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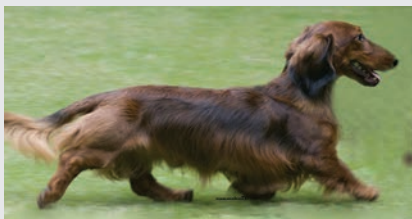
HEMANGIOSARCOMA RESEARCH

Artificial Intelligence Aids Early Detection of Cancer

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DACHSHUNDS MAY BENEFIT FROM HEMANGIOSARCOMA RESEARCH ADVANCES



“Gibson,” pictured above at 11 months old, died of hemangiosarcoma at age 10. His breeder and owner, Anne Carson, said the Longhaired Dachshund was doing well after surgery and chemotherapy, but sadly, the cancer had metastasized throughout his body.

Twelfth Night Dachshund breeder Anne Carson takes to heart the importance of educating Dachshund fanciers about hemangiosarcoma. Her firsthand experiences losing dogs to the aggressive, silent cancer that snares its victims without a sign of illness are insightful and passionate.

Sharing her stories at the annual meeting of members of the Dachshund Club of America (DCA) at the 2018 National Specialty, Carson asked those attending to stand up if they had lost a dog to hemangiosarcoma. Next, she asked if anyone had lost a dog to a tumor with no clear diagnosis, and last, if anyone had found a dog dead after a day or two of vague symptoms. More than half of the attendees were standing. All were listening closely.

Because of the high prevalence of back problems in Dachshunds, it can be a fine line determining whether spinal pain or something else causes a dog to not want to get up. In 2018, when “Gibson” (GCH Twelfth Night Braveheart L), a 10-year-old red male Longhaired Dachshund, was reluctant to stand and refused to eat, Carson attributed the problem to back pain.

It happened three times, though Gibson always recovered overnight — until the last time. Carson, of Atlanta, took Gibson to a veterinary neurosurgeon, presuming her special male would need back surgery. The energetic, funny Gibson had won her over as a puppy becoming the keeper, though it was his brother she had planned would stay.

“The neurosurgeon confirmed that Gibson had no neurological issues, but blood tests led him to conclude that Gibson’s anemia without elevated BUN (blood urea nitrogen) could be the result of internal bleeding,” recalls Carson, a member of the DCA board of directors for 12 years.

“That fear was affirmed after Gibson’s regular veterinarian did an abdominal X-ray that showed a large tumor on the spleen,” she says. “I took him to an oncologist who removed the spleen and the tumor the next day. Meanwhile, the lab results confirmed that the tumor was hemangiosarcoma.”

Carson, who has bred Longhaired Dachshunds since 1982, about one litter every two years, made plans to begin chemo-

therapy treatment as soon as Gibson healed from the surgery.

“I had trouble keeping him calm and confined after the surgery,” she says. “He was in a room by himself but could see the other dogs and wanted to play.”

Seventeen days after beginning chemotherapy, Gibson died. “The cancer had metastasized,” Carson says. “I was totally shocked by his death, because I thought he was doing so well.”

Gibson was not her first Dachshund to die from hemangiosarcoma. Carson lost “Scarlett” (CH Twelfth Night’s Miss Scarlett L) in 2002 at 10 years of age and “Hope” (CH Twelfth Night Hope Diamond L) in 2008 at 12 ½ years of age. Both females were related to Gibson. Scarlett lived three days following surgery to remove her spleen, and Hope survived four months after surgery and 12 weeks of chemotherapy.

“With hemangiosarcoma, when a dog is sick, it’s often too late,” Carson says. “They feel weak because the tumor bleeds, then when the bleeding stops, dogs feel fine again. The best advice I can give is to act fast if you notice anything abnormal. If a dog fails to eat or drink, has pale gums, unexplained vomiting, or refuses to perform usual activities, then you should see your veterinarian. Even if the dog seems perfectly normal the next day, as Gibson did.”

CLASSIFYING TUMORS

The heart-crushing agony of losing a beloved dog to cancer is bad enough. When the cancer takes a dog without signs of illness, it can be traumatic. This is



how it often goes with hemangiosarcoma, a cancer believed to be responsible for the deaths of tens of thousands of dogs in the U.S. each year.

Hemangiosarcoma is an unpredictable cancer that develops painlessly. As with Gibson, Scarlett and Hope, it is often advanced by the time it is discovered. Severe internal bleeding and sudden death are not unusual with this disease. A dog’s breed, age, gender, diet, and environment are not likely to impact the progression of the cancer, experts say.

“It is virtually impossible to pigeonhole this tumor into categories that work for other cancers,” says Jaime F. Modiano, VMD, PhD, the Perlman Endowed Chair in Animal Oncology at the

University of Minnesota. “The most challenging aspect of studying this disease has been accepting that many, and perhaps most, of our preconceived notions about what we thought we knew about the disease were incorrect. In order to make progress, we needed to start with a blank slate.”

