



# Personalizing Cancer

**S**trange as it may seem, an ailing pet rabbit named “Cocoa” prompted the formation of the Canine Hereditary Cancer Consortium and funding of \$5.3 million — the largest ever — for canine cancer research. That rabbit may one day get credit for sparking the advent of personalized medicine, a futuristic approach to treating cancer and other diseases based on an individual’s DNA.

Roe Froman, D.V.M., remembers well the day two years ago when her client, Susan Duesbery, brought in the Holland Lop rabbit for treatment at the veterinary clinic where she worked. During their conversation, Duesbery mentioned that her husband was a cancer researcher. Froman, who is president of the Clumber Spaniel Health Foundation, noted that hemangiosarcoma was a growing concern in Clumbers. She asked Duesbery whether she thought her husband might look into cancer in dogs.

The next day Duesbery’s husband called Froman. Nick Duesbery, Ph.D., deputy director of research operations at the Van Andel Research Institute (VARI) in Grand Rapids, Mich., had been studying the molecular biology of human sarcomas, particularly vascular tumors like fibrosarcoma, Kaposi’s sarcoma and angiosarcoma, the human equivalent of hemangiosarcoma, for the past 10 years. Founded in 1996, VARI is a nonprofit medical research facility that concentrates on the genetic and molecular origins of cancer and other diseases with a goal of developing effective therapies.

As Froman and Nick Duesbery discussed commonalities among canine and human cancers, they realized the potential mutual benefits of working together. After all, cancer is the leading cause of death in dogs age 10 years and older and the major cause of death in older humans. Already the sequenced human and canine genomes were allowing researchers to share information and exchange discoveries between species at an unprecedented rate.

Nick Duesbery and Froman quickly formulated a plan to study cancer in dogs taking a team approach. With a \$12,000, start-up grant from the Canine Health Foundation, researchers at VARI soon identified regions of DNA associated with hemangiosarcoma in Clumber Spaniels. Little did they know that their project would become part of a larger effort involving academic, industry and government organizations and that it would result in a revolutionary move to provide better cancer treatment not only for dogs but for people, too.

Wanting to expand their work, Nick Duesbery and Froman met with Jeffrey Trent, Ph.D., president and research director of VARI and the Translational Genomics Research Institute (TGen), and Paul Meltzer, M.D., Ph.D., chief of the Genetics Branch of the National Cancer Institute (NCI). Simultaneously, Trent recruited Mark Neff,

Ph.D., a well-known canine geneticist, to work at TGen and VARI. The final steps involved the alignment of nearly 30 scientific investigators at nearly a dozen institutions, culminating in an ambitious proposal by TGen to the



Research of hemangiosarcoma in Clumber Spaniels inadvertently led to the proposal to form the Canine Hereditary Cancer Consortium.

National Institutes of Health (NIH) to form the Canine Hereditary Cancer Consortium (CHCC).

“The goal of CHCC would be to take advantage of naturally occurring canine cancer models to promote improvements in the health and welfare of humans afflicted with rare tumors,” Nick Duesbery says. “Although helping humans would be the primary goal, the research would potentially lead to equally important canine discoveries.”

The sheer size and scope of the endeavor is what sets CHCC apart from other research efforts. It currently includes more than 30 veterinarians, physicians and basic scientists working in private practice, industry, research institutes, universities and the federal government. In addition to a two-year, \$4.3 million NIH grant, funding of \$1 million has been donated from private sources to support the research.

Undoubtedly, timing and similarities between cancers affecting dogs and people have played a role in the funding support. For years, progress in human medicine has relied in part on research with dogs. Likewise, for years, progress in canine medicine has relied in part on results with humans and the high level of funding for human medical research.

It was in April 2009, after President Barack Obama announced the American Recovery and Reinvestment Act funding for NIH, when Nick Duesbery, Trent and Meltzer met to write their core proposal. Their purpose was to take advantage of canine genetics and the high incidence of disease in certain breeds to gain insight into the underlying causes of cancer. This insight would be used to help guide clinical trials in humans.

