

February 9, 2015

Dear Scottish Terrier Owners, Friends, and Enthusiasts,

I am writing to share an update with you and to ask for your support for a study of high positive impact for the health of Scottish Terriers. Matching funds are now available for a one-to-one match for donations for bladder cancer research in our program! Every dollar donated will immediately become two dollars, up to \$100,000! Plus, many employers will also match donations made by their employees.

As many of you know, and have experienced, Scottish Terriers are 20 times more likely to develop bladder cancer (transitional cell carcinoma, TCC) than mixed breed dogs. Although TCC treatment has improved substantially, if we can intervene earlier in the cancer development process, we can do much more to help dogs! Driven by this goal, In September, 2014, at Purdue University we launched a 3-year bladder cancer screening / early detection / early intervention study for Scottish Terriers that do not yet have any evidence of bladder cancer. We were able to launch this hallmark study through generous support from the Scottish Terrier Club of America Health Trust, corporate partnerships, and donations from grateful pet owners. This has been a great team approach among veterinary scientists, technologists, dog owners and breeders, and breed clubs!

Normally we would not convey the results of a 3-year study in the first 6 months of the project. But, this study is different because we are already seeing remarkable results! We are finding 3 times as much cancer or pre-cancer in these "normal" Scottish Terriers than we expected to find at this point in the study. These dogs have no evidence of urinary tract problems when they enter the screening study. These early findings tell us that the screening approach is working! And, the early intervention component of the study is also showing tremendous potential so far! We are enclosing a study summary with more information.

A significant challenge we are facing, however, is having ample funds to continue the study. By finding much more cancer than expected, the study is costing much more than predicted. In the initial budget projections, the costs associated with screening were expected to comprise one third of the budget. The other two thirds of the budget would be needed to pay for cystoscopy in dogs with abnormal ultrasound and urine tests (to make the diagnosis of pre-cancer, cancer, or other conditions in the bladder), and for the interventional component aimed at causing regression of pre-cancer and early stage cancer. We have already performed cystoscopy and early intervention in 12 more dogs than expected! Additional dogs are incurring more costs as we monitor



College of Veterinary Medicine

suspicious areas in their bladders. This has already put us \$57,000 over budget for year one of the study, and year one still has 6 months to go! We expect the costs of years 2 and 3 will also exceed the initial budget.

This study is SO IMPORTANT, we just have to work together to find the resources to make it happen! Would you please consider making a donation to continue this study? Through a generous donation made by Evan and Sue Ann Werling for Brandi's Cancer Challenge Fund, any donation made for this study will be matched one-to-one (each dollar immediately turns into two dollars!) up to \$100,000. Brandi's matching funds not applied to the screening study will go to match funds for other critical bladder cancer research in our group. The Werling's have challenged us to grow their \$100,000 donation into \$900,000, and will award us with further support when we meet their challenge. Would you please spread the word to your friends and co-workers about this study and the matching opportunity and ask about employer matching opportunities?

Thank you very much for your support. I have no doubt that this study will change bladder cancer management (for the better!) in Scottish Terriers and dogs in other high-risk breeds. This study could also drive a much needed paradigm shift from cancer treatment to cancer prevention in veterinary oncology. And, with the similarities between invasive bladder cancer in dogs and humans, the study is expected to ultimately benefit people facing bladder cancer as well as dogs.

Checks should be made to PURDUE FOUNDATION and the memo line should read SCOTTISH TERRIER SCREENING STUDY. A **donation form** is included. Thank you!

Sincerely,



Deborah W. Knapp, DVM, MS, Dipl. ACVIM (Oncology Specialty)
Dolores L. McCall Professor of Comparative Oncology

Enclosures

STUDY INFORMATION SHEET AND PRELIMINARY FINDINGS

Study Title: Screening and Early Intervention to Positively Transform the Management of Bladder Cancer in Scottish Terriers

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Background: At Purdue University, our team is conducting a study of screening and early intervention for bladder cancer in Scottish Terriers. The specific type of bladder cancer that is most common and the form we are studying is invasive transitional cell carcinoma or "TCC" (also referred to as invasive urothelial carcinoma, iUC). Scottish Terriers are 20 times more likely to develop TCC than mixed breed dogs and dogs in other breeds. Although there has been a lot of progress in the treatment of TCC in dogs, the cancer is still not usually curable, can detract from quality of life, and is ultimately fatal in many dogs. Therefore, it is essential to identify ways to prevent TCC from occurring or to find and treat it earlier when it is expected to respond much better to treatment.

When TCC develops in the bladder, the bladder does not go from being normal to being TCC immediately, rather multiple steps including dysplasia, carcinoma in situ, early stage TCC, and then advanced TCC occur. If the cancer development process is detected and stopped at an early step, then it may be possible to prevent the disease from ever becoming the late stage TCC that we currently see. This is similar to the strategy applied in people when using colonoscopy to detect pre-cancer, thereby preventing colon cancer. With the help of countless numbers of Scottish Terrier owners and friends, we have launched this screening / early detection / early intervention trial.

