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ROTTWEILER Update

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HEMANGIOSARCOMA RESEARCH

Diagnostic & Treatment Advances

ROTTWEILERS MAY BENEFIT FROM HEMANGIOSARCOMA RESEARCH

Virtually all Rottweiler breeders and owners have at some point been touched by canine cancer. Most will agree none is as scary as hemangiosarcoma (HSA). Challenging to diagnose and equally difficult to treat, HSA often renders a one-punch knockout when a tumor ruptures causing dogs to bleed to death internally.

Promising research at the University of Minnesota is gaining a heavy-weight advantage over this devastating cancer. The work represents more than two decades of investigations. A combination diagnostic and treatment strategy offers a unique approach. The Shine On Suspicion (SOS) blood test identifies features of rare cells in the blood linked to this insidious cancer, allowing for potentially earlier treatment. Dogs that are thought to be at high risk for HSA via findings from the SOS test may then be able to receive a novel targeted toxin therapy called eBAT, developed at the University of Minnesota, which may extend their lives.

PHOTO: GAY GLAZBROOK

These recent advances originated from the Shine On study that ran from 2016 to 2019 and the ongoing Shine On continuation study that will extend to 2024. The health foundations of three highly affected breeds — the Golden Retriever Foundation, American Boxer Charitable Foundation and Portuguese Water Dog Foundation – provided funding for these AKC Canine Health Foundation studies.

Bear in mind that although the SOS blood test and eBAT are gaining favor in clinical trials, both are months to years from being widely available in veterinary clinics. "We hope to move the SOS blood test to the real world soon, so dogs can be tested through their veterinarian," says Jaime F. Modiano, VMD, PhD, the Perlman Endowed Chair in animal oncology at the University of Minnesota. "eBAT will remain experimental until it is approved by the Food and Drug Administration as a treatment modality, and then additional work will be needed before it can be used for preventive purposes."

Tracy Arcari of Jay, Maine, can't help but wonder if things would have gone differently for her male Rottweiler, "Vator" (CH Vonkiltzen's Klear The Way), had the SOS blood test identified him as high risk for HSA and had he been treated with eBAT. Vator was Arcari's first show puppy after nearly 15 years fostering rescued Rottweilers. The handsome male loved to go to dog shows. He also liked herding, carting, tracking, and

HEMANGIOSARCOMA RESEARCHER TAKES QUESTIONS FROM ROTTWEILER ENTHUSIASTS

Dr. Jaime F. Modiano

Jaime F. Modiano, VMD, PhD, the Perlman Endowed Chair in animal oncology at the University of Minnesota, has studied canine hemangiosarcoma (HSA) for more than 20 years. The *Rottweiler Update* invited these breeders and owners who have experienced HSA firsthand in their own dogs to ask this leading researcher for his insights about this complex, insidious cancer.

Q **What is the prevalence of HSA and at what age does this cancer commonly affect Rottweilers?** *Jeff Shaver, Janar Rottweilers, Houston, Texas, vice president of the American Rottweiler Club and the Rottweiler Health Foundation*

A It is impossible to estimate a precise prevalence rate for HSA without knowing the cause of death for an entire breed population. We definitely see HSA frequently in German Shepherd Dogs, Golden Retrievers, Portuguese Water Dogs, Boxers, and several other breeds that are presumed to be at high risk. We also see HSA frequently in other breeds, including Rottweilers, and in mixed-breed dogs. It is important to remember that any dog of any age of any breed and of any sex intact or neutered is at risk for HSA. The median age — when 50 percent of dogs are older and 50 percent are younger — for this disease across breeds is approximately 9.5 years.

Q **Are there studies suggesting that dietary supplements or specific types of diets can delay the progression of HSA in dogs?** *Laura Wright-Smith, Spirit Mountain Rottweilers, New Castle, Colorado*

A There is no credible data to support any supplements or diets for canine cancer prevention. There are data suggesting that lean body mass may be protective for cancer. A lean body mass provides significant health benefits as dogs age, so feeding an appropriate amount of a complete and balanced dog food is helpful even if it does not provide significant cancer protection. We do not recommend feeding special diets or supplements under the assumption that "it might help, it won't hurt, or it must be good because it's all natural." None of these approaches conform to best medical practices.

