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Medical News & Perspectives

Researchers Turn to Canine Clinical Trials to Advance Cancer Therapies

Julie A. Jacob, MA

About 6 million dogs are diagnosed with cancer each year, and more than half of dogs older than 10 years will develop cancers such as osteosarcoma, lymphoma, or melanoma (<http://1.usa.gov/1OAxjB>). But the heartbreaking diagnosis for dog owners is a treasure trove of potential data for oncology researchers. In clinical trials at academic research centers across the country, veterinarians and physicians are studying how pet dogs respond to cancer therapies and analyzing the genetic makeup of these tumors. Although medicine and veterinary medicine, for the most part, have been viewed as 2 different worlds, with little exchange of information between the two, that is beginning to change.

"We've come a long way in the last 10 years in understanding what we know and don't know about canine cancers to define the type of questions that can be efficiently answered within that model," observed Amy K. LeBlanc, DVM, director of the National Cancer Institute's (NCI's) Comparative Oncology Program (COP).

In recognition of the potential utility of canine cancer models, the NCI established COP in 2003 to promote comparative oncology research (<http://1.usa.gov/100dFg9>). The NCI also created the Comparative Oncology Trials Consortium (COTC) to manage comparative oncology clinical trials conducted at a network of 20 academic veterinary medical centers (<http://1.usa.gov/1ORcTSQ>). And just last year, the National

Academy of Medicine held a workshop on comparative oncology and issued a report addressing how to best integrate clinical trials of pets with naturally occurring cancers into human oncology research (<http://bit.ly/1Rvn2d2>).

There's even been interest in exploring tumor biology in nondomesticated animals such as elephants to better understand mechanisms of cancer suppression (Abegglen LM et al. *JAMA*. 2015;314[17]:1850-1860). The surge in comparative oncology research may be due to a convergence of factors, noted Will Eward, DVM, MD, an assistant professor of orthopaedic surgery at Duke University School of Medicine, who researches and treats sarcoma in both human and furry, four-legged canine patients.

"I don't know if as pet insurance becomes more common, more people are seeking high-end treatment [for pets], or if we've reached a critical mass of researchers who are looking at humans and other species," said Eward.

Advantages Over Mouse Models

Traditionally, the development of new cancer therapies has followed the 3-step process: laboratory studies, mouse models, and human clinical trials. However, that model doesn't always work well. Only 11% of oncology drugs that appear promising in mouse models turn out to be safe and effective, according to the National Academy of Medicine workshop report.



Karen Clifford/University of Missouri

"The track record for the current way we progress [in drug development] from the laboratory to the clinic is pretty lousy," said Neil Spector, MD, an associate professor of medicine at Duke University School of Medicine who serves on the Consortium for Comparative Canine Oncology steering committee. "Any other industry that had a [low] rate of success would be pretty unacceptable... something different has to be done."

The high failure rate may be due to the stark difference between a laboratory mouse and a human, Eward explained. The study mice may be genetically engineered or have compromised immune systems. They live in sterile laboratories, unlike people who are constantly exposed to pollution, bacteria, UV light, and other environmental factors. Their tumors are homogenous, unlike the heterogeneous tumors that people develop.

With domesticated pet dogs, however, "they live in the same environments and are exposed to the same carcinogens," said Eward. "When you look at naturally occurring cancers [in dogs], we see the same risk factors, the same things associated with [tumor] growth and development."

"A great example is sarcoma," Eward said. "It occurs in the lower part of the femur and the upper part of the tibia, and it occurs in the same place in dogs. Kids at risk are tall, rapidly growing kids. You see the same things in dogs. You're more likely to get it if you're a Great Dane or an Irish Wolfhound than a Chihuahua."

Yet at the same time, certain differences between dogs and humans also make them ideal clinical trial subjects. Dogs have a much shorter life span, so their cancers progress more rapidly, enabling researchers to assess the cancer's progress and the effect of a treatment in a year or two, whereas a human clinical trial might take years longer.

