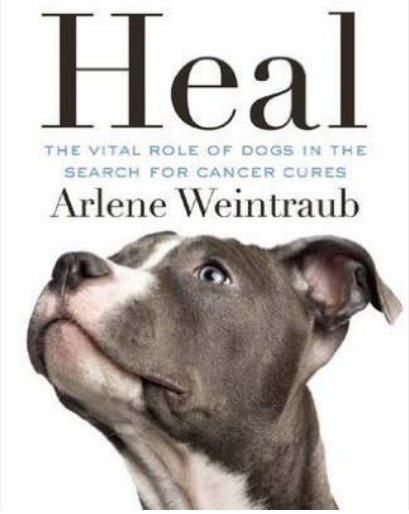
Belgian Sheepdog and Tervuren Gastric Cancer Study Update

January 2016

We have found that several breeds of dogs are at increased risk of developing stomach cancer (gastric carcinoma). This observation along with assembled pedigrees that show familial clustering of gastric cancer cases, lead to the conclusion that there is a genetic (heritable) basis for this disease in dogs and that through genetic study, we might identify better ways to prevent, diagnose and treat canine stomach cancer. Over the last several years this work has been supported by the National Cancer Institute, the National Human Genome Research Institute, the Canine Health Foundation, and most recently by a variety of donors including the Belgian Sheepdog and Tervuren clubs as well as a number of individual donors. The support from the Belgian Sheepdog and Tervuren community has been absolutely essential to the continuation of our work in the face limited biomedical research funding, both public and private, for all species,. ***Thank you for allowing the McNiel Comparative Oncology Laboratory to continue this work.*** We would also be remiss if we did not mention the valuable contributions from our canine friends in the form of blood and tissue samples.

Media Coverage:



This past fall, the canine stomach cancer study became the basis for a book chapter in a new book called “Heal: The Vital Role of Dogs in the Search for Cancer Cures,” written by science writer, Arlene Weintraub. This book covers many of the different efforts to study cancer in dogs for the benefit of both dogs and humans, including our own effort. Check it out! Weintraub lost her sister to stomach cancer and as a consequence has an active interest in stomach cancer research that may improve outcomes in people diagnosed with this disease. Stomach cancer in humans is one of the most common causes of cancer death worldwide and there have been few advances its treatment in decades. We hope that our efforts to understand canine stomach cancer will also benefit people.

What have we been up to?

We continue to expand the Canine Gastric Cancer Database and Sample Repository
Our repository now includes over 1000 dogs, including 240 with stomach cancer. Dogs are included in the repository if they have a diagnosis of gastric carcinoma or if they are an older dog

representing one of several breeds with an increased risk of stomach cancer. Our numbers of the Belgian breeds as of December 2015 are provided in the table below.

Breed	Confirmed GC	Suspected GC	Other Cancer	"Healthy"	Total
Belgian Malinois	0	1	4	26	31
Belgian Sheepdog	19	4	19	87	129
Belgian Tervuren	59	10	25	223	317

Genome-wide Association Study Progress:
We have been collaborating with the laboratory of Dr. Elaine Ostrander at the National Human Genome Research Institute to conduct a genome wide association study to investigate the causative mutation(s) of gastric cancer in high-risk breeds. This research involves comparing more than 100,000 different genetic markers in dogs with and without stomach cancer to find which markers are seen more commonly in dogs with stomach cancer compared to those without. While we last reported that we had an encouraging genetic locus in the Tervuren, we have now decided that this was a false positive result. However, we have only completed genotyping for a subset of our samples and are currently evaluating the dataset to determine which additional samples will be genotyped.

Are all Belgian Breeds at risk for stomach cancer?

While it is clear, based on data from a national database (the veterinary medicine database or VMDB) that both Belgian Sheepdogs and Tervuren have an increased risk of stomach cancer. The risk in Belgian Malinois is less clear. We are still interested in documenting whether Malinois actually get stomach cancer.

We have also embarked on some new initiatives:

1. Development of canine gastric carcinoma cell lines:
Cancer cells grown in culture have been extremely valuable tools for understanding cancer in humans and more recently in dogs. Using tissue samples submitted to our laboratory, we have started to grow the tumor cells in our laboratory. This is important because cell lines allow us to study live cancer cells and learn about their biology. As the genes important to canine stomach cancer are uncovered these cultured cells will allow us to determine how these genes are working to cause cancer. This type of study would greatly decrease the chances of false positive results from genome wide association studies that, as we have learned, can occasionally be misleading. In addition, this provides a means to test the sensitivity of cancer cells to drugs including cutting edge molecularly targeted products that have already lead to treatment breakthroughs for many human and some canine cancers.

We presented these initial studies at the American Association for Cancer Research Annual Conference in Philadelphia last spring:

Manar AbdelMageed, Monica Betancur-Boissel, Parthena Foltopoulou, Sureshkumar Muthupalani, James G. Fox, Elizabeth A. McNiel. A Naturally Occurring Model for Gastric Cancer. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research, Philadelphia, PA, April 2015.

2. Molecular profiling of canine gastric cancer.
A great deal has been learned recently about the biology of human gastric cancer using large scale genomic analysis of 295 cancers. These data published in the journal Nature in the fall of 2014, demonstrate the stomach cancer in people is comprised of about 4 different molecular subtypes. We plan to also analyze canine stomach cancer samples to determine their underlying molecular biology. This information may provide clues to the underlying causes and will also help us determine better ways to diagnose and treat stomach cancer in dogs. In addition, we will compare this information to that determined for human stomach cancers. If canine and human stomach cancers share their molecular underpinnings then advances for either species may help the other.

3. Sequencing of the Belgian Tervuren and Belgian Sheepdog.
The Ostrander Lab at the NHGRI, our longtime collaborators in the study of gastric carcinoma, are engaged in sequencing the entire genome of particular dog breeds. Whole genome sequencing provides high resolution genetic data that will greatly assist in uncovering genetic disease genes. The Ostrander lab has included samples from our repository including samples from Tervuren and Sheepdogs in this effort. This information will enhance our ability to identify DNA sequence changes in dogs affected by stomach cancer compared to those without.

We still need more samples from dogs!

We are still in need of blood samples from dogs diagnosed with gastric cancer and healthy dogs over the age of 8 years.

We are asking for a 6ml blood sample from healthy dogs and 5-generation pedigree at time of enrollment. For affected dogs we ask that a 6ml blood sample, 5-generation pedigree and, if available, diagnostic confirmation of gastric cancer (biopsy report, ultrasound report, etc) be submitted at time of enrollment. For dogs that are affected by gastric cancer, we are also asking owners to strongly consider submitting tumor samples to the study. These can be taken at time of surgical biopsy or post mortem. Please contact us at 517-636-4715 for more information about tumor tissue donation.

Thank you again for your continued support of this research! Our current and future progress would not be possible with out the enthusiastic support of the breed clubs and their members.