

## **Studies in pet dogs with cancer: improving the outlook for people with cancer, as well as the outlook for “man’s best friend”.**

One of the strengths of the Purdue Cancer Center is that it brings together scientists with a wide array of expertise. Dr. Debbie Knapp, a veterinary medical oncologist and cancer researcher in the Dept of Veterinary Clinical Sciences, and her colleagues in the Purdue Comparative Oncology Program fill a rather unique role in the Center. At the same time that they provide compassionate care for pet dogs and cats with naturally-occurring cancer, they conduct studies to learn more about how cancer develops, progresses, and responds to treatment. Certain forms of naturally-occurring cancer in pet dogs very closely resemble those same forms of cancer in people. For this reason, the information learned from pet dogs is not only helping dogs, but is leading to new studies in human cancer patients.

Dr. Knapp’s team focuses much of their effort on finding better ways to detect, prevent, and treat urinary bladder cancer. The invasive form of this cancer (invasive urothelial carcinoma, or InvUC) causes extensive morbidity and takes the lives of more than 14,000 people each year in the United States. InvUC in dogs very closely resembles the cancer in humans in regards to its appearance through the microscope, its development and progression including frequency and sites of metastasis, and how it responds to treatment. And importantly, Drs. Deepika Dhawan and Jose Ramos-Vara working with Dr. Knapp have shown great similarity between canine and human InvUC at the molecular level. Thus, InvUC in dogs provides an excellent model of this cancer in humans. Knapp and colleagues have taken advantage of this opportunity to make progress against InvUC on many fronts.

### *Prevention of InvUC*

In order to know how to prevent a cancer from forming, one must have an understanding of what causes the cancer. In the case of InvUC, it is caused by a combination of what an individual is born with (heritable factors), and what the individual comes in contact with during their life time (environmental factors). In humans, approximately 50% of bladder cancer cases are due to smoking. But what causes the other 50%? This is where pet dogs may provide some of the answers. In regards to the heritable factors, pet dogs provide a unique opportunity for study because certain breeds of dogs have much higher risk for InvTCC than other dogs. Scottish terriers, for example are approximately 20 times more likely to develop InvTCC than other dogs indicating a strong heritable component to the cancer in these dogs. Knapp has teamed up with Dr. Elaine Ostrander in the Cancer Genetics Branch at the National Institutes of Health to evaluate genome scans on the DNA from Scottish terriers with InvUC as well as the DNA from similar dogs without InvUC. Once the heritable factors are identified in the dogs, then these same factors will be assessed in humans. This could ultimately lead to a way to determine who is at risk for this cancer and strategies to prevent the cancer.

The heritable factors are just one part of cancer risk. The second part is environmental exposure. Knapp teamed up with Drs. Larry Glickman and Marcia Dawson to uncover some of the factors in the environment which increase the risk for bladder cancer in dogs. They conducted a case control study in which Scottish terriers with InvUC were compared to Scottish terriers of the same age that did not have cancer. Pet owners filled in a lengthy questionnaire concerning the exposure to various chemicals, type of diet and water consumed, and other factors. One of the concerning findings from the study was that dogs exposed to lawn herbicides and pesticides were 7 times more likely to develop InvUC than dogs not exposed to lawn treatments. In a follow-up study, Drs. Glickman, Knapp, and Angus Murphy, have demonstrated the presence of lawn chemicals in the urine of dogs who live in households that apply lawn products. This means that the lawn chemicals are making it inside the dogs' bodies. This may occur through the dogs licking their fur that has the chemicals on it, or possibly through other routes. This emphasizes the need to restrict the dogs' exposure to lawns that have been treated, especially those recently treated. Some pet owners that wish to treat their lawns, are now electing to treat parts of their yard at different times, such as treating the front yard one week and the back yard the next week to try to provide an area with less chemicals for their pets. It is important to point out that it is not yet known what combination of heritable and environmental factors are required to allow cancer to develop in each individual. These studies are just beginning to help scientists assemble this information.

Although some of the findings from the case control study certainly caused concern, there was a much more positive finding from the work. That finding was the reduction in InvUC risk attributed to ingestion of vegetables. In fact, dogs in the study who consumed vegetables at least 3 times per week had a 70% reduction in bladder cancer risk. The vast majority of dogs in the study ate predominantly dry dog food, but received vegetables as supplements or treats. Many pet owners reported giving their dogs baby carrots as treats. This is an easy, inexpensive thing for pet owners to do, to feed their dog vegetables. Although the study focused on Scottish terriers, it is likely that other dogs would benefit too. This work parallels studies in humans demonstrating the beneficial effects of vegetable consumption.

