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Veterinarians and physicians are poised to deliver a knockout blow to the cancers that their patients share

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When Renee Holden saw the large lump under her cat's tongue, her instincts told her it wasn't good. She just knew that her 13-year-old calico Ginger had cancer. The prognosis wasn't any better. Ginger was diagnosed with squamous cell carcinoma, an aggressive cancer that is common in older cats.

The disease "has this insidious onset," says Elizabeth McNiel, a veterinary oncologist at Cummings School's Foster Hospital for Small Animals. "Nobody really knows it's there until it's very advanced." Because Ginger had late-stage cancer, surgery was not an option. And chemotherapy and radiation therapy would do little to extend her life.

"I was told Ginger had just a very short time to live," says Holden, "maybe a matter of a few weeks."

In the brief time they had left together, Holden and Ginger were able to do something to advance our understanding of cancer in both people and animals. Through the Tufts Human-Animal Cancer Collaborative, a partnership among oncology researchers, veterinarians and physicians, Ginger received an experimental drug for treating squamous cell carcinoma.

McNiel and two colleagues from the National Institutes of Health ran the drug trial to determine whether an engineered protein, based on toxins

produced by the anthrax bacteria, can target and kill oral tumor cells such as those causing Ginger's disease. The drug, called intercomplementing toxin (ICT), has shown promise in mice.

Holden says she was fortunate to enroll Ginger in the first clinical trial of ICT in cats. "There are things that are available to pets that are not available to humans," she says. "It gave me some hope. And it allowed Ginger to live a little bit longer."

A Nucleus of Expertise

Ginger and other companion animals are on the frontline of a field known as comparative oncology, which evaluates how cancer behaves and is best treated in people and other species. Tufts is one of just 20 U.S. academic institutions that are part of the National Cancer Institute's Comparative Oncology Trials Consortium, which designs and conducts clinical trials of new ways to treat cancer.

"Tufts University is unique in that we have a well-established, strong cancer center at the medical school and Tufts Medical Center in Boston and a very strong cancer center at the veterinary school in Grafton," says Andrew Evens, a professor at the medical school, director of the Tufts Cancer Center and chief of the division of hematology/oncology at Tufts Medical Center.

That nucleus of expertise in human and animal medicine could help streamline the federal drug-approval process. Less than 5 percent of new treatments for cancer and other diseases receive Food and Drug Administration approval for use in human medicine, McNiel says.

Comparative oncology researchers say this is because methods for evaluating new treatments rely too heavily on testing in lab animals in which cancer has been artificially induced. "We are testing the drugs in

mice that have been genetically modified, exposed to chemicals that promote the growth of certain cancers or injected with tumor cells," McNiel says.

"Not to sound cynical, but we've become great at curing mouse cancers," observes Sandra McAllister, a breast cancer researcher at Brigham & Women's Hospital in Boston. "Certainly, that species has done a lot to help humankind. But when we start with mice, we are making a big leap that doesn't always land us in the right spot. If we can add more relevant models of each disease to study, that benefits all of us."

Another Human-Animal Bond

At Tufts, researchers and clinicians are studying diseases that occur naturally in pets, just as they do in people. Because people and their pets share the same environment, and therefore are susceptible to the same factors that cause cancer and other diseases, companion animals are more predictive of the progression and treatment of disease in humans. "This model is a lot closer to the way cancer occurs in real life," says Kristine Burgess, V97, a veterinary oncologist at the Foster Hospital.

McAllister, who studies the role that neighboring normal tissues and cells play in metastatic breast cancer, sought to work with Burgess for just that reason. Unlike lab rodents, some dogs naturally develop mammary carcinoma, which behaves like breast cancer in people. With consent from clients whose pets were undergoing treatment for mammary tumors at the Foster Hospital, Burgess provided McAllister with surplus biopsy tissue.

These animal tissues may help oncologists determine why some women's cancer returns or spreads despite aggressive treatment, while other women are cured. "If you look under the microscope at a mammary tumor formed in a dog or a breast cancer formed in a human, in many

cases they look identical," McAllister says. The normal cells and tissues surrounding tumor cells in dogs are also significantly more akin to those seen in humans than in mice, she notes.

Dogs with mammary cancer could also provide clues about the role of hormones in promoting breast cancer, says McAllister. "That's the thing that really astounds me," she says. "It's really rare for dogs that are spayed to develop mammary cancer. In unspayed dogs, it develops at a really high rate—at an even higher rate than it does in women."

A Bridge Between Species

For Cummings School patients, the Tufts Human-Animal Cancer Collaborative promotes more robust research aimed at fighting life-threatening cancers. McNiel spends 75 percent of her time with the 17 cancer researchers at the Molecular Oncology Research Institute at Tufts Medical Center in Boston and the rest of her time treating animals at Cummings School of Veterinary Medicine, 40 miles west in North Grafton. As a bridge between human and animal medicine, McNiel has been able to connect Foster Hospital clinicians with their counterparts in human medicine.

