# Clinical Trials Going to the Dogs: Canine Program To Study Tumor Treatment, Biology

After nearly 3 years of groundwork and planning, the Comparative Oncology Program (COP) at the National Cancer Institute took a step forward in February with the launch of a new canine clinical oncology trial. Although testing drugs in dogs is not a new concept, the $1.2 million program at the NCI's Center for Cancer Research incorporates an integrated approach to drug discovery and development by using technology based on knowledge of the recently sequenced dog genome, as well as many new efforts that have been designed to make the dog trials work much like drug studies done in humans.

The aims of the new approach are threefold: The first is to develop a set of reagents, including oligonucleotide microarrays and proteomic assays, to help predict drug toxicity, efficacy, and drug mechanism in dogs. The premise is that, because of the pronounced genetic similarities between man and dog, applying these technologies should result in a highly predictive model that would give rise to much more efficient drug development for humans. Second, like human clinical trials cooperative groups, NCI has established a multicenter Comparative Oncology Trials Consortium of top-tier veterinary oncology institutes that will collaborate using standardized protocols. And finally, it's essential, according to veterinary oncologist and program head Chand Khanna, D.V.M, Ph.D., to increase awareness of the suitable use of "naturally occurring cancer models in pet dogs" within the cancer research community.

The bottom line is that the dog is much closer phylogenetically to humans than rodents, which are the classic toxicity models that researchers use to prepare their investigational new drug (IND) applications for submission to the U.S. Food and Drug Administration prior to beginning human phase I trials. Also, many of the nearly 70 million U.S. dogs tend to get some of the same cancers as humans, and pet owners are highly motivated to offer their creatures top-quality health care. The upshot is that there is a ready-made base of canine patients available to veterinary institutions.

One of the more obvious and practical advantages of canines versus rodents in preclinical studies is the dog's larger body size, which allows for easier collection of serum, urine, and tissue biopsy samples. And dogs, like humans, develop malignancies spontaneously without experimental exposure to carcinogens or artificially induced immunologic or genetic modification. Veterinary oncologist David Vail, D.V.M., of Colorado State University in Fort Collins, is an active member of the COP clinical trials consortium. He says one of the great benefits of canine clinical studies is that the hepatic enzyme homology of dogs "is two orders of magnitude more similar to people than that of rodents," which is of considerable importance when the goal is to translate discoveries into useful human therapies. And for the purposes of an experimental model, it helps that animal tumors progress more rapidly than those in their human counterparts, making data accrual faster.

The companion animal population provides many animals with cancers of the same histologic types as humans, such as non-Hodgkin lymphoma and osteosarcoma, the latter being most prevalent primary bone tumor in both dogs and human children. "More importantly, companion animal tumors often possess the same molecular targets, regardless of histology, that can be readily utilized for proof-of-concept, proof-of-target analysis," Vail said.

**Chand Khanna (shown here with Gracie, a lymphoma patient) is heading up NCI's Comparative Oncology Program, which will take advantage of the similarities between canine and human cancers to test cancer drugs in clinical trials of dogs.**

Veterinary oncologist and postdoctoral fellow Melissa Paoloni, D.V.M., collaborated with Santa Clara, Calif.–based Affymetrix to develop the original dog genome array. "In our current work, we've seen examples of the similarity between the osteosarcoma expression profiles in man and dog," she said. They had expected to see the highly expressed genes in both sets to be defined by species, meaning there would be one group of canine osteosarcoma samples with similar gene expression clustered together and a second pediatric osteosarcoma group with similar gene expression clustered together, she said. But instead the canine and pediatric samples were intermixed, sharing a genetic signature. This was the genomic proof of principle that the COP team was looking for that "disease trumps species," according to Paoloni.

When the first dog trials begin, all data reporting will be standardized by use of an electronic system that is part of the NCI's drug development effort on the human side. "We're going to tailor that to the dog trials," Khanna said. He would like to see the new sophisticated data gathering included in the IND package as a drug enters the human clinical development phase from his program. There is no clear precedent within the FDA for how tumor-bearing dog studies would be reviewed. "So we've had discussions with the FDA," Khanna said, "to find out how we can have this data included in a package for a human IND application. We want to ensure that the data is prepared in a way that the FDA is used to seeing clinical trial data," he said.

### The First Trial

The trial that begins this month is testing a novel targeted vector system based on modified viral bacteriophages

developed by NCI surgeon and senior investigator Steven Libutti, M.D., and Renata Pasqualini, Ph.D., and Wadih Arap, M.D., Ph.D., of the University of Texas M. D. Anderson Cancer Center in Houston. The phages are designed to bind to eukaryotic cells in tumor vessels and express the cytokine tumor necrosis factor (TNF). The result is that the tumor vasculature gets closed off and starves the tumor. "We've done studies in small animals and mice with tumors," Libutti said, "and when we've delivered the phages systemically into the mice by injecting intravenously, the targeted phages go only to the tumor vessels."

The COP team will treat at least four tumor-bearing dogs with the TNF–bacteriophage system. These dogs will already have been slated for amputation or tumor resection. Four days after infusion, the cancerous tissues will be removed and examined for evidence of TNF. Nontumor tissues will also be examined for traces of the drug. If TNF has been expressed in the desired areas, and if toxicity is not an issue, the team expects to move straight ahead to the next step, definitive therapy of a tumor-bearing dog with expectation of tumor shrinkage.

Although the first few drugs coming through the program are being sponsored by the NCI, Khanna wants to recruit pharmaceutical and biotech companies to use the program. One or two drug developers have raised the question of how the FDA might react to some adverse reaction in a tumor-bearing dog that did not occur in healthy rodent models.

"My own opinion is that that the comparative canine studies are separate and distinct from the toxicology studies that are part of an IND," said Gregory Curt, M.D., senior medical director at AstraZeneca Oncology in Garrett Park, Md. "In my experience, the FDA is extremely reasonable, and I think the more scientifically grounded information you give them, the better. It can only help."

### A New Genomics Data Bank

In addition to the trials consortium, Khanna is starting a Canine Comparative Oncology and Genomics Consortium, a community of investigators whose mission is to assemble a 3000-patient biospecimen depository, which will consist of canine tumors, blood samples, urine, and buffy coats. They will be stored at the NCI and made publicly available through a scientific review of requests from government, academic, and pharmaceutical groups. "They will be able to access tissues and perhaps query for expression profiles of specific targets," says Khanna. "These could result in new targets and initiation of new trials."

**—George S. Mack**

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