“We added an important and novel twist,” says Nick Duesbery. “Our proposal called for the introduction of a revolutionary new approach, called personalized medicine, to treating dogs and people. Personalized medicine is the practice of using an individual’s genetic information to guide clinical treatment. It holds promise that therapies tailored to an individual’s genes will increase drug selectivity and response, resulting in a better clinical outcome.

“Imagine if we could predict ahead of treatment which dogs, or people, would respond to a given therapy and which would not. What if we could

tell a doctor which patients would respond adversely to a drug? This kind of information based on genetics would be a tremendous aid to veterinarians and physicians as they guide their patients to the most effective treatments.”

A major obstacle to the advancement of personalized medicine in humans has been the challenge of deciphering genes involved in cancer.

The variable genetic background of humans hampers discovery of genetic mutations. Purebred dogs, on the other hand, have a more uniform genetic profile due to selective breeding, which enables reliable gene differences associated with disease or response to treatment to stand out.

“The ultimate goal,” Froman says, “is improved diagnostics, more individualized therapies, and perhaps even DNA tests that can help us, as breeders, make better informed decisions and breed healthier dogs. The true beauty of this project is that dogs are helping people and other dogs.”

### A Focus on Five Cancers

Initially, the focus of CHCC is on understanding the genetic causes of five cancers: hemangiosarcoma (angiosarcoma in humans), oral melanoma, osteosarcoma, malignant histiocytosis, and non-Hodgkin’s lymphoma. The prevalence of these cancers in dogs, and thus the potential of learning more about cancers that are less common in humans, contributed to their early selection for study.

## Participating CHCC Institutions

The Canine Hereditary Cancer Consortium (CHCC) has received funding of \$5.3 million, of which \$4.3 million is a National Institutes of Health grant, to study canine cancer. An additional \$1 million is from private sources. Scientists, veterinarians and physicians at the following institutions are participating in the research:

- Auburn University
- Australian Shepherd Health and Genetics Institute
- Canine Health Foundation
- Colorado State University
- Michigan State University
- National Cancer Institute
- Spectrum Health System
- The Translational Genomics Research Institute (TGen)
- TGen Drug Development
- Tufts University
- University of Pennsylvania
- Van Andel Research Institute (VARI)
- Wake Forest University
- West Michigan Academy
- Yale University

Bernese Mountain Dog



“Hemangiosarcoma and osteosarcoma are 100 times more common in dogs than in people,” Nick Duesbery says. “These tumors are particularly common in older large breeds, such as German Shepherd Dogs, Golden Retrievers and Clumber Spaniels.”

State-of-the-art research tools used by some of the participating CHCC institutions for human cancer research will hopefully help to fast forward the research. For example, at TGen in Phoenix, where the emphasis is on developing earlier diagnostics and better treatments for complex diseases such as cancer, neurological disorders and diabetes, researchers use sophisticated next-generation gene sequencing tools that allow them to sequence large regions of DNA and even whole genomes. They also use transcriptome sequencing to sequence transcribed genes.

At VARI, researchers use gene expression arrays to simultaneously analyze the expression of 20,000 genes that are turned on or off in cancers. Fluorescence-activated cell sorting is used to separate heterogeneous mixtures of cells into homogenous subgroups. Researchers also apply genetic epidemiology and sophisticated computational biology in their work.

The overall project is both diverse and complex. It includes studies of:

- Lymphoma in several breeds of dog by Nicola Mason, Ph.D., B.Vet.Med, at the University of Pennsylvania;
- Malignant histiocytic sarcoma in Bernese Mountain Dogs by Vilma Yusbasiyan-Gurkan, Ph.D., at Michigan State University;
- Melanoma in Schanzuers by Trent at TGen; and
- Osteosarcoma in Rottweilers and Greyhounds by Meltzer and Chand Khanna, D.V.M., Ph.D., at the National Cancer Institute.

Involvement with scientists at the National Cancer Institute, the nation’s premier cancer research center, is key to the success of the program, says Trent.