Filling that blank slate eventually led to employing artificial intelligence to analyze large and complex data sets that look for defined algorithms and statistics to identify the cancer. This type of analysis could lead to

more accuracy in classifying hemangiosarcoma tumors based on their patterns, explains Dr. Modiano.

At the 2018 Connective Tissue Oncology Society meeting in Rome, Dr. Modiano’s research group introduced artificial intelligence as a way to interpret the results of a test designed to detect cells associated with the presence of hemangiosarcoma in the circulation of dogs. It is yet to be determined whether these cells in the blood are precursors to the tumor, actual circulating tumor cells, or cells

WHEN A DOG HAS HEMANGIOSARCOMA

A silent disease, hemangiosarcoma develops painlessly. The only hints that a dog may have the cancer are recurring lethargy and pale mucous membranes due to anemia. Most dogs have an advanced form of the cancer when it is discovered, which explains why severe internal bleeding and sudden death occur frequently and unexpectedly.

Although this cancer can affect any dog of any age and gender, it is most common in older dogs; more than half of the dogs that develop hemangiosarcoma are over 10 years old. It usually originates from a cell in the bone marrow that settles in the thin layer of cells that line the interior of blood vessels. Although the most common sites for tumor formation are the spleen, skin, heart, and liver, the tumor cells have access to the blood supply, allowing them to potentially seed and grow in virtually any organ in the body.

The disorganized growth of tumor cells in the walls lining the blood vessels disrupts normal blood flow, leading to blood clots and hemorrhage. Mini-hemorrhages can heal quickly with dogs showing only mild signs, but severe hemorrhage from within a tumor can be fatal.

Sadly, most dogs die before treatment can begin. Without treatment, dogs may die in a

few hours or possibly within one to two weeks. With treatment, the expected survival is four to six months, though this is dependent on the tumor’s location. Tumors that occur in or under the skin typically are less aggressive, and dogs whose visible tumors are accessible tend to do better with the standard of care.

The standard of care is surgical removal of accessible tumors, depending on the location, followed by chemotherapy. Treatment is meant to prevent fatal blood loss and to extend life, but is seldom curative. Chemotherapy delays the recurrence of metastasis, which occurs in virtually every dog diagnosed with the cancer.

About 5 to 15 percent of dogs with hemangiosarcoma will survive a year or longer, even with conservative treatment. Because there currently are no reliable tools to determine which dogs are likely to be long-term survivors, anecdotal evidence of long-term survival with alternative therapies is an unreliable indicator of efficacy and could create false hopes and unrealistic expectations for owners and veterinarians. Thus, it is recommended that treatment should be based on objective data.

that are a component of the niche that allows the tumors to grow and eventually metastasize.

“The goal is to deploy a blood test that can detect hemangiosarcoma in its earliest stages before tumors actually form and to pair that detection with rational, targeted drugs that can prevent or significantly delay tumor formation and tumor progression,” Dr. Modiano says.

The researchers at the University of Minnesota have been studying hemangiosarcoma for many years. In 2019, [they will complete a three-year study, the Shine On Project](#), which was supported with \$432,000 contributed by the Golden Retriever Foundation, the American Boxer Club Charitable Foundation and the Portuguese Water Dog Foundation, breeds that show a high prevalence of this cancer.

“The unprecedented collaboration among these three breed club foundations and their dedication to canine health have driven this project forward, helping to make a significant difference for all dogs,” says Dr. Diane Brown, CEO of the AKC (American Kennel Club) Canine Health Foundation, which administers and manages the grant. “This approach to a particularly aggressive form of cancer in dogs has the potential to eventually change the landscape and improve outcomes for all dogs diagnosed with this horrible disease.”

Prior to the start of the Shine On Project, Dr. Modiano and his team developed a blood test to detect the “suspect cells” in



dogs diagnosed with hemangiosarcoma. They also independently developed a promising chemopreventive drug called eBAT, which is a targeted bacterial toxin that is exceptionally safe and has demonstrated efficacy in the treatment of hemangiosarcoma.

With Shine On, their focus turned to refining the test to identify dogs at risk for developing hemangiosarcoma and those that have the suspect cells present in their blood but have no evidence of a tumor, and then using eBAT to attack the hemangiosarcoma stem cells and kill them before they have a chance to form a tumor.

The three phases of the Shine On Project are ongoing. They are:

- **Phase 1:** Defining the parameters for using the blood test to confirm the presence of

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DACHSHUND CLUB OF AMERICA FUNDS TWO HEMANGIOSARCOMA STUDIES



The Dachshund Club of America provided funding of \$20,000 in 2018 to support two canine hemangiosarcoma studies.