What's more, pet owners are usually eager to enroll their dogs in clinical trials because available therapies may be limited and expensive and such trials offer free hope for their beloved companions. The pet owners' enthusiasm translates into a dedicated adherence to the requirements of the study and doing whatever they can to help the researchers.

"The compliance rates are phenomenal," said David Vail, DVM, chair of veterinary oncology at the University of Wisconsin School of Veterinary Medicine, which is

part of the COTC network. "The autopsy rates [on dogs who die] are 80% plus, and that is virtually unheard of [in human patients]."

Valuable Data

Canine clinical trials in progress or completed are already demonstrating the value of comparative oncology.

For example, noted LeBlanc, a canine clinical trial of the immunocytokine NHS-IL12 as a therapy for treating dogs with melanoma yielded useful information on the drug's safety and efficacy (Paoloni M et al. *PLoS One*. doi:10.1371/journal.pone.0129954 [published online June 19, 2015]). The data on the drug's efficacy were key to the study sponsor's decision to go ahead with a phase 1 clinical trial, she said.

"That data helped support an investigational drug application for a [human] clinical trial that is going on at [National Institutes of Health]," LeBlanc said. "The principal investigator commented how helpful it was to have the dog data."

And at the University of Wisconsin, the veterinary school is participating in a COTC trial of rapamycin to treat pet dogs with osteosarcoma, which affects about 8000 canines and 800 children each year. The clinical trial, which is studying the dosing and scheduling of the drug, should be completed within 2 years, with another year needed to analyze the data, Vail said. Another independent study found that the protein BMI1, which has been implicated in human tumor growth and chemoresistance, may play a similar role in canine primary and metastatic osteosarcoma, suggesting canine models could be used to test the therapeutic potential of BMI1 inhibitors (Shahi MH et al. *PLoS One*. doi:10.1371/journal.pone.0131006 [published online June 25, 2015]).

Researchers at Cornell University College of Veterinary Medicine are planning to study whether a combination of 2 new promising drugs is more effective in treating lymphoma in dogs than each drug alone. Such a clinical trial in humans is currently impossible because neither drug has been thoroughly studied individually, said Kristy Richards, MD, PhD, an associate professor of oncology at Weill Cornell Medical College and an associate professor of biomedical sciences at Cornell University College of Veterinary Medicine, who leads the research.

"With the dogs, we can say 'We think the combination will be best' and go forward [to human trials] with that," said Richards, who prefers not to name the drugs until the trial begins.

As an oncologist, Richards said she is sometimes asked why she's conducting research on dogs. Her response: the results of canine studies may help facilitate the development of treatments for humans.

"I love the fact that the [dog] subjects benefit from the research, but my primary motivation is that I want to cure people with lymphoma," said Richards. "[With dogs] they relapse faster, the kinetics of their disease are faster, we can take biopsies easier."

"We have all these potential study subjects sitting there... why not use that to help speed things up?" she added.

Researchers are also looking at genetic data to help pinpoint mutations most likely to cause certain types of cancer. The canine genome, which was sequenced in 2005, has provided a foundation for future research on the genetic underpinnings of diseases also common in humans (Lindblad-Toh K et al. *Nature*. 2005;438:803-819). Due to selective breeding of dogs over the centuries, many purebreds are susceptible to specific diseases that can be linked back to inheritable germline mutations. Given the large number of breeds and their shared ancestry, inheritable germline mutations associated with complex diseases such as cancer are easier to identify in purebred dogs than in human populations (<http://bit.ly/1PUx9Xe>).

At Duke, for example, Eward and his research team have been doing genetic sequencing on human and canine osteosarcoma tumors and comparing the somatic, or nonheritable, genetic mutations common to both.

"That number of 5 genes that are common to osteosarcoma in dogs and humans matters because if you have a huge number [of mutations in] like 3000 genes, it's kind of hard to figure out which of the 3000 genes to study. If you boil it down to 5 genes, it's a much more reasonable thing to study," said Eward, who noted that the research has not yet been published.