“CHCC provides an opportunity to potentially advance both human and canine health through better understanding of disease,” says Meltzer. “We hope to use cutting-edge genomics tools to identify the similarities and differences between humans and canine cancers. We are optimistic that this may help highlight aspects of these diseases that can be investigated to develop new treatments. My colleagues and I at NCI are pleased to be part of the CHCC team.”



## How to Donate to CHCC

The Canine Hereditary Cancer Consortium is seeking blood and tumor samples from dogs affected by cancer. For information about how your veterinarian can submit samples, please visit [www.vai.org/helpingdogs](http://www.vai.org/helpingdogs), send an e-mail to [CHCC@vai.org](mailto:CHCC@vai.org) or call 616-234-5569.

Since learning in October 2009 that CHCC would receive funding, researchers have begun collecting samples from dogs with cancer. Getting the word out is critical to their success. Both purebred and mixed-breed dogs are eligible, and purebreds

do not have to be registered. Blood samples from unaffected dogs that are related to affected dogs are also of interest.

The researchers will tap into DNA stored at the Canine Health Information Center (CHIC). Sponsored by the Orthopedic Foundation for Animals and the Canine Health Foundation, CHIC provides a database of health testing information about individual dogs and a DNA Repository from which investigators can request DNA samples for research. Samples stored at CHIC and those submitted to CHCC will be shared among researchers to help advance research.

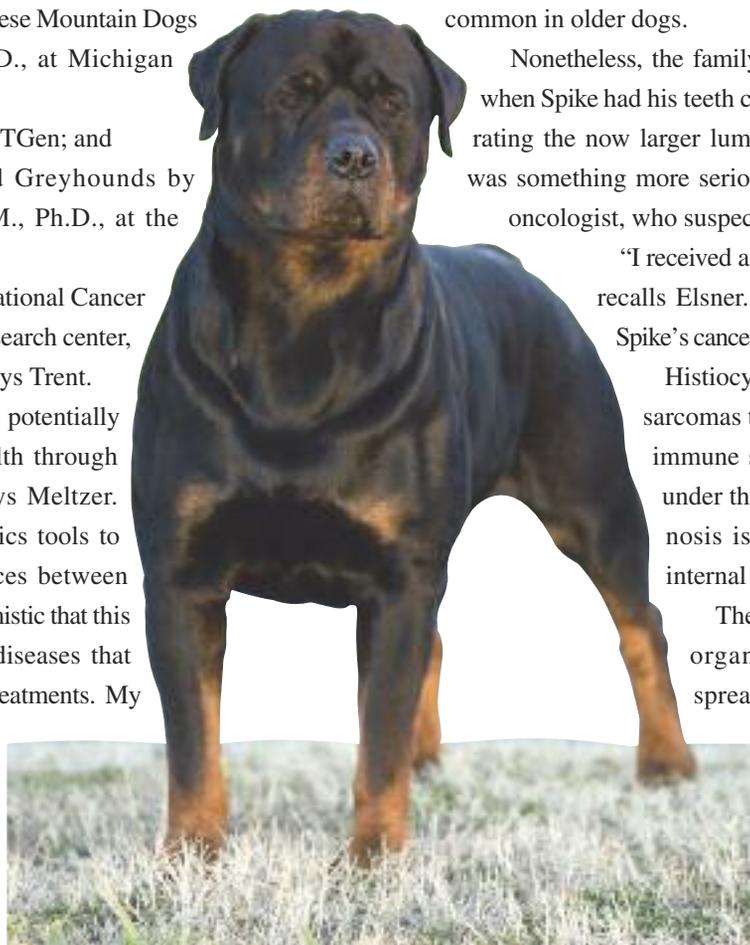
One of the early samples received at CHCC came from a 6 ½-year-old Bullmastiff named “Spike,” whom his owner, Louis Elsner of Palos Heights, Ill., described as “part ham, part lover, never a problem and a full-time companion.” In September 2009, the Elsners noticed a small lump on Spike’s side, which the veterinarian determined was a lipoma, a harmless fatty tumor common in older dogs.