#### *Treatment of InvUC*

In the ideal world, InvTCC would be prevented, and never allowed to even form. Although with continued efforts in prevention research, it is possible that this will become a reality in the future, there are still thousands of dogs and humans currently becoming victims to this cancer. Therefore, it is important to continue to define better ways to treat InvUC. Knapp and colleagues are working hard on this front. Many pet owners allow their dogs to participate in humanely conducted clinical trials, such as trials in people. The dogs live at home with their families and then travel to the Purdue University Veterinary Teaching Hospital for one to a few days each month for evaluation and treatment. There are several reasons that many of the pet animals treated in the PUVTH enroll in clinical trials: (1) the pets often have a cancer for which there is no know standard effective treatment, and the trial offers hope for the pet, (2) the treatments given are typically well tolerated, and thus quality of life usually remains good, (3) the information learned will help other pet animals with cancer, (4) the findings from the trial

may lead to better treatment for humans with cancer, and (5) in some instances, outside funding may help defray the cost of treatment for the pet. Although Knapp and colleagues are working on several new approaches to treatment, 3 will be mentioned here.

Several years ago, Knapp and Dr. Thomas Needham made an interesting observation, the marked regression of cancer in pet dogs who were receiving a pain medication called piroxicam, and no other cancer treatment. Piroxicam is classified as a nonsteroidal anti-inflammatory drug, a class of drugs which includes aspirin, ibuprofen, and other over the counter pain medications. When Knapp joined the Purdue team, she and Drs. Ralph Richardson, Gerald Bottoms, and Tom Chan conducted several studies in dogs with cancer, and were excited to confirm the antitumor effects of piroxicam and similar drugs. Piroxicam causes dramatic reduction in tumor size in approximately 20% of dogs with bladder cancer, and importantly stops the cancer from growing in another 55% of dogs. Certain biological effects can be measured in tumor tissues that parallel the reduction in tumor size. Drs. Knapp and Dhawan at Purdue have teamed up with Drs. Richard Foster and Liang Cheng at the Indiana University School of Medicine to study these same biological effects in people with InvUC. Briefly, in the study, people are taking a drug similar to piroxicam for 2-6 weeks between diagnosis and cystectomy (surgical removal of the bladder, the standard treatment for this cancer in humans). Analyses of tissues examined from the initial biopsy and from tissues collected at the time of surgery are demonstrating the same biological effects in humans as were observed in the dogs. This opens up many avenues of study to incorporate piroxicam-like drugs into further trials in human bladder cancer therapy.

In a new approach to bladder cancer therapy, Knapp has joined forces with Dr. Noah Hahn (IUSM) and Dr. Ken Nephew (IU, Bloomington). The collaborators are working on a demethylating approach to treat cancer. Briefly, one of the reasons cancer cells grow so effectively is that the cell machinery that should stop cell division is not working as it should. One of the “defects” in this machinery in cancer is the addition of methyl groups to the DNA in tumor suppressor genes which keeps these genes from working. Drugs are now being identified that “demethylate” the tumor suppressor genes and thus restore their ability to halt the cancer growth. The group is conducting a treatment study in dogs, along with careful methylation analyses in Dr. Nephew’s lab. Dr. Hahn is eager to identify ways to apply these drugs in human trials in the future.

One of the most exciting areas of anticancer agent development is in nanoparticle cancer “drug” construction. Drs. Knapp and Dhawan have teamed up with Dr. Jim Leary on this endeavor. Nanoparticle cancer agents are especially intriguing because they can be designed in a way to only kill cancer cells while not harming normal cells, and they can be designed to treat each individual’s cancer. This is quite a feat when considering that the particles that are constructed are often 1000 times smaller than a red blood cell. Briefly, different components of the particles can be designed to allow the particles to bind to and enter cancer cells (but not normal cells), and to then kill the cancer cells. Once the technology is optimized for building the particles, then the components in each type of particle can be designed to attack the molecular features of each individual’s

cancer. By individualizing cancer care, this will greatly increase the efficacy while reducing the risk of side effects.

*Using the life cycle of dog cancer to develop predictive models*

At the same time Knapp and colleagues are conducting the molecular and clinical studies in dogs with bladder cancer, they are working with Dr. Seza Orcun who is developing a systematic approach and capture and analyze all of the information in an integrated way. It is likely that all of the data being generated during the dog's life with cancer (its "life cycle") contains information or patterns of information that will subsequently be able to be used to predict what will happen to each individual with cancer. Some of the questions that could be answered would include: will the cancer progress quickly in this individual or not? Will the cancer spread in this individual, or will it remain localized? [there is a 50/50 chance in people with InvUC that the cancer will spread to distant organs.] Will the cancer respond to drug "A" or will it respond to drug "B"? What test results are most important in making these predictions? The intriguing thing about studying this whole process in dogs is that with the compressed life span of the dog, the cancer life cycle can be studied in dogs in a matter of a few months to a few years, while a similar study in humans would require decades. Drs. Orcun and Knapp are working on ways to capture the information and do the analyses in order to help select the informatics design for parallel and future human studies.

In conclusion, the work being done by Dr. Knapp and colleagues fills a unique and important role in the Purdue Cancer Center. Scientists in the center are always looking at novel angles to better understand cancer and to develop more effective ways to approach cancer management. With all the promising work in the Center, the future looks bright.