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ABCF MESSENGER

Official Newsletter of the American Boxer Charitable Foundation, Inc.

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GIVING THE NON-EGGHEADS AMONG US A CLEARER UNDERSTANDING OF SCIENTIFIC RESEARCH

The success of the ABCF in raising large amounts of money to fund research into Boxer-related diseases is well documented and understood. We are well aware, however, that the results of the studies we support are a little more difficult to understand and appreciate. There is a good reason for this: the term "Research Scientist" conjures up images of a serious, white-coated genius hunched over a bubbling beaker or furiously scribbling arcane formulas on a giant blackboard. In fact, research scientists look, dress, and act pretty much like the rest of us. It's the manner in which scientists present their work that the differences between "them" and "us" become apparent. They tend to use really big words and tongue-twisting phrases to describe their studies. We have to take into account the fact that the results of these studies are published in scientific journals and are intended to be read and reviewed by the scientific community. Certainly some members of the Boxer Community are familiar and comfortable with words like "enzyme telomerase" or "receptor tyrosine kinase inhibition" but to the rest of us, the non-eggheads, these are a bunch of letters strung together that have no meaning. Therefore, the ABCF has a real challenge in demonstrating to our contributors the fruits of our labor. It is extremely difficult to convince researchers to describe their work in a way the general public can readily understand: it's quite difficult to explain scientific subjects without using scientific language. Also, we are inclined to have more emotional responses to the issues being discussed whereas scientists take a more clinical approach. This does not mean they are unemotional about their work—in fact they tend to be quite passionate. They just express that passion in clinical terms.

Contributors to the ABCF are entitled to know that their dollars are well spent, that progress is being made in the fight against the diseases that affect the breed we love. The Foundation has made it clear to the institutions sponsoring funded research that we fully expect to be privy to the findings of those studies. It must be understood that researchers' primary obligations in that regard are to the institutions themselves, therefore, though available to us, the reports are written for scientific review and not the general public. Researchers not only willing and able to 'translate' scientific reports for us, but also able to find the time to do so are a rare find. Therefore we are delighted to present the articles on the following pages provided by Noriko Tonomura, DVM, PhD and Purina Pro Club. We believe readers will find both articles clear, concise, and highly readable.

Thanks to Judy Voran for obtaining these articles for the ABCF Messenger.

PROGRESS REPORT ON ABCF FUNDED GRANTS

Noriko Tonomura, DVM, PhD
Dog Disease Gene Mapping Project
Broad Institute of MIT and Harvard

How far have we come in finding cause for hereditary dog diseases?

After sequencing the dog genome and developing the tools to find causes for inheritable diseases in dogs, The Dog Genome Project at Broad Institute of MIT and Harvard are actively working on multiple projects with collaborators through out the world. Please check the list below (listed by disease) to find out more.

Please consider helping research: Your Boxer can help!

We would like blood samples from your Boxers. We are going to extract DNA from blood cells, and we only need 5ml (1 teaspoon) of blood in a purple top tube (a.k.a. EDTA tube).

We need samples from dogs that are:

- Suffering from a hereditary diseases, especially ones listed below
- Older (8+) and healthy dogs, meaning ones without hereditary diseases

If you have multiple dogs, please consider donating samples from everyone. We accept samples from any dogs in terms of their relation to each other.

In order for us to put your dog's DNA to good use, it is also critical for us to obtain a record of proper diagnosis from your veterinarian. Please do as much as you can (i.e. histology, ultrasound, etc) to aid making an accurate diagnosis, and please remember to send us a copy of your dog's medical record.

Current active projects involving Boxers

Hemangiosarcoma (HSA)

HSA is a rapidly growing and highly invasive, malignant tumor of blood vessels. It can grow large without being noticed, and often cause of death is due to rupturing of the tumor resulting in massive bleeding.

Breeds needed for our study: Golden Retrievers, Labrador Retrievers, Chinese Shar-Peis, **Boxers**, Pugs, and Rhodesian Ridgebacks

Current status: We have finished genome wide screening (Golden Retriever) and fine-mapping (Boxer and others), and we are looking into a few candidate genes closely. We are currently collecting tumor sample -- if your dog has, or is suspected to have hemangiosarcoma, and if you would like to send us a tumor sample, please contact Dr. Truesdale at Central Ave Veterinary Clinic, Seekonk MA (508-761-8525), or Dr. Tonomura

(tonomura@broad.mit.edu).

