NEWS

Studying Pets’ Cancers May Yield Health Benefits For Humans

By Susan Jenks

Initially tested in pet dogs with bone cancer, a new drug that delays metastasis now helps children with the same disease in Europe.

The immune modulator, which mops up microscopic cancer cells, has not been approved in the United States, researchers say. But, the use of mifamurtide (trade name Mepact, marketed by Takeda) overseas illustrates how companion animals, especially dogs, can serve as preclinical models for faster drug development, with surprising health benefits to both dogs and people.

Unlike the mouse model, they say, dogs develop cancers that share many characteristics with human disease: long latency periods, natural causation, genetic complexity, similar tumor size, and even drug resistance. In osteosarcoma, these parallels appear quite striking.

"Osteosarcoma is really the poster child of comparative oncology," said Timothy Fan, D.V.M., Ph.D., associate professor in the department of veterinary clinical medicine at the University of Illinois at Urbana–Champaign. "It’s a disease that is genetically indistinguishable [in dogs] from that seen in humans."

Scientists long have recognized that cancers arising spontaneously in dogs, and more rarely in cats, can be useful for studying human cancers. But a resurgence in interest has come mostly within the past decade, with the resolution of the canine genome in 2005 by an international team of researchers, led by the Broad Institute at the Massachusetts Institute of Technology, in Cambridge, Mass. and Harvard University, also in Cambridge. This past June, the Institute of Medicine’s National Cancer Policy Board held its first workshop in Washington, D.C., on the topic: “The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research.”

"Each dog breed represents a closed population genetically," offering tremendous advantages for studying complex genes and their role in cancer and other diseases, said Elaine A. Ostrander, Ph.D., chief of the Cancer Genetics and Comparative Genomics Branch at the National Human Genome Research Institute. A leading authority in the field, Ostrander cowrote an analysis of the canine genome’s resolution (Nature 2005;438:803–9).

Even though the American Kennel Club recognizes at least 185 distinct dog breeds, she said “it’s important to remember they’re all members of the same species.” If scientists are studying a particular illness in a particular breed, Ostrander said, it’s very likely they share common ancestry and carry similar genetic mutations not seen in a different breed.

Her lab has collected 50,000 DNA samples from dogs so far. Most samples come from American Kennel Club–approved breeds, Ostrander said, although researchers accept blood or saliva swabs from an occasional feral dog elsewhere in the world or from pets of volunteers who contact the institute.

“Our focus is on cancer markers and susceptibility genes and how these spill over to help human diagnoses and treatment of disease,” she said.

A recent example involves a tumor marker identified in dogs who develop bladder cancer (Mol. Cancer Res. 2015; 6:993–1002). Ostrander and her colleagues discovered a BRAF mutation in the urine of pet dogs that not only triggers their disease but also has been implicated in multiple human cancers. The marker carries an 85% predictability rate, Ostrander said, setting the stage for early diagnostic testing as well as a system for evaluating BRAF-targeted therapies in both dogs and people.

As one of the workshop organizers, Ostrander attributes renewed attention to the canine genome, in part, to the 10-year lag since the genome’s sequencing. Also, “we’re at the beginning of what we hope will be a huge slew of papers coming out soon,” she said. “We’re finding the same [genetic] vocabulary exists between humans and dogs.”

The University of Illinois’s Fan cited several other reasons for the recent focus on companion animals in cancer research. Not only have the technologic capabilities of veterinarians grown, he
said, but also societal factors come into play. “People increasingly view dogs as part of their families with high emotional value,” he said, “so they’re willing to do whatever they can for them.”

Cancer occurs often in companion pets, with age the main risk factor, just as in people. Estimates suggest that half of dogs older than 10 years die from cancer, whereas roughly one-third of cats do. Although cats are part of the spontaneous-cancer equation, Fan said, “huge gaps in the feline genome” remain. Researchers therefore view companion dogs as a better bridge between traditional rodent models and human trials for testing new drugs, devices, and imaging techniques.

Research Infrastructure

The National Cancer Institute–managed Comparative Oncology Trials Consortium supplies the infrastructure for coordinating animal clinical trials nationwide. Through this mechanism, a consortium of 20 academic centers, veterinarians participate in clinical trials to treat dogs with cancers.

Because data from research studies can be generated quickly, given dogs’ comparatively short life spans, “endpoints in drug development may be achieved in about one-fifth the time of human trials,” said Rodney Page, D.V.M., director of the Flint Animal Cancer Center at Colorado State University, in Fort Collins. The university is part of the consortium.