Nonetheless, the family decided to have the lipoma removed when Spike had his teeth cleaned several months later. After aspirating the now larger lump, the veterinarian grew suspicious it was something more serious. Spike was referred to a veterinary oncologist, who suspected the dog had a sarcoma.

“I received a phone call from the specialty hospital,” recalls Elsner. “The pathology report indicated that Spike’s cancer was a fast-growing histiocytic sarcoma.”

Histiocytic sarcomas are malignant soft-tissue sarcomas that arise from cells that are part of the immune system. They also may develop on or under the skin or on internal organs. The prognosis is poor, especially if the cancer is on internal organs.

The veterinarian scanned Spike’s internal organs to make sure the cancer hadn’t spread. The results showed a mass in his heart. Now, the options were limited. The Elsners chose radiation and



Rottweiler



A DNA blood sample from a Bullmastiff named "Spike" was one of the early samples received at CHCC.

chemotherapy, which could give Spike the most time. It was during the chemotherapy that the family learned about CHCC and the need for samples. A sample from Spike's blood work was forwarded that day.

In mid-April, Spike suddenly became ill. Despite all efforts, the Bullmastiff passed away several days later. "We were devastated and remain so today," Elsner says. "Try as we may to climb out of this black hole, it remains almost impossible. Spike was our friend, a family member and a beloved pet. I don't think we'll ever get over losing him."

Another early sample came from "Murphy," a mixed-breed rescue dog. Owner Martha Thierry of St. Clair Shores, Mich., says, "Murphy was a great little guy, who was turning into a great old dog — the kind of dog who knows you so well you don't have to say anything."

One day she came home to find Murphy in distress. He was diagnosed with a tumor on his spleen. The worst news was the biopsy results: hemangiosarcoma. Unfortunately, there is no effective treatment for this cancer, which affects the lining of the blood vessels and often causes spontaneous bleeding in the spleen or heart. It also spreads quickly through the bloodstream. Murphy lived six months after being diagnosed.

After hearing about the CHCC study, Thierry decided to participate. "I was very excited to get involved because I hated the feeling of not

being able to do more for my dog. I initially was going to bring Murphy to the oncologist to get his sample sent before his next appointment, but the technician said to wait until his next appointment a couple of weeks away. He never made it to the next appointment, but when I brought him in on his last day, I made sure a sample was taken before he was euthanized. It made me feel better despite my sadness."

Samples have also come in through group efforts. More than 100 Italian Greyhound samples have been submitted, and the number is growing. Newfoundland enthusiasts have contributed more than 185 samples, and nearly 100 samples were received at the Scottish Deerhound Club of America National Specialty.

Thelma Garcia of Deer Park, Texas, says, "Several of our Italian Greyhound Club of America Rescue foster dogs are entered into the study. We have been seeing so many dogs coming into rescue with suspected hemangiosarcoma

lesions that when Dr. Froman told us about the study, we were determined to help the breed by participating with as many dogs as we could."

Froman became so dedicated to the CHCC initiative that she left her private practice veterinary job to begin working at VARI to help with the collection of blood and tumor samples. "I feel this work is very important," she says. "By working together — owners, scientists, veterinarians and breeders — we can help to unravel some of the mysteries of cancer."

Support also comes from the Canine Health Foundation, the largest nonprofit organization that funds health research exclusively for canines. As a member of the CHCC external advisory committee, Christine Haakenson, Ph.D, director of research for the Canine Health Foundation, plans to "help through our relationship with breed clubs. We will help to communicate the need for samples and share information about the progress."

Though personalized medicine is still in the early stages in both humans and dogs, researchers are optimistic about its potential. Those who submit samples from their beloved pets are hopeful they may one day provide insights. As Elsner, the owner of Spike, the Bullmastiff, says, "I sincerely hope that Spike's participation in the work being done by CHCC will help the cause and ultimately animal lovers around the world. Spike would be proud in helping to accomplish that." ■