Study Overview: With their owner's consent, 110 Scottish Terriers have been enrolled in the study. Like all of our studies, this one is approved by the Purdue Animal Care and Use Committee. The participating Scottish Terriers must be at least 7 years old, and must have no evidence of bladder disease, i.e. the dogs appear perfectly normal in regards to the urinary system. The dogs are screened every 6 months for 3 years with a bladder ultrasound, physical examination, and multiple urine tests including newly

developed tests. If the ultrasound and other test(s) suggest that cancer could be developing, then cystoscopy is performed to obtain biopsies of the abnormal areas in the bladder and/or urethra. In this cystoscopy procedure, a thin tube-shaped fiberoptic scope is passed up the urethra into the bladder. The veterinarian can see the inside of the urethra and bladder and then obtain small pieces of tissue from the abnormal looking areas. The pathologist then reports if cancer or pre-cancer or some other condition is present. The biopsies are a must, otherwise it would be just a guess as to what is going on in the bladder.

If pre-cancer (dysplasia, carcinoma in situ) or early stage cancer is found, then the dogs can participate in an early intervention trial of the drug Deramaxx. In advanced TCC cases, Deramaxx (like its related drug, piroxicam) can cause remission in ~17% of dogs and can prevent cancer progression in another ~55% of dogs. It is expected that when Deramaxx is given earlier in the cancer development process, that it will be more effective. There is already some evidence for this in a small group of dogs in which early stage TCC was found, and surgical removal of the TCC plus Deramaxx resulted in a median (average) survival time of 750 days from diagnosis to death. This is more than twice as long as the median (average) survival time for dogs with more advanced TCC treated with Deramaxx.

Dogs in the screening study that develop pre-cancer or early stage cancer, and that then receive Deramaxx, will be evaluated at 6-week intervals at Purdue. These evaluations will include physical exam, medical history, urinary tract ultrasound, blood and urine tests, and periodically x-rays and complete abdominal ultrasound to look for spread. If, the pre-cancer or cancer should begin to progress at some point, then other treatments could be pursued off study.

Preliminary Findings: The bladder cancer screening study is already proving even far more important than anticipated! The expectation going into the study was that over the 3 years of the study, that ~30% of the Scottish Terriers would develop pre-cancer or TCC. But, with the study having started only 6 months ago, and with just the first of 6 rounds of screening completed, pre-cancer or TCC (mostly TCC) has already been detected (and confirmed by cystoscopic biopsy) in ~15% of the dogs! In addition, "suspicious" areas in the bladder are being followed in another 15% of dogs. These dogs with suspicious areas have subtle changes that we will monitor with ultrasound and then biopsy if the areas emerge any further. Another exciting finding in the study is that to date, the remission rate with Deramaxx has been much higher than has been observed in dogs with advanced bladder cancer.

Importance and Impact: The study results to date have been astounding!! To visualize the expected impact, one should envision a complete change in how TCC is "managed" in Scottish Terriers. With the current standard management of TCC, bothersome symptoms signal the dog owner and the veterinarian that there is a problem, and far too often, late stage and sometimes already metastatic TCC is found. Rather than following this approach of "reacting to" advanced cancer, this study is going to shift the

emphasis to early detection and intervention. The study could go down as one of the most important in veterinary oncology because of this paradigm shift from treatment to prevention!

There is every indication at this point that the value of the study is going to exceed expectations! It appears very likely that the conclusion will be that screening and early intervention are crucial, but this needs to be confirmed as the study progresses. The continued study will also help determine the age to begin screening dogs, the appropriate interval for screening, the most useful tests to find TCC and pre-cancer early, and to assess the initial and continued response to Deramaxx. Multiple different urine tests are being evaluated, including new tests developed in at Purdue, and by study collaborators Drs. Elaine Ostrander and Matthew Breen. There is also added value to the study in information being gained on the correlation between the development of cancer, environmental exposures, and the activity of carcinogen-metabolizing enzymes detected from cheek swab analyses by the study collaborator Dr. Lauren Trepanier.

There is also another important dimension to the study findings. In addition to helping change the outlook for Scottish Terriers and dogs in other high-risk breeds for TCC, this study is expected to ultimately benefit people facing bladder cancer. There is tremendous similarity between TCC in dogs and invasive bladder cancer in humans. Invasive bladder cancer kills > 16,000 people every year in the US, and bladder cancer (superficial and invasive forms) result in health care costs of \$4 billion yearly! By proving that screening and early intervention are effective in dogs, and by defining which urine tests are most useful in dogs, this could lead to studies for screening people who have high risk for bladder cancer. The scientific community, including those working on human cancer, recognize that pre-cancer and "early cancer" is "less genetically advanced" than late cancer, i.e. early cancer cells are less "messed up" at the molecular level than cells in advanced cancer. Cancer starts out because of something wrong with one to a few genes and signaling pathways in the cells. As cancer progresses, however, more and more abnormalities in different genes and pathways occur. These new abnormalities allow the cancer cells to continue to grow in the face of anticancer drugs, i.e. the drugs stop working. There are cancer drugs, however, that are expected to be very effective in early cancer, even if they are not effective in late cancer. There is not a traditional "experimental" tumor model (experimentally-induced rodent tumors) of invasive bladder cancer that mimics human cancer, however, to study this. This study and future studies of Scottish Terriers could provide an unparalleled opportunity to evaluate drugs in early cancer that will help Scottish Terriers, other dogs, and humans.