"We tend to form our alliances around particular cancer types," says Phil Hinds, professor and chair of developmental, molecular and chemical biology at Tufts School of Medicine. His lab is working with McNiel to investigate how genes and proteins may fuel the development of osteosarcoma, an aggressive and difficult-to-treat bone cancer in children that also occurs in large-breed dogs.

"The way people think about their fields is sufficiently different that you tend to get more insights when you bring these fields together," says Hinds. "It becomes very useful to mix them. Everything overlaps, and you have to be open to using every discipline you can to solve the

question in front of you."

Another example of the synergies that Hinds describes is the collaboration between McNiel and Philip Tsichlis, director of the Molecular Oncology Research Institute at Tufts Medical Center. "He had some interesting data concerning mast cell tumors and bladder cancer," McNiel says. "We happened to be talking in Boston, and I said I was interested in those diseases in dogs. That conversation evolved into two projects."

With support from the Animal Cancer Foundation, the Morris Animal Foundation and a Tufts fund that encourages collaboration across disciplines, Tsichlis, the Jane F. Desforges Professor at Tufts School of Medicine, and McNiel are investigating how genes in people and pets trigger normal cells to become malignant.

"Our work centers on a protein called NDY1, which stands for 'not dead yet,' " McNiel says. Tsichlis discovered and named the protein while studying lymphoma in rats. He found one gene that appeared to be involved in the development of lymphoma and mixed it with skin cells from healthy rodents.

"It immortalized the cells so that they kept growing and growing and growing, whereas cells without the added protein eventually die," she says. Their findings suggest that NDY1 might promote cancer in mast cells, which are part of the immune system and cause the most common skin cancer in dogs. If they can figure out a way to turn off the protein, McNiel says, "the mast cell cancers may not be able to survive."

The researchers believe NDY1 may play a similar role in bladder cancer. The protein is found in greater concentrations in highly invasive bladder cancers—which account for most bladder cancer in dogs—than in the more superficial bladder cancers seen in the vast majority of human

patients.

Until 2009, when the FDA approved the use of the drug Palladia to treat canine skin cancer, the agency's Center for Veterinary Medicine had not approved any veterinary oncology drugs. Veterinarians used—and continue to use—chemotherapy and other drugs that have been approved for humans. Because biomedical research funding has overwhelmingly gone to cure human diseases, McNiel says that most veterinarians resort to scouring the medical literature to see what is working in humans and then modify that for "whatever creature you happen to be treating."

Dog-specific Drugs

Comparative oncology research is changing that. Take Tanovea, a drug developed to treat lymphoma, one of the most common cancers in dogs, and non-Hodgkin's lymphoma, the comparable cancer of the lymph nodes in humans.

"Initially, a pharmaceutical company was looking at a lymphoma drug that would be given to humans or dogs," says Burgess, the veterinary oncologist who is working with Evens, director of the Hematology and Oncology Program at Tufts Medical Center, to study the disease. Humans and dogs both received Tanovea during a clinical trial conducted at multiple institutions, she says, "and it turned out to be a very effective therapy in the dogs." Tanovea will likely become the third oncology drug to receive FDA approval for exclusive use in dogs.

George, a 6-year-old bull mastiff, participated in the Tanovea trial at the Foster Hospital. Although the disease has come back a few times since he was first diagnosed 20 months ago, he's currently in remission. The average life expectancy for a dog with lymphoma is around 12 months.

"They are considering [George] a success story," says his owner, Joann Stewart Meyer. "We were fortunate to be able to do this for him." The tried-and-true chemotherapy drugs can be very effective in treating this type of cancer, she says. "But I think it's really important that [veterinarians] are trying out new drugs, because for some cancers in dogs, there hasn't been a lot of change in how we try to beat the disease."

The hope of advancing the well-being of all animals is usually what motivates owners to enroll their pets in clinical trials, more so than an expectation of an immediate cure, says Burgess. "I think a lot of people do hope, obviously, that their [pet] will be one of those that will respond well to an investigational drug. But people come in with the understanding that sometimes that's not the case. We'll do our best, but we may only, at the very most, get a lot of information that will help others."

Such was the case for Ginger, the cat whose oral cancer was treated with the experimental anthrax-based drug. Over the two weeks of the small preliminary study, veterinarians injected the drug directly into the tumors of Ginger and two other cats. "They did find a small amount of shrinkage, which I was very excited about," says her owner, Renee Holden.

The cancer eventually got worse, though, and Holden made the difficult decision to euthanize her beloved companion on New Year's Day 2014—eight weeks after she first underwent treatment.

Holden, who works in a genetics lab involved in human clinical trials, says she had no idea similar research was happening for pets until McNiel treated Ginger. "It's probably people like her that really help advance medicine," she says. "I felt like this was a great opportunity to have a little piece of that."

Provided by Tufts University