Main collaborator: Chieko Azuma (Tufts University)

Funding: AKC/CHF

Mast Cell Tumor (MCT):

MCT is cancerous proliferations of mast cells. Although they can and will spread throughout the body, the danger from mast cell tumors arises from the secondary damage caused by the release of chemicals that they produce. These chemicals can cause systemic problems that include gastric ulcers, internal bleeding, and a range of allergic manifestations.

Breeds needed for our study: Golden Retrievers, Labrador Retrievers, German Shepherd Dogs, Pugs, Shar-Peis and **Boxers**

Current status: We have started genome wide screening (Golden Retriever), and getting ready for fine-mapping. We still need samples from Golden Retrievers as well as Boxers that are affected by Mast Cell Tumor.

Main collaborators: Cheryl London (Ohio State University), Lisa Barber (Tufts University)

Funding: Morris Animal Foundation

Lymphoma

Lymphoma is a cancer of the lymphocytes, which can occur in the lymph nodes, spleen, liver, and other organs. Characteristics are high white blood cell count, swollen lymph glands, lethargy, and loss of appetite. It is a treatable cancer, but if left untreated, it will eventually lead to death. There are many subtypes of this cancer, but most are categorized as B cell lymphoma, or T cell lymphoma.

Breeds needed for our study: Golden Retrievers, Cocker Spaniels, Rottweilers and **Boxers**

Current status: We are actively collecting samples. Since there are many subtypes exist, making an accurate diagnosis is very critical. If your dog is newly diagnosed with lymphoma, consider contacting Dr. Tonomura (tonomura@broad.mit.edu) **before** you start any type of treatment.

Main collaborators: Matthew Breen (North Carolina State University), Jaime Modiano (University of Minnesota), Kristine Burgess (Tufts University)

Funding: Pending

Mammary tumors

Mammary tumors are tumors of the mammary gland. They are the most common tumors found in unspayed female dogs. Several subtypes exist but seem to segregate in the same families.

Breeds needed for our study: English Springer Spaniels, **Boxers** and Cocker Spaniels.

Current status: We are actively collecting samples. Since there are many subtypes exist, making an accurate diagnosis is very critical. Please have your veterinarian perform histological examination of the tumor.

Main collaborators: Henrik von Euler (Swedish University of Agricultural Science), Elizabeth McNeil (University of Minnesota)

Funding: Pending

Degenerative Myelopathy (DM):

DM is a degenerative neurological disease where the dog's immune system attacks both the myelin and axons of the nerves in the spinal cord (similar to Multiple Sclerosis in humans). The first signs are hind limb weakness and lack of coordination, which can progress to the inability to walk at all.

Breeds needed for our study: **Boxers** and Corgis

Current status: We have started genome wide scan using Corgis, and we are still actively collecting samples from affected/unaffected Boxers and Corgis. In order to characterize DM in Boxers, we also need spinal cord samples from affected Boxers. If your Boxer is suffering from DM and would like to contribute by sending spinal cord sample upon necropsy, please contact Dr. Joan Coates (CoatesJ@missouri.edu).

Main collaborator: Joan Coates (University of Missouri)

Juvenile Renal Dysplasia (JRD):

JRD is an inheritable condition affecting the developmental maturation of the kidney. The key clinical signs of JRD include (but are not limited to) excess water intake and urination from young age (8 wks to 2 years of age), and small/irregular shape kidneys observed by ultrasound examination. JRD-affected Boxers often experience renal failure at very young age.

Breeds needed for our study: Boxers and Shih Tzus

Current status: We have started genome wide scan, and we are still actively collecting samples from affected Boxers, and their Dam, Sire and healthy siblings/half-siblings. In order to characterize JRD in Boxers, we also need kidney samples from affected

Boxers. If your Boxer is suffering from kidney failure and would like to contribute by sending kidneys upon necropsy, please contact Dr. Noriko Tonomura (tonomura@broad.mit.edu).

