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How dogs are teaching researchers new tricks for treating cancer

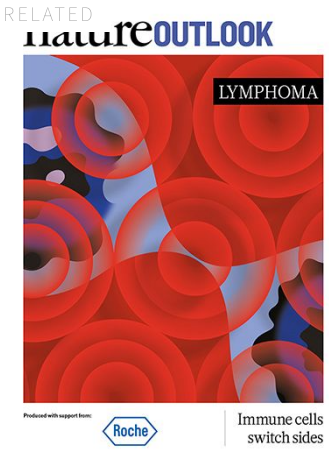
Studying lymphoma in canines yields insight into therapies for people — with a bonus of helping the animals.

Sarah DeWeerdt

Canine lymphoma is remarkably similar to the human disease. Credit: Cultura/Shutterstock

In 2003, newly minted MD Kristy Richards was preparing to move to Houston, Texas, to start a fellowship in oncology. At a friend's wedding, she got talking with a fellow guest from Houston, a veterinarian who treated dogs with cancer.

Richards was incredulous. "You give chemo to dogs?" she recalls asking.



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Richards' chance encounter shaped her career. She now has joint appointments at the veterinary school of Cornell University in Ithaca and its medical school in New York City. And she is on a quest to improve treatment for both people and dogs with lymphoma.

Her primary concern remains human health. "I want to cure lymphoma in people," she says. "I just happen to be able to say that I help the research organism that I'm working on." Veterinary researchers, too, are on the lookout for cross-species benefits. Although their main goal is to find ways to treat canine lymphoma, "if it works in humans, it's a bonus", says Jaime Modiano, a veterinary oncologist at the University of Minnesota in Minneapolis.

Modiano and Richards are part of a growing cadre of interdisciplinary researchers who have made lymphoma into a prime example of the 'one medicine' concept — the idea that human and animal physiology, health and disease are intricately linked.

The latest studies deepen understanding of when and why dogs provide a good model for human lymphoma, as well as how human and canine lymphomas diverge in terms of their prognosis, biochemistry and gene expression. Such research holds the promise of eventually improving treatment for both species. "Maybe where they don't match is just as important and interesting as where they do," says Amy LeBlanc, director of the Comparative Oncology Program at the US National Institutes of Health (NIH) in Bethesda, Maryland.

A shared environment

For reasons that are not well understood, lymphoma rates are increasing in humans and dogs, and it is one of the most common forms of cancer in both species.

Dogs have contributed to improvements in cancer treatment for humans since at least the 1960s, when researchers led by E. Donnall Thomas at the US Public Health Service Hospital in Seattle, Washington, used dogs as a model organism to develop bone-marrow transplantation protocols. In the decades that followed, researchers mapped an increasing list of similarities between canine and human lymphoma, such as the appearance of the cells and the architecture of affected lymph nodes. And in the 1980s, veterinary pathologist Victor Valli, then at the University of Guelph in Canada, began to classify dog lymphomas using rubrics established for human disease.

Interest in canine lymphoma as a model for human disease rocketed after the first complete dog genome sequence was published in 2005. Although knowledge of dog DNA still lags behind that of classic laboratory organisms such as the mouse, researchers say dogs have a lot of advantages as a model species. Dogs "live side by side with us", says veterinary oncologist and researcher Steven Suter of North Carolina State University in Raleigh. "They drink the water that we drink. Many times they eat the same food that we eat, they play in the same yards we do, covered with pesticides. They're exposed to the same air that we're exposed to."

situation that you can't accurately replicate in any other species," says LeBlanc. Studying naturally occurring tumours in dogs also has an ethical benefit, reducing the number of animals in which cancer is deliberately induced.

Canine chemo

Most lymphomas arise from B cells or T cells, two types of white blood cell. In humans, diffuse large B-cell lymphoma (DLBCL), the most common form of B-cell lymphoma, can be cured in two-thirds of cases by the combination of CHOP chemotherapy and rituximab, an antibody that targets a protein called CD20 found on B cells. But rituximab does not recognize the canine version of CD20. (Researchers are working on an anti-CD20 antibody for dogs, but it's not yet in wide clinical use.) Dogs also get lower doses of CHOP than humans, because veterinary protocols prioritize maintaining quality of life over curing the disease. As a result, chemotherapy rarely cures lymphoma in dogs; the animals relapse within 12–18 months on average.