Q **Is there evidence that annual prophylactic abdominal ultrasounds on older dogs are useful to screen for HSA?** *Rottweiler owners Kelly and Dr. Anthony Skiptunas, Wrightsville, Pennsylvania. Kelly is a member of the board of directors of the Rottweiler Health Foundation*

A Ultrasound of the abdomen is a low-risk procedure, though it can be costly and will only find tumors that are grossly visible. I have diagnosed HSAs in dogs that had a severe bleeding episode due to a ruptured HSA of the spleen despite their having ultrasounds done just weeks before showing no evidence of a tumor. Remember, too, that HSAs can arise in other organs such as the heart, bone marrow and muscle, so abdominal ultrasounds will not capture every site where HSAs occur. In our opinion, serial ultrasound imaging is best thought of as "owner preference" with no guarantee of success.

Q **Do you imagine that one day there will be a genetic marker to identify dogs at risk for developing HSA?** *Jeff Shaver*

A We have no evidence that HSA has a familial distribution or that a major component of risk is heritable. While there may be heritable factors that contribute to HSA risk, they appear to have low penetrance and only weakly influence the risk for disease. Virtually every cancer that we diagnose in dogs behaves sporadically, or not in a manner that indicates strong heritability. In other words, risk is individual, and the occurrence of cancer in a close relative, such as a littermate, parent or offspring, has no bearing on the risk of cancer for that individual. The major risk factor for HSA seems to be "being a dog," as we hypothesize that the turnover of cells in canine blood vessels is higher than what is seen in other animals, and older age, thus longer life results in more cell divisions, more chance for introducing mutations in dividing cells, and more risk.

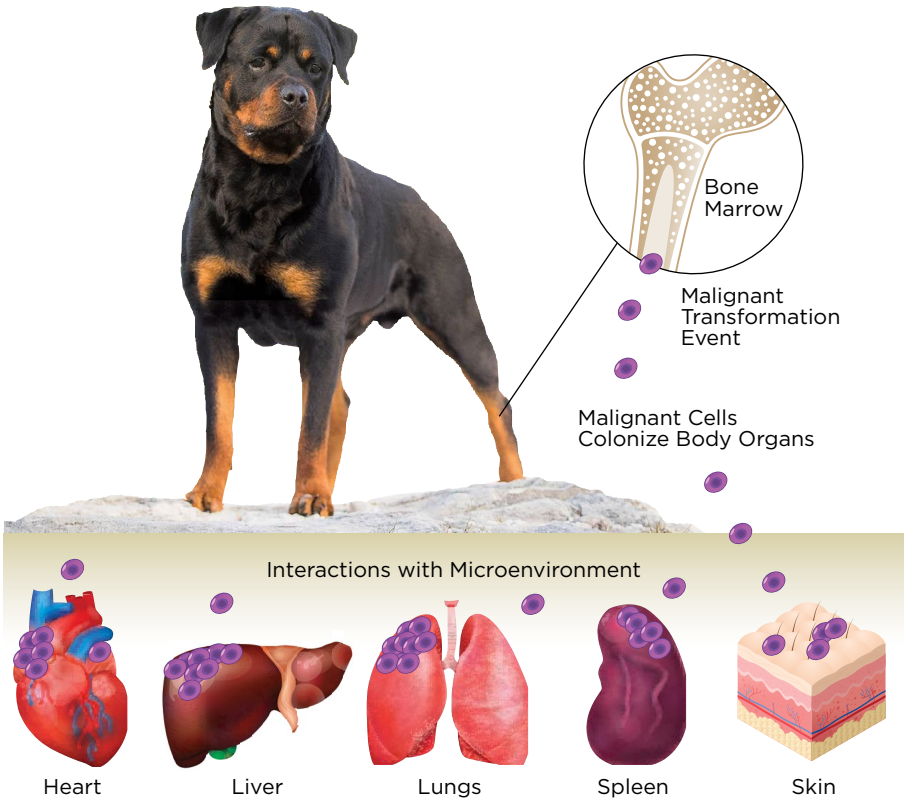
Q **Is it safe to breed a male whose littermate sister and dam were diagnosed with HSA?** *Laura Wright-Smith*

A As explained in the answer above, the short answer is yes. If you encountered cancer diagnoses in multiple related dogs, if the cancers were largely similar, and if the tumors developed in all the dogs when they were young, such as puppies, adolescents or young adults under the age of 3, it would be worthy of further investigation.

Q **Is there a relationship between osteosarcoma and HSA? One of our Rottweilers survived osteosarcoma and subsequently developed HSA five years later.** *Kelly and Dr. Anthony Skiptunas*

A Not that we know of. Both tumors are sarcomas that originate from connective tissues, both are very serious and possibly terminal, and both are very heterogeneous. That is where the similarities end. It appears that large-breed dogs may have a higher risk for certain cancers. This association between size and risk is unquestionably true for osteosarcoma, but it is uncertain if this is true for HSA. The observation that a single dog develops multiple tumors during his lifetime is sadly part of the risk of cancer and its relation to the processes of cell division and aging. Just because a dog develops one tumor does not mean that the dog is at greater or lower risk for developing a second tumor.