Main collaborator: Åke Hedhammar (Swedish University of Agricultural Science)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Boxer cardiomyopathy, or ARVC consists primarily of an electrical conduction disorder which causes the heart to beat erratically some of the time. If the erratic beats occur infrequently and singly, the dog will probably not have symptoms of heart disease. If the erratic beats occur in sequence, weakness, collapse or sudden death may result.

Breeds needed for our study: **Boxers**

Current status: We have finished genome wide scan and fine-mapping stage. We have identified a strongly associated region that contains many genes, and we need to narrow down to just a few genes.

Collaborators: Kathryn Meurs (Washington State University), Åke Hedhammar (Swedish University of Agricultural Science)

The American Boxer Charitable Foundation Interactive Memorial Wall

The ABCF Interactive Memorial Wall CD is a PowerPoint presentation dedicated to the memory of the wonderful Boxers we have lost. We cherish the memory of each and rededicate ourselves to addressing the health issues that affect our beloved Breed. The Wall is perpetual and will be added to each year to remind us why we support the Foundation and the future of Boxers.

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HEMANGIOSARCOMA RESEARCH FOCUSES ON GROWTH SIGNALING PATHWAYS

Excerpted with permission from The Purina Pro Club Boxer Update, July 2007

Hemangiosarcoma has become one of the most feared cancers in Boxers. Besides being increasingly common, it usually develops unnoticed with a dog showing few or no signs until the cancer progresses to the final stages.

At this year's American Boxer Club National Specialty held in May at Fort Mitchell, Ky., the Charitable Trust Foundation presented a slide show featuring photographs of notable Boxers that had recently died. One after another had died from cancer, and among them were dogs that had died from hemangiosarcoma.

Researchers across the country are working to learn more about the causes of canine cancer. Hemangiosarcoma is particularly challenging because it is an aggressive cancer that usually has metastasized, or spread, by the time it is diagnosed. This cancer comes from endothelial cells that line the blood vessels. As a result, the tumor has a constant blood supply and access to blood vessels, which helps to facilitate its spread throughout the body.

The good news for owners and breeders of Boxers is that researchers are making steady progress in the research of hemangiosarcoma. A recently completed study at the Oregon Cancer Center for Animals (ORCCA), located at Oregon State University, tested a new class of drugs, tyrosine kinase inhibitors, to determine their effectiveness in stopping cancer cell growth. Though the work is in the early stages, Stuart Helfand, D.V.M., professor of oncology and director of oncology services, is optimistic that drugs that interrupt growth signaling pathways may

one day show promise in treating hemangiosarcoma.

Meanwhile, Jaime Modiano, V.M.D., Ph.D., the recently appointed Perlman Professor of Comparative Oncology at the University of Minnesota, led research that resulted in a blood test to detect hemangiosarcoma when the cancer is in its early stages and thus when dogs have a greater chance of receiving effective therapy. The research continues to determine how early the blood test can detect disease and how to pinpoint cancer cells for effective therapy. Modiano developed the blood test while he worked at the University of Colorado at Denver and Health Sciences Center.

A Prevalent Cancer in Dogs
Hemangiosarcoma most often originates in the spleen. In time, the tumor ruptures, showering tumor cells throughout the abdomen where they implant and grow. Many dogs die from acute internal hemorrhaging secondary to the tumor rupturing or from the rupture of the tumor near or in a critical area. Veterinarians primarily see hemangiosarcoma in the spleen, liver, skin and heart. Other less common primary sites are the kidneys, mouth, muscle, bone, brain, urinary bladder, and peritoneum, a large membrane in the abdominal cavity that lines the abdominal cavity and organs. Though tumors can become larger than a grapefruit, sometimes it's not possible to feel the tumor during palpation. The most common sites of metastases are the lungs and liver, yet in dogs with multiple tumors, it may be difficult to determine the primary tumor site. Hemangiosarcoma occurs more often in dogs than any other species and repre-

sents about 7 percent of all canine cancers. The prevalence in Boxers is not known exactly. Other breeds at risk are German Shepherd Dog, Golden Retriever, Great Dane, English Setter, Pointer, and Sky Terrier. The cancer is most commonly seen in male dogs between 8 and 10 years of age, although it also is seen in young dogs.

