

Man's Best Friend in More Ways Than One

Cancer drug development typically begins with in vitro research before proceeding through varying degrees of investigation in cell lines and laboratory animals, eventually culminating in human clinical trials. However, this often arduous development path may now find an ally in a relatively new branch of oncology research, referred to as comparative oncology. Initiated and directed by Chand Khanna, D.V.M., Ph.D., the CCR Comparative Oncology Program complements translational research through the characterization of relevant and naturally occurring cancer models that develop in pet animals as a window to evaluate novel therapies.

(Photo: Frances and Peter Way)



Prince.

It was nearly Christmas when Prince, an amiable, nine-year-old Labrador retriever was diagnosed with oral malignant melanoma. His owners, Frances and Peter Way, wanted the best treatment for their companion, so when veterinarians at Colorado State University's (CSU) Animal Cancer Center suggested a clinical trial, the Ways readily agreed. Prince's melanoma was very aggressive, similar in many ways to human melanoma, and the Animal Cancer Center was part of a consortium, sponsored by CCR's Comparative Oncology Program (COP), through which dogs are treated with experimental therapies to prepare for their use in human clinical trials. Prince was treated with

a new immunotherapy and achieved a robust response, living for almost a year. “That’s a lot longer than we think he would have otherwise,” said Peter Way, from Fort Collins, Colo. “We were hoping for a cure, but we also knew this would help the science, and I was glad that Prince could participate. It fit his spirit and his attitude; he was a great dog.”

Addressing a Lost Opportunity

To date, the COP has treated more than 150 dogs over the course of nine clinical trials conducted by its leadership of the Comparative Oncology Trials Consortium (COTC), a collaborative network of 20 veterinary schools from around the country overseen by Melissa Paoloni, D.V.M. Khanna conceived of the COP

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while he was a postdoctoral fellow in CCR, in the lab of Lee J. Helman, M.D. At the time, he was working on tumor metastasis and osteosarcoma, a bone cancer that occurs in pediatric patients and is also common in dogs. “It became clear to me that there would be great value in including pet animals with cancer within our CCR studies,” Khanna said. “There are very few human cancers that don’t also occur naturally in pet animals. To me, not learning from their cancers to help inform human clinical trials seemed like a lost opportunity.”

In 2004, with backing from Helman and Carl Barrett, Ph.D., then Chief of CCR’s Pediatric Oncology Branch and CCR’s Director, respectively, Khanna established the COP. Its mission, Khanna explained, is to improve the assessment of novel treatments for humans by treating pet animals—primarily dogs with naturally occurring cancers—while also trying to give these animals better quality of life by offering them the benefit of cutting-edge research and experimental therapies. “The ultimate goal was for NCI to engage

Members of the Comparative Oncology Trials Consortium

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| Auburn University
Auburn, AL | North Carolina State University
Raleigh, NC | Tufts University
North Grafton, MA | University of Guelph
Guelph, ON Canada | University of Pennsylvania
Philadelphia, PA |
| Colorado State University
Ft. Collins, CO | Purdue University
West Lafayette, IN | University of California
Davis, CA | University of Illinois
Urbana, IL | University of Tennessee
Knoxville, TN |
| Cornell University
Ithaca, NY | Texas A&M University
College Station, TX | University of Florida
Gainesville, FL | University of Minnesota
St. Paul, MN | University of Wisconsin
Madison, WI |
| Michigan State University
East Lansing, MI | The Ohio State University
Columbus, OH | University of Georgia
Athens, GA | University of Missouri
Columbia, MO | Washington State University
Pullman, WA |



(Image: VSB Associates)

The Comparative Oncology Trials Consortium (COTC) is an active network of 20 academic comparative oncology centers, centrally managed by CCR’s Comparative Oncology Program.

(Photo: R. Baer)



Chand Khanna, D.V.M., Ph.D.

the drug development community, and to lead a consortium of veterinary schools in a program to supply clinical research results that might accelerate new human treatments, and simultaneously help pet animals with cancer," Khanna said.

A Logical Partnership

According to Khanna, enrolling pet dogs in clinical trials has the potential to offer some key insights into human drug research. Dogs routinely develop osteosarcoma, lymphoma, bladder cancer, head and neck cancer, malignant melanoma, and mammary cancer. Moreover, human and canine cancers are very similar with respect to their genetics and biological features. On a practical level, the compressed life span of a dog and the more rapid course of cancer progression makes it easier for scientists to evaluate the benefit of novel cancer therapy in a short period of time. Repeat biopsies are often easier to perform in dogs than they are in people, making canine pre- and post-dosing tissue studies to investigate drug-target interactions feasible. Additionally, thanks to the public release of the canine

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genome sequence in 2005, scientists can now understand the molecular changes that are associated with a treatment response and a treatment failure. And finally, the COTC studies spontaneously occurring tumors in pet dogs, which are far more similar to human cancer than tumors induced artificially in mouse models of cancer. "It's also important to note that the COTC provides cutting-edge cancer treatment to pets whose owners might not otherwise be able to help them," said Paoloni. "It can cost thousands of dollars to pay for cancer therapy in a dog, and unfortunately that puts it out of reach for many families, so our efforts can help both human and veterinary cancer patients."

According to Khanna, COTC projects emerge from collaborations with the drug industry and other

research organizations involved in cancer drug development. The COP then chooses participating sites based on their availability, access to advanced technology (such as PET scans, for instance), and other factors. Once approved, researchers at chosen sites enroll dogs according to eligibility criteria that—mirroring the situation with human clinical trials—can be very strict. For instance, many studies exclude dogs with other comorbidities, such as renal failure or cardiac disease.