Richards and her team are taking a similar approach, sequencing tumors from 100 dogs with lymphoma to compare both germline and somatic genetic mutations in these tumors with those found in human lymphoma tumors. Their work builds on an

earlier study by other researchers that found somatic mutations in the gene *TRAF3* in about 30% of canine lymphoma and *TRAF3* deletions in about 9% of human diffuse large B-cell lymphoma tumors (Bushell KR et al. *Blood*. 2015; 125[6]:999-1005).

"The germline mutations will help us learn more about the biology of cancer predisposition and oncogenesis, and the somatic mutations, especially the ones in shared pathways, will help us learn more about cancer formation and progression but also provide good therapeutic targets," said Richards.

The team will also compare human and canine clinical data such as disease stage, tumor phenotype, and progression-free survival, she said.

Limitations to Canine Trials

Like any clinical trial model, canine trials are not a cure-all to speed new treatments.

"It's never been our position that the dog should be in every single drug development [process]," said LeBlanc. "It's irresponsible to believe that the dog will solve all the drug development problems."

One limitation is dogs' size: they're larger than mice and require larger drug doses, which increases a trial's cost. Canine clinical trials also take longer than mouse model trials.

In addition, pharmaceutical companies may be reluctant to sponsor a canine clinical trial, fearing that an adverse effect that occurs in a dog might derail clinical trials in humans, Richards noted.

Furthermore, some cancers common in humans, such as breast cancer, are rare in dogs. Still, Vail noted, comparative oncology research may unearth common features between unrelated cancers in humans and dogs, pointing to possible paths for further research. For example, mast cell cancer, a common tumor in dogs, is rare in humans. However, identical receptor

tyrosine kinase signaling pathways have been implicated in the growth of mast cell tumors in dogs and gastrointestinal stromal tumors in humans, thus identifying a potential therapeutic target common to both cancers, explained Vail.

"The drug target can trump the tumor type," said Vail.

According to researchers, perhaps the biggest hurdle to canine clinical trials is that many physicians and researchers are still not aware of the wealth of clinical data to be mined from the millions of dogs who develop cancer each year.

"We would love to see better treatments for our pets," said Spector, who had to have his own dog euthanized because of a metastatic mast cell tumor. "Can we not only improve the cutting-edge therapies for veterinary patients, but then take the lessons learned and create much more efficient therapies for humans? It really is a win-win for everyone." ■

The JAMA Forum

Addressing Social Issues Affecting Health to Improve US Health Outcomes

Gail Wilensky, PhD

In a recent *JAMA Forum*, Ashish Jha, MD, MPH, wrote about tackling the social determinants of health as a process that will require taking "small steps on a long journey" (<http://bit.ly/1JM5hFM>). I agree with him about the complexity raised by the social issues affecting health. And his admonition that investments in social determinants such as education, housing, and nutrition may not reduce spending on medical care—especially in the near term—are important warnings.

I want to use a different rationale in advocating more attention to the social determinants of health: they reflect our best opportunity to improve health outcomes reported for the United States that are relatively poor, despite how much we spend on medical care.

For many years, the United States has focused on the need to slow spending on health care. Although levels of spending increases for health care have been histori-

cally low during the last 7 years, the higher spending reported for 2014 is expected to continue for the next decade, averaging 5.8% per year (<http://bit.ly/1JsXPgt>). That would bring the share of the gross domestic product (GDP) spent on health care from 17.5% to 19.6% by 2024. The estimated spending growth rate may not be precisely correct, but the end of the recession and the continued numbers of baby boomers entering retirement age guarantee continued upward pressure on health care spending.

Fortunately, there are many strategies available to help slow health care spending, some of which are currently being tried. Some of the most promising pilot projects include various types of payment changes, including bundled payments across clinicians and institutions that reward improved value, as well as changes that encourage the delivery of more integrated, evidence-based care. There are also efforts to provide better, more



Gail Wilensky, PhD

reliable and easily accessible information on quality and prices.

I'm not suggesting that sustaining a slower rate of growth will be easy. The mixed