Signs of hemangiosarcoma are subtle. Once the cancer has spread, a dog may show physical weakness, a distended abdomen, rapid pulse, fast breathing or panting, weight loss, pale gums, and anemia. Lethargy, depression and lack of appetite are common. Early signs of the cancer may be intermittent. A dog's breathing may become labored because internal bleeding reduces the oxygen content in the bloodstream. However, if the bleeding stops and the dog reabsorbs blood from the abdomen, a process called autotransfusion, a dog may appear normal. In addition, lethargy may resolve, and appetite may improve.

If hemangiosarcoma is discovered early, when the tumor is easiest to treat with surgery and chemotherapy, a dog may survive seven to eight months. After surgery to remove a tumor, a dog can leave the hospital two days later, tail wagging and feeling great, but the tumor will regrow in two to four months, Helfand says. Without treatment, life expectancy is about two months.

The 'Lock-and-Key' Approach
At the Oregon Cancer Center for Animals, which opened two years ago, Helfand directs research that concentrates on a "lock-and-key" approach to understanding cancer.

"A 'lock' is a protein, or a receptor on a cell that is specific to the cell's function, and the 'keys' that fit the lock are growth factors that stimulate endothelial cells and bind the receptors, or locks," he explains. "Cancer is a disease in which bad cells grow rapidly, and sometimes a lock may mutate and switch on without the need to receive signals from an external key," Helfand says. "As we learn more about these lock-and-key interactions, we may be able to better understand the behavior of hemangiosarcoma and other cancers. "If we can shut down the cancer pathway when the key is in the lock, we may be able to block normal internal signaling that triggers the cell nucleus to divide. If we could prevent the key from going into the lock or disrupt the downstream proliferation signals, we could potentially block cancer growth."

Results of the recently completed hemangiosarcoma study, funded by the Morris Animal Foundation, have yet to be published in a scientific journal so Helfand can share limited information about the findings. "We feel comfortable reporting there are potential targets, or so-called locks in the lock-and-key analogy, that are worth pursuing," Helfand says. "Our work concentrated first on determining whether the locks exist and then determining whether it is possible to successfully block the cancer pathways in order to arrest cell growth. "Finding drugs that interfere with these pathways that are well tolerated in dogs will be a challenge but is something that

Recognizing Signs of Hemangiosarcoma

Hemangiosarcoma is often called the "silent cancer" because it develops slowly and is essentially painless. Signs of this lethal cancer are frequently not evident until the advanced stages when the tumor is resistant to treatment.

Owners should watch for signs of hemangiosarcoma and report them right away to their veterinarian. Signs of hemangiosarcoma include:

- **Intermittent fatigue;**
- **Weight loss or lack of appetite;**
- **Pale gums;**
- **Unusual bleeding;**
- **Rapid pulse;**
- **Fast breathing or panting;**
- **Sudden or unexpected weakness;**
- **Waxing and waning weakness;**
- **Development of lumps or tumors; and**
- **Depression.**

potentially can be addressed in future research. The important thing is that we can use the lock-and-key strategy to find more effective treatments for hemangiosarcoma as well as other canine cancers. "I believe it is just a matter of time, which partly is dependent on additional funding, before we learn how to adapt growth factor blockers so they can effectively help dogs diagnosed with hemangiosarcoma."

In the meantime, until an effective therapy is discovered for Boxers diagnosed with hemangiosarcoma, breeders and owners should pay attention for subtle signs of this life-threatening cancer. The sooner the cancer is diagnosed and treatment can begin, the more likely a dog will live longer. ▲

Purina appreciates the support of the American Boxer Club and particularly

Joyce Campbell, D.V.M., chairwoman of the ABC Health and Research Committee and a trustee of the American Boxer Charitable Foundation, in helping to identify topics for the *Purina Pro Club Boxer Update* newsletter.