Also, because genetic similarities exist for other cancers, besides osteosarcomas, outcomes may be more predictive of what to expect in people, at far less cost, he and others said.

Only about 11% of drugs showing anticancer activity in the mouse go on to gain approval for human use, according to pharmaceutical data. Moreover, cancer drugs carry significantly higher attrition rates than those in other therapeutic arenas—a 5% success rate, for example, compared with a 20% success rate in cardiovascular drug development (Nat. Rev. Drug Discov. 2004;3:711–6).

“In the classic xenograph trial (using the murine model), we give them drugs and it’s kind of cheating,” said Amy LeBlanc, D.V.M., director of the comparative oncology program at NCI. “It’s a homogenous model. And when we apply drugs in this context, it lacks the stroma or genetic complexity of cancer in humans.”

Another limitation involves size. Because mice are diminutive, researchers cannot track disease longitudinally over time. “We can’t ask questions about basic toxicity,” LeBlanc said. In comparison, dogs are so solicitous during testing, “we know how they’re feeling most of the time,” she said. “Or, their owners tell us, ‘my dog isn’t feeling well.’”

Researchers also can test drugs in dogs that have had no previous treatments. “We routinely run novel investigative drug studies this way,” LeBlanc said. “This doesn’t happen in humans,” given ethical constraints.

Nevertheless, dogs enjoy rigorous protections as research subjects, with consent forms and oversight similar to that seen in people, according to LeBlanc. “And, the nice thing is these animals still live at home.”

Hurdles

A report from the Institute of Medicine workshop, presently under external review, will outline the advantages of integrating animal studies into clinical pathways for humans. The final document also will lay out gaps in knowledge, including the need for further molecular characterization of canine tumors.

“We still need to do the genetics in much more detail in the dog model,” said Michael Kastan, M.D., Ph.D., director of Duke’s Cancer Center, in Durham, N.C., and chairman of the workshop organizing committee. “We’re much further along in understanding human genetics than that of the dog.”

However, over the past decade, he said, targeted therapies, based on genetics, have changed how researchers use companion animals.

“This is a wonderful gift for the pet community,” Kastan said, as pet owners have the option of treating cherished pets with targeted, nontoxic therapies that may extend their lives by months, sometimes years. At the same time, by enrolling a pet in clinical research, new treatments may arise for people.

“I think we’re in our infancy with this,” he said. “But the data we obtain in dogs can inform human trials and help the animals, too. It’s mutually beneficial.”

Tapping into that benefit, workshop participants agreed, will require educational awareness about the opportunities comparative oncology affords and additional funding. Financial support for a cancer atlas in dogs, similar to the human atlas, would help propel the canine genome along toward solving the heterogeneity problem in human tumors, Ostrander said.

Also, funds to develop additional reagents would yield better understanding of immune function, Page said. At least 150 reagents exist in humans and mice to see whether a drug is working, he said, whereas veterinarians draw upon just 30–40 in dogs—and even fewer in cats.

Golden Retrievers

Meanwhile, as cancer treatments in people and animals move slowly toward personalized care, the largest observational trial ever in companion dogs recently got under way. The 10-year Golden Retriever Lifetime Study should yield genetic clues about why this breed experiences such a high rate of cancer, as well as more general information about environmental and nutritional risks.

Investigators know dogs and humans share roughly the same number of genes, but dogs rarely get colon cancers, nor do they often develop lung cancer. “Even though dog tumors have a lot of similarities to our own, dogs don’t smoke,” for example, Kastan said. “They live in our environment but lack our bad habits.”

Altogether, 3,000 dogs have been enrolled in the study, funded by the Morris Animal Foundation, a global nonprofit headquartered in Denver. Fully half of the retrievers are expected to develop cancer.

Page, the principal investigator, compares the research effort to the Framingham Study, which has monitored residents of Framingham, Mass., for cardiovascular disease risks since 1948. “It should be transformative for animal health and cross over to human health as well,” he said.

Sadly, for Leonard Lichtenfeld, M.D., deputy chief medical officer of the American Cancer Society, and the workshop’s final speaker, whatever information emerges comes too late for Lily, his beloved 11-year-old Golden Retriever. Lily died of lymphoma shortly before the workshop began.

Writing in his cancer blog afterward, Lichtenfeld admitted he gave little consideration to comparative oncology before the meeting. Nor did he realize, he said, how personal a journey such knowledge would be.

Still, the promise comparative oncology research holds—for dogs, their owners, and science—intrigues him. Quoting a colleague’s succinct observation, he wrote, “Some of the answers to the treatment of cancers in humans may, in fact, be walking right beside us every day.” 