ONCOLOGY RESEARCH

New Hope For Dogs With Cancer

By Kristi Fender

It is one of the most difficult conversations a veterinary professional has to have with a client—delivering the news that their pet has cancer. Progress is being made as researchers find therapies and treatments that help animals with cancer live longer and with better quality of life. *Today's Veterinary Practice* spoke with academic investigators to learn what's going on at the forefront of veterinary cancer research, and one theme emerged clearly: immunotherapy is big. Many researchers are looking for ways to shut down the disease process by activating the body's natural defenses. But this isn't all that's being studied. Today, researchers in laboratories and clinics of veterinary schools across the U.S. are making significant strides in treating—and hopefully someday preventing—cancer in pets.

COLORADO STATE UNIVERSITY

One of the largest and most exciting veterinary oncology studies happening right now is the Vaccine Against Canine Cancer Study (**vaccs.org**), which could potentially protect dogs against 7 different types of cancer. The study is taking place at Colorado State University (CSU), the University of Wisconsin-Madison, and the University of California, Davis, with Douglas Thamm, VMD, DACVIM (Oncology), director of clinical research at CSU's Flint Animal Cancer Center, leading the charge.

"I would love to see this vaccine become something that's useful and widely available for dog owners to potentially delay or prevent cancer," Dr. Thamm says.

The components of the vaccine being studied are derived from a series of neoantigens arising from errors in RNA processing, Dr. Thamm says. Unlike the novel proteins that result from DNA processing, which are highly individual to each patient, RNA-derived neoantigens appear to be common among multiple kinds of tumors in multiple species. Stephen Johnston, PhD, creator of the vaccine and director of the Center for Innovations in Medicine at Arizona State University, found that it was protective against cancer in mice.[1]

"If you inject these proteins in mice and challenge the mice with tumors, tumor growth is delayed or prevented," Dr. Thamm says.

Of course, efficacy in mice does not guarantee usefulness or safety in other species. While the vaccine has major translational potential for human health, dogs are a logical "proof of concept" species to study before testing in people, Dr. Thamm continues. Their shorter lifespan allows researchers to gather data relatively quickly, and spontaneously arising tumors in dogs are a much more faithful model of human cancer. Plus, the canine species benefits as well.

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The study has enrolled 350 of its target 800 dogs so far (participants must live within 150 miles of one of the 3 universities), which will be followed for 5 years. The dogs are screened to make sure they're free of pre-existing cancer and other lifespan-limiting conditions, then given the vaccine (or placebo) every other week for 4 doses, then a 1-year booster.

The vaccine is designed to cover the top canine tumors, including carcinoma, fibrosarcoma, hemangiosarcoma, lymphoma, mast cell tumor, and osteosarcoma. Dogs are monitored for the presence of these cancers and other diseases, and most of their healthcare costs are covered during the study period, including any cancer treatment necessary. The study is funded by the Open Philanthropy Project (**openphilanthropy.org**).

VIRGINIA TECH

At the Virginia-Maryland College of Veterinary Medicine, Nick Dervisis, DVM, PhD, DACVIM (Oncology), associate professor of oncology, recently completed a pilot study looking at a new ablative technology: high-frequency irreversible electroporation (H-FIRE) in dogs with liver cancer.[2]

What exactly is H-FIRE, and how does it work? First, let's look at electroporation itself: "We apply electrical pulses at a specific voltage and frequency to open nanopores in the cell membrane," Dr. Dervisis says. Irreversible electroporation means the nanopores don't close: "The current view is that the cells become leaky and die off because they cannot hold all the intracellular material inside them." And high-frequency application means these electrical pulses do not stimulate the heart or other muscles in dangerous or painful ways, making it safer for the patient.

In their pilot study, Dr. Dervisis and his colleagues treated dogs with liver tumors with H-FIRE before the tumors were surgically removed, then analyzed the tumors to determine the effects of treatment. The goals were to show that H-FIRE can be delivered percutaneously, that it's safe for the patient, and that it stimulates the patient's immune system—it's thought that tumor cells "hiding" from the body's natural defenses become visible to the body once intracellular material leaks from the cell membrane. This allows T-cells to target those cells and destroy them.

Dr. Dervisis says it also appears that H-FIRE preferentially targets cancer cells. "With liver cancer, where the treatment typically fails is at the margin," he says. "You don't want to leave cancer cells behind when you resect the tumor or when you irradiate, but that means you're killing a bunch of normal cells. With H-FIRE we have some preliminary data suggesting we can preferentially target neoplastic cells, leaving the normal cells intact or at least causing lesser damage that can be repaired."

The target is to be able to treat dogs with nonresectable or metastatic cancer of the liver—patients that currently have few options. The team also has received funding to study H-FIRE in lung cancer in dogs.

