FEATURES

FROM BARK TO BEDSIDE

Clinical trials in pets are ramping up, but will they benefit human health?

By **David Grimm**

Frankie, a 15-year-old brown dachshund with a gray muzzle and tired eyes, rests on a pillow and pink blanket on an exam table at the University of Pennsylvania School of Veterinary Medicine (Penn Vet). A catheter draws blood from her neck into a gray machine the size of a minifridge, which clicks and whirls as it returns clear fluid to her body through another tube. The dog is strapped down by a red leash, but the restraint hardly seems necessary; she looks like she could fall asleep at any moment. At least until veterinary internist J.D. Foster sticks a thermometer in her butt.

A black mass has engulfed Frankie's bottom-right canine tooth—a melanoma that could eventually metastasize. If her owner had taken her to a traditional vet clinic, the doctor would have likely recommended removing part of her jaw, followed by a strong course of chemotherapy. But here at Penn Vet, Foster and his team are trying a new approach: cleaning Frankie's blood with an experimental polymer that removes immune system blockers, which may allow her to better fight the cancer. If the treatment works, it probably won't extend Frankie's life—but it could make her last few months a lot more pleasant. It also just might lead to a new way to combat skin cancer in people, Foster says. He scratches Frankie behind the ears as she closes her eyes on the pillow. "You're a good girl," he coos.

Frankie is the third of 13 canines in the study—a clinical trial that's part of a growing push to develop new therapies for people by

PHOTO: JOHN DONGES

Frankie the dachshund takes part in an experimental melanoma trial at the University of Pennsylvania School of Veterinary Medicine.

testing them in sick dogs and cats instead of lab rats or mice. Pets are a better model of human illnesses than rodents, advocates contend: They live in the same environments, sometimes eat the same food, and get many of the same diseases, particularly cancers, that we do. So, the thinking goes, they could hold the key to developing new therapies for humans at a fraction of the normal cost—and potentially yield a trove of new medicines for pets themselves.

"There's an opportunity for everyone to benefit," says Amy LeBlanc, who oversees pet clinical trials at the U.S. National Institutes of Health (NIH) as the director of its Comparative Oncology Program in Bethesda, Maryland. The number of such trials is booming, she notes, with hundreds conducted over the past decade.

But others question whether these studies will really have an impact on human health. "It's a very interesting idea, and it all sounds very nice," says Larry Baker, an oncologist at the University of Michigan, Ann Arbor, and the former chairman of one of the largest human clinical trial organizations in the United States. "But this field has yet to prove itself."

PET CLINICAL TRIALS date back to the mid-1970s, when vets tested lymphoma vaccines in household dogs. Later trials tackled other cancers with bone marrow transplants and inhaled chemotherapies—all with the hopes of translating the approaches to humans. But the studies were few and far between, and there was no coordinated effort to bring them into the mainstream.

That began to change about a decade ago. More than half of U.S. households had pets by that point, and owners were spending billions of dollars a year on veterinary care alone. There was also a growing crisis in the traditional drug development pipeline. Typically, researchers first test experimental therapies in laboratory rodents, then in larger animals such as monkeys, before moving to human trials. But the success rates have been abysmal. It can take 16 years to bring a new drug to market, at a cost of up to $2 billion, and 10,000 promising compounds may lead to only one U.S. Food and Drug Administration (FDA)–approved treatment. Cancer therapies fare particularly poorly: Only 11% of oncology drugs that work in mice are ever approved for people.

"Drug development is not a sustainable model the way it is now," LeBlanc says. "It's too much money and too much time."

Enter pets. Unlike lab animals, which are highly inbred and raised in environments so sterile they typically only get cancer when researchers obliterate their immune systems and inject them with tumors, dogs and cats are genetically diverse and live in the real, messy world. So it's no surprise that they get diseases, from cancer to arthritis to muscular dystrophy, that seem to mimic ours. A type of breast cancer in cats has been associated with the same protein—HER2—as one of the most aggressive breast cancers in women, and the bone cancer osteosarcoma is nearly identical—both clinically and genetically—in dogs and people. That may be why a lot of the same drugs help both us and our pets. The most common therapies for human non-Hodgkin lymphoma work in dogs, and those that don't work in dogs don't work in people.