FORMATION AND SPREAD OF CANINE HEMANGIOSARCOMA



- The malignant cells can remain dormant for extended periods of time
- Interactions between malignant cells and their microenvironment allow cancerous tumors to grow
- Tumors can develop in many places at the same time, or they can develop in one organ and spread to others

doing tricks. He was game for anything Arcari wanted him to learn.

"Vator owned the world," she says. "He was full of himself and thought everything was about him. He was sweet with children and had a clownish personality."

When Vator was 10 years old in August 2019, Arcari noticed he didn't seem himself. The former veterinary technician took Vator for bloodwork that yielded nothing unusual. With little to go on, Arcari wrestled with trying to decipher whether Vator was experiencing an age-related decline or something else.

In December 2019, Vator fell down stairs on his way outdoors. "As he got up, he looked weak and lethargic," she says.

When Arcari took Vator for a dental cleaning in January 2020, the veterinary staff who had known him since he was a puppy agreed he did not seem himself. "An ultrasound showed an enlarged spleen," she says. "The veterinarian performed surgery and removed an orange-sized tumor. Since there was no indication of metastatic cancer in his stomach, liver or kidneys, Vator's spleen was removed, and we began treating him for hemangiosarcoma after a pathology report."

Vator bounced back from the surgery and started acting like himself one week later. It was short-lived. In February, Vator's lethargy returned along with decreased appetite and vomiting. "When I let him out before bedtime one evening, he was slow to come back," Arcari says. "I found him collapsed. He had dropped dead."

The complexity of HSA is notable as reflected in the diversity of its manifestation in individual dogs. More than 50 percent of affected dogs die within four to six months, almost 90 percent within a year. A tumor ruptures causing acute, severe blood loss, collapse, shock, and sudden death in many cases.

"We have defined three different types of HSA by classifying them at the molecular level, and we now have evidence that one of these molecular types accounts for most of the cases that show longer survival times with standard of care," Dr. Modiano explains. "This cancer has high metastatic propensity and is extremely drug-resistant, making it one of the most aggressive cancers seen in dogs."

PROFILING HSA

Although much is unknown about HSA, characteristics of the cancer define its idiosyncratic nature. "One of the most challenging things about HSA is that it grows silently and initially without clinical signs," says Dr. Modiano. "The diagnosis is typically made when the cancer is in the advanced stages and hard to treat."

More than 50,000 companion dogs in the U.S. are believed to develop HSA each year, estimates the University of Minnesota research team. Naturally, people who have lost dogs to this cancer seek ways to prevent it from occurring in other dogs. "There is no known effective preventive," he says.

A victim of hemangiosarcoma who succumbed two months shy of turning 11 years old, "Vator" (CH Vonkiltzen's Klear The Way) had a clownish personality and lived life fully.

"Altering lifestyle behaviors, reducing environmental concerns, or feeding special diets or supplements have no impact on the development of this cancer."

HSA starts in bone marrow cells that help to form new blood vessels throughout the body, giving tumor cells access to multiple tissues. Tumors primarily occur in the spleen, followed by the heart, skin and liver. The HSA cells incite the formation of abnormal vessels where blood tends to pool and clot. Eventually these clots obstruct the vessels and prevent fresh blood and nutrients from reaching the tumor environment, causing cells to die. This cell death causes ruptures in the tumor, allowing blood to escape into the abdomen, heart sac, chest, or subcutaneous tissue, depending on the tumor location.

Substantial blood loss can lead to anemia. Clinical signs, including pale gums, weakness and lethargy, may be subtle and resolve as dogs reabsorb the blood components and make new blood cells. This accounts for why HSA is seldom detected until the later stages of the disease.

If a tumor mass is suspected, a definitive diagnosis is based on a thorough physical examination followed by imaging tests, such as an ultrasound or radiography. If a mass is detected, a biopsy is examined by a pathologist, and if HSA is confirmed, it is important to learn whether the tumor has spread to other areas. This determines the stage of cancer progression. Sensitive computed tomography (CT) and positron emission tomography (PET-CT) are used more commonly today to visualize tumor masses.