Also at Virginia-Maryland on the ablative front, Joanne Tuohy, DVM, PhD, DACVS-SA, assistant professor of oncology, is looking at histotripsy for the treatment of canine appendicular osteosarcoma. Histotripsy, she explains, is a focused ultrasound technique that enables clinicians to ablate (destroy) tumor cells without heat. The process utilizes acoustic cavitation, which, when applied to a tumor, creates a "bubble cloud" in the area where cells are being destroyed.

"It's very difficult to control what heat does to normal tissues that surround the tumor," Dr. Tuohy says. "When we use something like histotripsy without heat and instead use acoustic cavitation, these bubble clouds that get generated within tumor tissue expand and contract, essentially disintegrating the tissue into its subcellular components. Having this precise way to disintegrate tumor cells allows us to spare surrounding tissues."

Dr. Tuohy has received funding for a very early proof-of-principle clinical trial to determine if the technology can reliably kill all tumor cells in a particular tumor or just a percentage of them. She and her team will apply the technology to osteosarcoma tumors in dogs before the limb is amputated as part of a standard treatment approach, then examine the results of the histotripsy process on the tissue. "Another question we would like answered is, what kind of immune cells then come into the area being treated?" Dr. Tuohy says. "There's a theory that histotripsy can induce an immune response that could potentially be effective against the tumor and any cells wanting to metastasize to other areas."

While histotripsy has been studied in humans, it has never been investigated with bone disease, so Dr. Tuohy says she's excited about the potential for this technology to help humans with osteosarcoma, which is

remarkably similar to the canine version. Another plus? "We're looking at a way we can potentially preserve the limb so that we don't have to amputate the limb in order to destroy the tumor," she says.

Dr. Tuohy says her team wouldn't be poised on the brink of this study without the help of local and regional veterinarians. "The local veterinary community has sent us tumor samples so we could do our preliminary studies and gather the supportive data," she says. "They have played a very big role."

PENN

The University of Pennsylvania School of Veterinary Medicine also has a couple of immunotherapy clinical trials in the works through its Comprehensive Cancer Care service, according to Ashleigh Cournoyer, DVM, specialty intern; Jennifer Lenz, DVM, DACVIM (Oncology), assistant professor; and Cynthia Clendenin, VMD, director of comparative oncology trials.

In one study, researchers are treating dogs with B-cell lymphoma using CAR T-cell therapy, a personalized approach that involves modifying a dog's own immune cells to target lymphoma cells in the body. "We're basically teaching their immune system to attack their own cancer," says Dr. Cournoyer.

A future study will look at dogs with bladder tumors, Dr. Cournoyer says. This investigation will examine the effect of an injectable drug that acts as an immune checkpoint inhibitor in dogs with urothelial carcinoma. In simple terms, a checkpoint inhibitor targets a regulatory pathway that a cancer cell can exploit to "put the brakes on" the immune system. By inhibiting that process, researchers can "release the brakes" and unleash the power of the immune system to eliminate cancer cells more easily.

Penn is looking at other approaches to cancer treatment beyond immunotherapy as well. One study is examining FLASH proton radiation for the treatment of osteosarcoma. This treatment is a new approach that uses short pulses of electrons at ultra-high-dose rates to deliver a large dose of radiation in just a fraction of a second. "The idea is to protect normal tissue and simultaneously maximize the anticancer effects," Dr. Clendenin explains.

Veterinary oncologists are also enrolling patients for a clinical trial comparing LOPP (lomustine, vincristine, procarbazine, and prednisolone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy for dogs with T-cell lymphoma. While CHOP is standard of care for veterinary patients with lymphoma, "we've seen time and time again that T-cell lymphoma patients tend to do worse when treated with CHOP than those with B-cell," says Dr. Lenz. "There are other protocols out there, with LOPP being one of the most common, but they've never been compared directly. We're doing a prospective trial to directly compare these two approaches, which our literature is lacking. Please send us your T-cell lymphoma dogs!"

"One question people often ask is whether a study benefits the individual animal in the trial, science, or human patients," Dr. Clendenin observes. "We certainly hope to benefit all of the above… Every patient teaches us about treating the next patient."

ILLINOIS

A study at the University of Illinois is using an immunotherapy approach to combat metastatic disease in dogs with osteosarcoma. In this trial, dogs receive radiation therapy along with an injection into their tumor designed to stimulate the immune system. "Radiation will kill some of the tumor in the leg, but the goal is to activate the immune system to recognize the tumor, not only in the leg but more importantly any metastasis in the lungs," says Timothy Fan, DVM, PhD, assistant director for shared resources and professor of veterinary clinical medicine. Up to 90% of dogs with osteosarcoma will develop metastatic disease in the lungs, Dr. Fan says, so controlling this aspect of the disease could be a major development.

