop Devlin
- Barbara & Michael Guerin in memory of Stella, our "crazy PWD", who will be forever in our hearts
- Mary & Ron Guziak
- Julie Hicks in memory of AM/CAN/INT'l CH Stargazer's Hit the Deck CD AX AXJ RE CWDX GROM "Decker"
- Linda K. & Krista K. Hunt, Kalista PWDs in memory of Pat Qvigstad
- Linda K. & Krista K. Hunt, Kalista PWDs in honor of "Krickie" Kalista's Knee Jerk Reaction CGC Delta Therapy Dog
- Linda K. & Krista K. Hunt, Kalista PWDs in honor of Kalista's Lil' Sip of Mocha RN AX MXJ NF THD for her MXJ
- Linda & Krista Hunt, Kalista PWDs in memory of CH Lake Breeze Nautilus Captain Nemo UDX RN NA NAJ loved & missed by Dorothy Jackson
- Linda K. & Krista K. Hunt, Kalista PWDs in memory of "Tarpon" CH Peja Conch Cruiser CD AWD
- Karen Latham in memory of Koko
- Carol Mattingley in memory of "Oreo" - Deewal Oreo Speedwagon Aries
- Janet & Andrew Masetti in memory of Brinca
- Cheri & Paul Mezydlo
- Karen & Walter Paulick as a Thank You to Marge & Charles Schreiber for selling us the greatest dog - Misty
- Peggy Ann Perkins in memory of Madeira's Truly Scrumptious "Zoe"
- Peggy Ann Perkins in memory of Rocco
- Marge & Charles Schreiber in memory of Oreo
- Marge & Charles Schreiber in memory of Liv
- Kathleen Skeels
- Kathleen Souza in memory of Am/Can/Int'l CH Stargazer's Hit the Deck CD AX AXJ
- Kathleen Souza in memory of CH Cortereal Poseidon Adventure RN AOM AWD
- Kathleen Souza in memory of CH Deewal Oreo Speedwagon Aries CD RN OA OAJ
- Kathleen Souza in loving memory of Ch. Anelakia I Lokelani
- Kathleen Souza in loving memory of Legado Deusa de Ashbe
- Norman & Susan Stewart in memory of Myrtle Rimmer
- Helen & David Walton in memory of Dory
- James and Vanessa Ward in memory of Allie
- Janis Watts in memory of "Molly" Legado Fresca De Flagstaff
- Catherine & Nagasiva Yronwode in memory of Eris and in honor of Sophie