A donation of \$15,000 helps support an AKC (American Kennel Club) Canine Health

Foundation-funded [three-year, \\$168,857 study at Tufts University](#). Lead investigator Cheryl London, DVM, PhD, DACVIM (Oncology), research professor at the Cummings School of Veterinary Medicine of Tufts University and Tufts School of Medicine, is studying how the PI3K/AKT/mTOR pathway contributes to hemangiosarcoma cell growth, eventual spread and drug resistance. The goal of this research is to identify combinations of drugs that can effectively target this pathway and more effectively extend survival times.

“Inhibitors of the PI3K pathway have shown promise in blocking the growth of hemangiosarcoma cells in the laboratory,” Dr. London says. “Exactly how this happens is not entirely known, but sometimes these tumors carry mutations that activate the PI3K pathway and thus

enable the cancer to grow and spread. Interestingly, similar PI3K mutations are found in the companion human cancer, called angiosarcoma. We are working with colleagues on the human side studying this cancer to find new, more effective combination therapies to more effectively treat this cancer in both dogs and people.”

A \$5,000 donation to the Morris Animal Foundation is supporting [a study at the University of Minnesota](#) led by Erin B. Dickerson, PhD, associate professor of veterinary clinical sciences. The club also gave \$5,000 to this study in 2017.

The \$172,431 study, which began in 2016, is investigating the abnormal activation of signals that trigger or facilitate the development of cancer. “Signaling pathways are coordinated chemical activities in a cell that collectively control one or more cell functions, and specific pathways are critical for tumor growth,” Dr. Dickerson explains. “We are studying how these identified pathways contribute to hemangiosarcoma growth and whether drugs can interrupt the process to reduce tumor growth and chemotherapy resistance. Our goal is to find a new approach to treat this aggressive cancer in dogs.”

hemangiosarcoma cells to help distinguish between dogs that have the cancer from those that do not. About 80 dogs have been studied, and the preliminary analysis suggests that a family of algorithms separates the four categories of samples being collected: 1) no evidence of disease, 2) benign splenic abnormalities, 3) hemangiosarcoma, and 4) cancers other than hemangiosarcoma.

- **Phase 2:** Determining whether blood testing for hemangiosarcoma cells will help predict when tumors become resistant

to treatment and thus when a dog in remission might relapse. More than 20 dogs have been studied, indicating that the number of suspect cells in blood is relatively stable until animals are treated. This number decreases with treatment, and so it is expected to help track the duration of remission. In future research, the team hopes to gain insights into how therapy management might extend remission times and prevent unexpected life-threatening bleeding episodes.

- **Phase 3:** Establishing how well the blood test works for early



detection and how well eBAT works to eliminate hemangiosarcoma cells before tumors have a chance to form. About 140 dogs are enrolled in this part of the study. Although the analysis is in its early stages, Dr. Modiano says that patterns found in the blood suggest that the test may be helpful in identifying risk for pathological conditions, including splenic abnormalities and cancers.

“We are using artificial intelligence to analyze data from Phase 3,” says Dr. Modiano. “As we hone on the patterns, the accuracy of how we classify samples will improve based on those patterns. Ultimately, we will assign classifications by predicting, or inferring, the probability that unknown samples belong to particular groups that were defined in the training phase.

“Our goal is to reduce the health burden of this cancer in dogs and

humans who develop the rare cancer angiosarcoma, which is similar to hemangiosarcoma. A method to detect hemanigosarcoma in its earliest stages and an effective mechanism for preventing it would be a giant leap forward in the management of this disease.”

Carson welcomes the possibility of recognizing the cancer sooner. “If we could one day understand how to diagnose the cancer in the early stages, it would be wonderful,” she says. “We need to support research of this cancer and get involved in helping others to understand hemangiosarcoma.” ■

Purina appreciates the support of the Dachshund Club of America and particularly Charlotte Borghardt, chair of the DCA Health Committee, in helping to identify topics for the *Dachshund Update*.

DOUBLE YOUR DONATION VIA THE CANINE CANCER RESEARCH INITIATIVE

Recognizing the challenges and slow progression in the development of new approaches for diagnosing and treating canine cancer, such as hemangiosarcoma, the AKC (American Kennel Club) Canine Health Foundation (CHF) has launched the [Canine Cancer Research Initiative](#). This fundraiser for cancer research is supported by the American Kennel Club, which will match donations and CHF Donor Advised Fund transfers to the Canine Cancer Research Initiative up to \$250,000 in 2019. The match is provided to support research of canine-specific cancers. Currently, the AKC Canine Health Foundation is supporting four hemangiosarcoma studies totaling over \$906,089.



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