The goal of treatment is to slow down or delay the spread of disease — and importantly, to prevent a life-threatening bleeding episode. The standard of care is surgery to excise a tumor mass followed by chemotherapy. "Generally, the prognosis for tumors that involve the heart, liver and other internal organs is worse than for tumors of the spleen," Dr. Modiano says. "Tumors localized to the skin fare better than tumors of the spleen."

PROMISING ADVANCES

The combination SOS blood test and eBAT treatment developed at the University of Minnesota are HSA game-changers. More than 40 features of rare cells in the blood of dogs diagnosed with HSA were used to develop the SOS

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> Jaime F. Modiano, VMD, PhD, the Perlman Endowed Chair in animal oncology, University of Minnesota.

HEMANGIOSARCOMA RESEARCH INITIATIVE

In 2018, the AKC Canine Health Foundation launched the Hemangiosarcoma Initiative to learn more about this aggressive common canine cancer. Altogether since 1995, the Canine Health Foundation has provided $4.1 million to support 28 grants focused on hemangiosarcoma. The Shine On studies featured here are examples of research that is part of this portfolio and that offer the potential of making a difference in the lives of dogs and their owners who are affected by the fatal cancer.

blood test. Artificial intelligence is used to analyze a dog's susceptibility to developing HSA based on these parameters.

The ability to recognize dogs at risk for developing hemangiosarcoma, via the SOS blood test, before tumors form is half the battle. An effective treatment — ideally, a preventive treatment — that targets tumor cells and prolongs life, possibly even saves lives, would constitute a battle victory won.

eBAT, short for EGF-bispecific angiotoxin, delivers a lethal bacterial toxin payload to tumor cells by attacking two proteins, epidermal growth factor receptor (EGFR) and urokinase-type plasminogen activator receptor (uPAR), found on the cell surfaces of HSA tumors. The discovery that the proteins are expressed at the same time triggered the hypothesis that the tumors would be sensitive to a targeted therapy that attacks both simultaneously.

The prevention properties of eBAT include the ability to:

- Kill cells that initiate and maintain the tumor
- Eliminate blood vessel cells and possibly other cells that form the niche environment the tumor needs to survive
- Eliminate the immunosuppressive myeloid cells from the tumor environment, which allows the immune system to recognize and react against the tumor

"After eBAT is injected into a vein, it enters tumors where it specifically kills malignant cancer cells that display EGFR and uPAR on their surface," Dr. Modiano says. "Another unique property of eBAT is that it kills inflammatory cells and blood vessels in and near tumors, making the environment inhospitable for the cancer cells. Importantly, eBAT does not cause any severe side effects."

As the Shine On continuation study begins, it adds the lifetime surveillance feature for the 209 dogs enrolled. The SOS blood test backed by AI analysis will enlighten the research team as to which dogs show early-stage HSA and thus are at high risk for the cancer. These dogs will be treated with eBAT

Vator, center, is pictured with his sons, "Glock" (U-CH GCH VonBremen's Can'T Buy Me Love), left, and "Preacher" (U-CH CH VonBremen's Clearly From Serenity).

to strategically prevent tumors before they form, and their performance will be compared to high-risk dogs that do not receive eBAT.

The study will generate knowledge related to the accuracy of the SOS test to predict whether dogs will develop HSA, how long before tumors develop in dogs designated as high risk, whether low- and medium-risk dogs eventually develop tumors, and whether high-risk dogs treated with eBAT change status to low or medium risk.

"The concept is that the properties of the SOS blood test and eBAT set this combination apart. They not only predict if a dog is at high risk or perhaps has an incipient HSA, but also provide a way to reverse that and prevent the tumor from ever forming," says Dr. Modiano.

Arcari whose beloved Vator collapsed and died two months shy of his 11th birthday is proud to share her life today with his 4-year-old sons, "Preacher" and "Glock." Nagging doubts make her worry if they, too, are at risk for HSA.

Dr. Modiano recognizes those concerns but mitigates them based on the lack of evidence supporting familial transmission or major heritable components to the risk of HSA. "Heritable factors may contribute to risk, but they appear to have low penetrance and only weakly influence a dog's risk for disease," he says.

While the SOS blood test and eBAT await approval for veterinary clinical use, the best advice for the owner of a dog suspected of having cancer is to see a specialist. "We recommend consulting and following the advice of a specialist," Dr. Modiano says. "It is important to conform to best medical practices and not give in to practices that give false hope. Talk to your dog's health care team to understand the results of tests and options available." ■

Purina thanks Roberta Kelley-Martin, president of the Rottweiler Health Foundation, for helping us to identify topics for the *Rottweiler Update*.

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