But this sad fact does provide an opening for research because it means pet owners don't have to forgo a potentially curative therapy to try an experimental one. "We can explore novel therapeutic combinations before relapse," says Cheryl London, a veterinary oncologist at Tufts University in North Grafton, Massachusetts. For example, in 2017, London and Richards received a grant to study a chemotherapy-free regimen in dogs with lymphoma. If the treatment proves effective in dogs, it could one day result in a less-toxic lymphoma treatment for humans.

Dog lymphomas typically affect lymph nodes in the animals' legs, which can be easily monitored and biopsied. In a study published in July[1], researchers tracked the effect of experimental drugs in dogs with lymphoma by measuring the affected lymph nodes with calipers — a distinctly low-tech and cost-effective solution compared with the computed tomography scans that are often used to monitor human disease.

This study took place at nine sites that are part of the clinical-trial network of the NIH's Comparative Oncology Program. Researchers divided 84 dogs into 3 groups and gave each group one of 3 different topoisomerase 1 inhibitors. Other drugs in this class are approved for use in various human cancers and work by damaging the DNA in dividing tumour cells. The researchers found that one molecule, LMP744, was especially good at shrinking cancerous lymph nodes in the dogs.

The data — including information about when biopsies should be taken, how patients should be followed up and which biomarkers can be used to track response to the drugs — will help researchers to design trials of the drugs in humans, says LeBlanc.

Root causes

Sometimes, drugs designed for humans and tested in dogs can lead to improvements in veterinary medicine. In 2014, European researchers found that adding a cancer vaccine to standard chemotherapy prolongs the survival of dogs with DLBCL[2]. The vaccine might soon enter human trials, says veterinary oncologist and lead author Laura Marconato at the Veterinary Oncology Centre in Bologna, Italy, and it has transformed her own clinical practice. "We now can really select the perfect candidate to respond to immunotherapy, and that's a revolution from the clinical trial that we have published," she says.

picture has become more complicated.

“To say that the dog is a good model you need to study really, really deep,” says Marconato’s collaborator Luca Aresu, an immunologist at the University of Turin in Italy who has investigated gene expression, gene regulation and tumour genomics in canine DLBCL. Studies by Aresu and others suggest that canine and human DLBCL often involve the same biochemical pathways, but sometimes different genes have gone awry.

Such differences mean that researchers must be cautious when using dogs to test targeted therapies for lymphoma, because these therapies depend on the presence of specific mutations in the tumour cell. However, the similarities that do exist might point researchers to fundamental aspects of tumour biology.

And in some cases, apparent differences between dog and human lymphoma actually diminish with deeper study. In 2015, researchers identified mutations in a gene known as *TRAF3* in nearly half of canine B-cell lymphomas[3]. The gene had not previously been implicated in human lymphoma, but when the authors checked, sure enough they found *TRAF3* mutations in about 9% of human DLBCL samples. The gene “might not have been recognized as being important without the canine data”, says London.

Breeds apart

T-cell lymphoma has a relatively poor prognosis in both dogs and humans. But it is more common in dogs, accounting for 25–35% of lymphomas, compared with less than 15% in humans. Because more canine patients are available, studies of T-cell lymphomas in dogs can advance more quickly. This year, London and her colleagues reported promising results from a molecule called RV1001 — which targets a signalling molecule in the phosphoinositide 3-kinase family — in dogs with T-cell lymphoma[4]. The results helped to pave the way for orphan-drug approval of a human version of the drug for use in T-cell lymphoma, London says.

Certain dog breeds, such as golden retrievers, boxers and German shepherds, are especially prone to developing T-cell lymphoma. Such breed-specific susceptibility patterns could help researchers to identify genes that contribute to inherited risk of lymphoma, says Anne Avery, an immunologist who studies canine lymphoma at Colorado State University in Fort Collins. Owing to a history of inbreeding, dogs have lower background genetic diversity than most human populations. This means that it should be possible to pinpoint susceptibility genes more quickly and with smaller studies than would be necessary in humans. Avery has just launched a search for genetic risk factors for T-cell lymphoma in boxers; she expects to recruit 150 cases and a similar number of controls over the course of 2 years.

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Eventually, such efforts could open up the possibility of prevention studies using drugs designed to stop lymphoma before it starts. These studies would be wildly impractical in humans, because of our species’ diffusely distributed risk and long lifespan. But conducting a study in a high-risk breed and following the dogs across their much shorter lifespan would be feasible.

about giving chemotherapy to dogs that shaped her own career. “And then the light comes on,” she says of her conversations with human oncologists. “And they’re like: ‘Oh so you could do this and this and this’.”

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