The American Boxer Charitable Foundation is a major supporter of the Purina health programs. Your continued support of the Foundation helps ensure that the fight against canine diseases that affect Boxers is ongoing and productive.

Learning More About Cancer

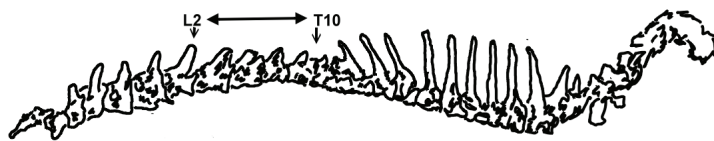
To learn more about the treatment of hemangiosarcoma and other canine cancers, you may visit the following Web sites:

- The Encyclopedia of Canine Veterinary Medical Information at www.vetinfo.com/dencyclopedia/hemangiosarcoma.html.
- The Modiano laboratory at the University of Minnesota at www.modiolanlab.org/cancer/cancer_hemangiosarcoma.shtml.
- The University of Georgia College of Veterinary Medicine at www.vet.uga.edu/VPP/clerk/frankhauser/index.php.
- The Perseus Foundation at www.perseusfoundation.org.

LONG-AWAITED DM STUDY UNDERWAY—SPINES NEEDED

WHAT YOU SHOULD KNOW

- Owners make the decision *when* to euthanize affected dogs. The study needs samples from dogs at various stages of the disease. Euthanasia is performed at the owner's vet with the owner present (if desired).
- Veterinarians surgically remove a portion of the spine immediately following euthanasia. The entire spine is not required, only the vertebrae from T10 to L2 as shown in the diagram. This represents a relatively small section of the spine.
- A concise, accurate veterinary history is vital to



the study therefore owners of affected dogs should maintain close contact with their vet throughout the progression of DM. Additionally, x-rays and any other tests are requested.

- The submission form for samples for this research can be found on the ABCF web site.

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Phenotypic Characterization and Mapping Genes Associated with Canine Degenerative Myelopathy in Boxers

Investigators: JR Coates, K Lindblad-Toh, GS Johnson, GC Johnson, DP O'Brien

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Funding Source: American Boxer Charitable Foundation and the American Kennel Club Canine Health Foundation

Participating Breed Clubs: American Boxer Club, Pembroke Welsh Corgi Club of America, Rhodesian Ridgeback Club of the United States

We would like to thank you for participating in this research project. Your involvement with this study is very much appreciated by the project investigators and participating breed clubs. Our ultimate goal for this project is reduce the prevalence of degenerative myelopathy (DM) in the Boxer and other breeds.

Abstract:

Degenerative myelopathy is a disease of the spinal cord causing progressive paraparesis. Though most commonly reported in German Shepherds, high disease prevalence also exists in other breeds, such as Cardigan and Pembroke Welsh Corgis, Rhodesian Ridgebacks, and Boxer dogs. The increased risk in specific breeds suggests a significant genetic predisposition and adds power to mapping any genetic risk factors. The purpose of this proposal is to map genes associated with DM in the Boxer dog and other breeds. We propose characterizing the phenotype in the Boxer dog using sequential antemortem neurodiagnostic testing, and neuropathology. A network of board-certified veterinary neurologists has been established to help diagnose dogs across the country. A small subset of 10 Boxer dogs will be further characterized directly by the principal investigator, to determine if the phenotype and clinical progression is identical to that seen in the Pembroke Welsh Corgi. Genome-wide association mapping will be performed to identify a genomic locus associated with DM in 50-100 affected and 50-100 age-matched boxers using the ~20,000 SNP array. If as expected the same phenotype is seen in Boxers as in the Pembroke Welsh Corgis and Rhodesian Ridgebacks, disease haplotypes are likely to be shared between these breeds. We will thus fine map using Boxers as well as smaller numbers of affected and control Pembroke Welsh Corgis and Rhodesian Ridgebacks. We expect to narrow the region to contain only 1-2 genes. This project will allow for more rapid development of genetic research to identify carrier and affected dogs of DM and thus eliminate the genotype of this late-onset disease from the population. Early, accurate distinction of DM from other neurological disease will facilitate therapeutic trials.