Paisley the pit bull gets an ultrasound as part of a clinical trial on irritable bowel disease at the University of Pennsylvania School of Veterinary Medicine.

PHOTO: JOHN DONGES

Researchers can also conduct more detailed studies on pets than they could in the past, thanks to advances in veterinary medicine—from kidney transplants to stem cell treatments—and breakthroughs like the sequencing of the dog and cat genomes. "We can ask much more scientifically rigorous questions that are more likely to intersect with human health," says Chand Khanna, who founded NIH's Comparative Oncology Program in 2003 and is now the chief science officer with Ethos Veterinary Health, a new Woburn, Massachusetts–based network of veterinary hospitals that plans to conduct clinical trials. "The mouse has prove[n] itself time and time again to be a bad investment. The dog is an alternative to something we know doesn't work."

A COUPLE OF FLOORS DOWN from Frankie, a brindle pit bull named Paisley is wagging excitedly in a small exam room. Her owner, Chelsea Burns, holds her tight on a black leash while a vet tech peppers her with questions: How often does she eat? How are her bowel movements? Burns hands over two grocery store bags filled with poop. "She's an overachiever," she smiles sheepishly.

Paisley is here for a different clinical trial, one that aims to figure out whether the gut microbiome—the ecosystem of intestinal bacteria linked to everything from allergies to obesity—can give clues to which therapies best treat irritable bowel disease. Today, Paisley will have a physical exam and an ultrasound to confirm she has the condition. Tomorrow, she'll get a colonoscopy and a biopsy of her intestines. If she qualifies for the trial, she and 50 other dogs will spend 7 weeks on a special diet—and possibly a course of antibiotics—with regular trips to Penn Vet for evaluation.

It all sounds a lot like a human clinical trial, and it is—replete with many of the same challenges. Burns has to sign an eight-page consent form, for one, and some pet clinical trial proponents have suggested adding a "patient advocate" to such studies to ensure that someone other than the emotionally attached owner is looking out for the cat or dog's best interest—two lines of red tape rat researchers don't have to cross.

What's more, owners like Burns consider their pets part of the family ("Paisley's pretty much like my child," she says), so there is a limit to the type of experiments that can be done on them. No veterinarian is going to euthanize someone's dog at the end of a trial to get a better sense of how a drug worked, for example, even though that could be incredibly informative. "You can try just about anything in the rodent world," says Dottie Brown, the director of the Veterinary Clinical Investigations Center at Penn Vet. "But these are people's pets."

Dogs and cats have other disadvantages. The same things that make them good models for human disease—more diverse environments and genetics—cause problems when scientists are trying to eliminate variables that could tell them why a drug didn't work. There are also plenty of human diseases that pets don't get, like prostate cancer and Parkinson's. Plus, researchers don't have to spend months recruiting lab rodents, and they can give them a much smaller dose of an experimental drug. That makes pet trials expensive, as does the fact that these studies—like those in people—typically cover the cost of care and procedures, which can run into the thousands or tens of thousands of dollars, especially when dealing with cutting-edge therapies like bone marrow transplants and radiation for brain tumors. "Doing a clinical trial in dogs is 10 times cheaper than doing it in humans," Brown says, "but 10 times more expensive than doing it in rats."

Those are all big reasons it's hard to get funding for these trials, LeBlanc says, especially from pharmaceutical companies. "They want to get their drug to market as soon as they can."

The government has also been loath to fund pet clinical trials because scientists know a ton more about rats and mice than they do dogs and cats, LeBlanc says. "NIH gets really uncomfortable with models that haven't been vetted in the same way as mouse models." That has forced veterinarians to scrounge money from their institutions or from pet-centric organizations, most prominently the Denver-based Morris Animal Foundation, a nonprofit that claims to have invested more than $100 million in animal health studies. Things might be easier if the field had notched some big successes. But Baker, who made his reputation treating children with osteosarcoma, says he hasn't seen many. He points to a couple recent trials that used experimental drugs to treat osteosarcoma that looked promising in dogs but fell short in people. Two other trials testing the antilymphoma drugs GS-9219 and Zydelig proved safe and effective in dogs, but toxic to humans. "We've been so desperate for new drugs, especially for kids, we want to see progress," Baker says. "But that doesn't mean being blinded by our optimism."