COP Trials

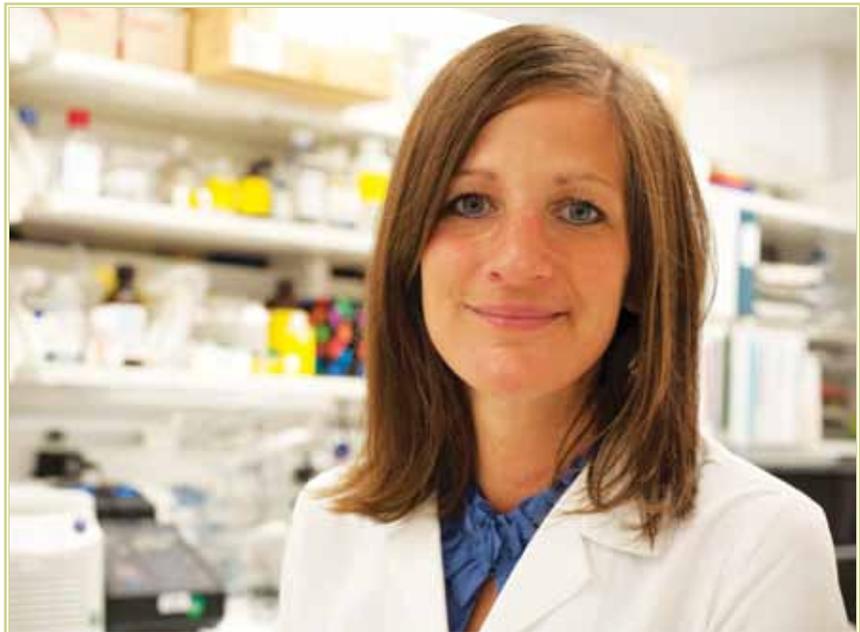
Prince was enrolled in a study of two immunocytokine fusion proteins in tumor-bearing dogs, which aimed to define optimal doses and early indications of antitumor activity. "He'd get a monthly injection and then periodic bloodwork," said Susan Lana, D.V.M., Chief of Clinical Oncology at Colorado State University Veterinary Teaching Hospital and Animal Cancer Center. "And we would follow the tumor as he progressed. Prince was a good candidate because, although his tumor was large, he was healthy in all other respects."

The first of the COTC's studies was sponsored by CCR and conceived through a collaboration of CCR's Surgery Branch and COP, and individuals at M.D. Anderson Cancer Center in Houston, Tex. Led by Paoloni, that study investigated the safety and effectiveness of using a bacterial phage to deliver tumor necrosis factor (TNF)—an inflammatory cytokine—directly into tumor blood vessels by intravenous dosing. TNF-alpha was already approved for local administration in melanoma and soft tissue sarcoma, but with systemic dosing, human patients ran a high risk of hypotension and other cardiovascular reactions. The phage was designed to avoid that problem by targeting a molecular marker on tumor blood vessels. Thus, the phage would theoretically spare normal vasculature

and avoid cardiovascular and other toxicities. However, it was not practical to test the phage in healthy animals without cancer because animals lacking the tumor marker would simply excrete the phage. During the trial, COTC scientists at five participating universities tested the phage in a pair of sequential studies. That data is now being used as a basis for the first Phase I clinical trial in humans, Paoloni said.

According to Khanna, many COTC studies strive to predict appropriate human doses of new cancer drugs. “We want to know the relationship between dose and effect at a molecular level.” Furthermore, he said, “There is a great need to answer simple questions that would optimize the success of future human trials. This can be as simple as: When is the best time to conduct a biopsy after dosing to see if a drug did what it was intended to do?”

In a pilot study that is nearing completion, the COTC is investigating the feasibility of collecting, processing, and analyzing tissues from multiple sites for molecular markers in under a week, a clinically necessary timeline. According to Paoloni, this particular study, which is sponsored by the Translational Genomics Research Institute (TGEN), a non-profit organization in Phoenix, Ariz., will confirm COTC’s future ability to participate in large-scale, molecular research in personalized medicine. “It’s crucially important that we can process tissues and generate accurate molecular readouts quickly,” Paoloni said. “There are many examples of failures that may occur with sample processing in the era of targeted cancer therapy. You cannot underestimate how important it is to be able to collect samples correctly—otherwise the promise of personalized medicine will be difficult to realize.” Lana agrees, pointing out that in a “non-clinical world” it might take months to generate that kind of information. “Patients with cancer can’t wait that long,” she said.



(Photo: R. Baer)

Melissa Paoloni, D.V.M.

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This pilot study, Paoloni said, precedes a trial planned for next year—also sponsored by TGEN—to determine if appropriate therapies can be prescribed on the basis of molecular profiling to support the clinical utility of individualized cancer care. Two additional trials planned for the coming year involve new areas of research for COTC investigators: one aims to determine if molecular results obtained from tumor biopsies can be predicted by advanced imaging technologies, and a second is focused on discovering the novel mechanism of action for a compound currently in the clinic. “These are both exciting studies,” Paoloni said.

Asked about long term plans for COTC, Paoloni envisions the future this way, “Essentially, we want to demonstrate the utility of this model so effectively that large pharmaceutical companies begin to develop their own comparative oncology programs. In that case,

the COTC’s role would be to oversee and advise on trials run by the pharmaceutical industry.”

The Way family’s opinion is that Prince was an active partner in the COP’s research. “It wasn’t easy,” they said. “Although we worked with great veterinarians in the program, it was emotionally hard to go through it. But we thought the program could benefit a lot of people, and that was important to us. We all have friends or family who have struggled with or died of cancer and this was a positive thing for us and our dog to do.”

To learn more about Drs. Khanna and Paoloni’s research, please visit Dr. Khanna’s CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=khanna>.

To learn more about the Comparative Oncology Program, please visit the Web site at <https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home>.