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Researchers at Illinois are also looking at 2 novel drugs to treat brain cancer in dogs. Both of these molecules can cross the blood-brain barrier and have unique abilities to kill cancer cells within the brain. "We're hopeful that these drugs used alone or in combination with one another or with radiation therapy will be able to dramatically improve the care of dogs with brain cancers," Dr. Fan says. These tumors are particularly overrepresented in boxers, bulldogs, pugs, and other brachycephalic breeds.

PURDUE

Michael Childress, DVM, MS, DACVIM (Oncology), associate professor of comparative oncology at Purdue's College of Veterinary Medicine, is enthusiastic about a collaborative trial being conducted at Purdue, Minnesota, and Pennsylvania veterinary colleges, with the University of Minnesota being the lead institution. The study is looking at the combination of propranolol and doxorubicin to treat hemangiosarcoma in dogs. "It's exciting; there hasn't been anything new to treat hemangiosarcoma in 20 or 30 years," Dr. Childress says.

Propranolol is an established, inexpensive drug that's used to treat cardiovascular issues such as hypertension and abnormal heart rhythms, but it's also been found to have anticancer effects, Dr. Childress says. It affects canine hemangiosarcoma cells in culture, and clinical effects have been observed in humans with angiosarcoma, the human tumor equivalent. The current multisite study is designed to determine the optimal dose for hemangiosarcoma of the spleen following splenic removal in dogs.

"The preliminary data on propranolol is promising," Dr. Childress says. "It's well-tolerated in the dogs that have been treated. We're not far enough into the trial to tell if there is extension of survival, but that's not really the purpose—the goal is to find an optimal dose that's tolerated and not causing side effects in a significant number of dogs."

A team at Purdue has also received funding to conduct a chemotherapy trial in dogs with B-cell lymphoma, a trial that involves combining "old drugs in a new way," Dr. Childress says. Typically, chemotherapy drugs are given 1 at a time once a week or every other week in a cyclical sequential fashion for lymphoma, Dr. Childress says. "It's been done that way for 20 or 25 years," he says. "That treatment extends life, it's effective, it often puts the cancer into remission—but it rarely cures it."

In fact, the cure rate is about 1% to 2%, Dr. Childress says, but if you look at the same drugs in humans with the same cancer, the cure rate is 30% to 40%. "In people, the drugs are given in combination," he says. "We're initiating doing that in dogs—trying to identify a way the drugs can be given in a safe and tolerable fashion so that they work in concert to treat more effectively than drugs as single agents."

The treatment was well tolerated in laboratory dogs, Dr. Childress says, so the next step is to see if it's safe in dogs with lymphoma. The goal of the upcoming study is to define the dose with the best anticancer effects while causing a tolerable level of side effects. "If that's successful, we will move on to efficacy trials," he says.

The Purdue team is also working with physicist David Nolte, PhD, who has developed a technology called biodynamic imaging (BDI), which measures intracellular motion within living 3D tissue samples. When tumor biopsy specimens are collected from a patient, a portion of that tissue is sent to Dr. Nolte's lab for BDI. "The samples are cut up into small chunks, loaded into the device, and exposed to chemotherapy drugs within the device," Dr. Childress says. "The BDI device can measure motion within the cells in response to chemotherapy, and the change in motion can be correlated with clinical response to a drug."

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Childress says BDI can predict canine response to chemotherapy with 80% to 85% accuracy. This may pave the way for clinicians to select an optimized chemotherapy treatment in dogs with cancer based on their BDI response. "Usually we look at whether an individual will respond to treatment using gene expression or mutation within a tumor," Dr. Childress

Resources

For updates on AVMA and university clinical trials, visit:

- ebusiness.avma.org/aahsd
- vet.upenn.edu/veterinary-hospitals/ryan-veterinary-hospital/services/comprehensive-cancer-care/cancer-care-clinical-trials
- vetmed.illinois.edu/research/clinical-trials
- purdue.edu/vet/pcop/clinical-trials.php

says. "But there's a significant enough number of patients where it doesn't work because their tumor doesn't have a specific mutation. This should be able to work across patients regardless of mutational status."

WHAT'S NEXT?

While this is by no means an exhaustive discussion of veterinary oncology research currently underway, the clinical trials highlighted here represent the trailblazing research going on at numerous veterinary schools. As researchers make new discoveries in established approaches to treatment as well as pioneering new technologies, veterinary professionals, cancer patients, and pet owners stand by, waiting for the technique that could make a difference—now or in the future. TVP

References

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2. Partridge BR, O'Brien TJ, Lorenzo MF, et al. High-frequency irreversible electroporation for treatment of primary liver cancer: A proof-of-principle study in canine hepatocellular carcinoma. *J Vasc Interv Radiol* 2020;31(3):482-491.e4. doi: 10.1016/j.jvir.2019.10.015

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