LeBlanc says there are signs that pet clinical trials can pay off. In 2013, for example, FDA accelerated its approval of a drug called ibrutinib for lymphoma in people after it showed promise in canine trials. And because dogs are easier to operate on than rodents, they have helped optimize ways to excise bone tumors in children without removing limbs.

Still, LeBlanc admits that the field has a way to go. "We don't have a slam-dunk transition to better human health," she says. "But I think that data is coming."

THERE ARE HINTS that pet clinical trials may be edging into the mainstream. Last summer, nearly 200 veterinarians and physicians met for the first time with funders, government regulators, and representatives from the pharmaceutical industry in Washington, D.C., to discuss how these studies could better contribute to human health. The workshop, sponsored by the U.S. National Academies of Sciences, Engineering, and Medicine, sparked new collaborations, and removed a major roadblock. The pharmaceutical industry had worried that if one of its drugs caused problems in a pet study, FDA would never approve it for people. But at the meeting an FDA representative said that was not the case. "That was a huge win for the field," Khanna says.

Since then, NIH has become more interested in these trials, too. In April, the National Cancer Institute announced that it would fund partnerships between veterinarians, physicians, and scientists to better understand the molecular biology of dog cancer. NIH also inspired the American Veterinary Medical Association to create its own version of ClinicalTrials.gov (a worldwide database of human clinical trials), which went online in June. And next year, the agency's Comparative Oncology Trials Consortium—a network of 22 North American academic centers—will begin releasing data from its largest pet clinical trial to date, a 160-dog study of canine osteosarcoma, which LeBlanc is overseeing. "We want to get better data into everyone's hands," she says.

The field is also hoping for its first big translational success. In 2015, New Haven, Connecticut–based Kolltan Pharmaceuticals announced that its experimental antibody drug KTN0158 dramatically shrank a common skin tumor in dogs, prompting it to begin clinical trials in humans. "The dog trial had a dramatic impact on our strategy to develop this product for people," says the company's president, Jerry McMahon.

He believes the main role of pet clinical trials in the future will be to help pharmaceutical companies like his minimize the risk of drug development. Instead of putting every drug that works in mice into the human pipeline, they can focus on the ones that help sick cats and dogs. "It makes the investment in human drug development more promising," he says. "It takes a while for things like pet clinical trials to become part of mainstream drug development, but I think they could be a powerful tool for the future."

Of course, there's always the possibility that pet clinical trials will never translate to people, and that they'll just help veterinarians develop better drugs for dogs and cats. But many advocates don't see that as a bad thing. "If we save these dogs, it has an impact on every single family that owns a dog," says Matthew Breen, a geneticist at North Carolina State University in Raleigh who has been part of more than a dozen pet studies. "When I get involved in these trials, it's about helping the family. If we're helping the human or the dog, is there really any difference?" ■

Sit. Stay. Heal. A sampling of pet clinical trials

Researchers are conducting hundreds of clinical trials on dogs and cats across the world. Here are a few that may have an impact on human health.

TRIAL	PURPOSE	LOCATION
Minibeam radiation for brain tumors	Testing whether small, parallel beams of radiation can treat malignant brain tumors in dogs.	U. of Saskatchewan, Saskatoon, Canada
GammaCore VET for seizures	Testing whether a handheld electronic nerve stimulator can treat epilepsy in dogs.	U. of Georgia, Athens
HER2/neu breast cancer vaccine	Testing an experimental vaccine against a type of breast cancer in cats that is also one of the most aggressive in women.	Veterinary Oncology Services, Middletown, New York
Stem cells for dry eyes	Testing whether an injection of stem cells from a dog's own fat can restore the eye's ability to tear.	Purdue U., West Lafayette, Indiana
Photodynamic therapy for lung tumors	Combining a drug with laser light to kill lung tumor cells in dogs.	Colorado State U., Fort Collins
Embolization for prostate cancer	Testing whether blocking blood vessels in the prostate gland can treat prostate cancer in dogs.	U. of California, Davis
Canine osteoarthritis pain	Testing two experimental anti-inflammatory medications.	U. of Minnesota, Twin Cities

From bark to bedside
David Grimm (August 11, 2016)
Science **353** (6300), 638-640. [doi: 10.1126/science.353.6300.638]

Editor's Summary