A

DOG HAS ITS DAY

BY AMOS ESTY

THE FUTURE of cancer treatment is: 12 YEARS OLD, WEIGHS 21 POUNDS, AND WEARS A PURPLE COLLAR.

Photographs by Eli Burakian (D'00)

In the early fall of 2011, the Orndorff family received some bad news. Eleven-year-old Jenny, a lively, adorable Schnauzer, had cancer.

The outlook was bleak. Jenny's veterinarian had spotted a large, rapidly growing tumor in her mouth. The vet removed as much of the tumor as possible, but he warned Jenny's owners, Sam and Sandra Orndorff, that it was likely that some cancer cells remained.

Unfortunately, he was right. Before long, the tumor had regrown and threatened to spread to Jenny's nose and surrounding bones. "We were really shocked," Sandra says.

The Orndorffs traveled to see specialists in upstate New York, but again the news was disheartening. Surgery was one option, but to be sure that all of the tumor was resected, the surgeon would have to remove part of Jenny's nose, leaving her disfigured. Radiation was another option, but the specialists said that it would take a course of 16 treatments, and even then there was no guarantee that the cancer wouldn't return.

The Orndorffs were at a loss. "I panicked," Sandra says. "I'm very emotional when it comes to her."

Then Jenny's vet told the Orndorffs about another possibility. Led by P. Jack Hoopes, D.V.M., Ph.D., a Geisel professor of surgery and of medicine, researchers at Geisel and Dartmouth-Hitchcock were starting a clinical trial to test the effectiveness of an experimental treatment using magnetic nanoparticles. The trial would enroll dogs who had developed specific kinds of oral tumors, and Jenny's cancer fit the description the researchers were looking for.

The Orndorffs could do nothing, accepting that Jenny had already had a long and happy life. They could choose surgery or radiation, which might rid Jenny of cancer at least temporarily but would come with a cost in quality of life. Or they could allow researchers to test an unproven treatment on Jenny, a dog they had doted on since she was just a few weeks old, with no guarantee that it would work.

The decision was easy. Jenny became the first dog enrolled in the trial. "It was just perfect timing," Sandra says.

The first meeting between Hoopes and the Orndorffs still sticks in Sandra's mind. Jenny was her usual energetic self. "You'd never think she was sick, would you?" Sandra asked Hoopes. "She's not sick," Hoopes replied. "She just has a tumor."

A longtime cancer researcher who is trained in veterinary medicine, Hoopes understood how important Jenny is to the Orndorffs. "No parent wants to think their kid is part of an experiment," he says. So he took the time to explain the research and the trial to them.

The goal of the trial is to test the effectiveness and safety of the nanoparticle treatment. There are three arms. In one, the dogs receive treatment only with the nanoparticles. In a second, they are treated only with radiation. In a third, they receive both the nanoparticle treatment and a reduced dose of radiation. Jenny was placed in this last group.

It's hard to conceive of exactly how small the nanoparticles are. As a comparison, Hoopes notes that about a million human cells could fit on the head of a pin, and each of those cells could hold as many as half a million nanoparticles.

The nanoparticles are made of iron oxide (a combination of iron and oxygen), and they are magnetic. When exposed to the right magnetic field, they heat up. Scientists have long known that heat can be used to kill cells. But the trick—as with every cancer treatment—is finding a way to kill tumor cells while leaving normal cells unharmed. "It's that specificity that people are looking for," Hoopes says. "That's what I think the whole field of cancer research is looking for."

By injecting the nanoparticles directly into the tumor, the researchers could target cancer cells, hopefully without affecting the normal cells surrounding the tumor. The particles appear to be completely safe in the doses used. Only when exposed to a magnetic field do they become lethal. And that is what makes Hoopes so excited about this trial.

To deliver the treatment, Hoopes injected an inky liquid containing the nanoparticles directly into the tumor. After waiting about an hour for the particles to spread throughout the tumor, Jenny's head was placed on a small table, under which was a magnetic induction coil. The coil delivers a magnetic field that interacts with the nanoparticles, causing them to heat up. Then, in Jenny's case, this treatment is followed by multiple doses of radiation over the next two weeks.

Hoopes says that because spontaneous tumors in dogs, such as Jenny's tumor, develop naturally and are similar in size and cell number to human tumors, they tend to be a better model than rodents for studying the development and treatment of cancer in humans. Within the next year, Hoopes plans to begin a trial in women with breast cancer who are good candidates for mastectomy, bringing the treatment that much closer to reaching the general population.

In the long term, Hoopes has even bigger plans. He is working with researchers at Dartmouth's Thayer School of Engineering to develop antibodies that could be attached to the nanoparticles. By creating antibodies that interact specifically with cancer cells, the nanoparticles could be delivered to tiny pockets of cancer cells hidden throughout the body. Often it is these metastases, not the primary tumor, that prove most dangerous. Ideally, the nanoparticles and antibodies could be injected into the bloodstream, allowing them to travel around the body and locate pockets of cancer cells, killing them before they grow large enough to be deadly.

The opening of the Advanced Surgery Center (AdSC) this summer will add to Hoopes's ability to conduct this research (see the sidebar on page 37 for more on the AdSC). Getting good images of the nanoparticles inside a tumor has proved to be difficult. Because the nanoparticles are magnetic, Hoopes can't use conventional magnetic resonance imaging (MRI) to track their movement. He is collaborating with a researcher at the University of Minnesota who has developed an algorithm that allows MRI to be used to see the nanoparticles, but at the moment Hoopes doesn't have access to an MRI machine that can be programmed with that algorithm and that is large enough to use with Jenny. The AdSC, however, will have such a machine.

"We think this will be a huge advance for us," Hoopes says. "This ability to locate and quantify the nanoparticles is very important."

Given how much is left to learn, Hoopes thinks of the research as being fairly early in its development. But that's not how it seems to the Orndorffs. "It's just mind-boggling," Sam says. "It's like science fiction."

Given Jenny's progress over the past year, the Orndorffs' enthusiasm is understandable. Within two weeks of her second treatment, the tumor had virtually disappeared. And according to Sandra, the only side effect was slight grogginess for an hour or so after waking from the anesthesia.

More than a year after her first treatment, Jenny is still as energetic as ever. Sandra is thankful. "We feel blessed," she says. "We're very glad she's part of the program."

Hoopes is thankful as well. Jenny's participation has helped him and his colleagues learn more about the use of nanoparticles and validated their faith in the direction of the research. "This is the future of cancer therapy," Hoopes says.

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Jack Hoopes prepares Jenny for treatment with nanoparticles. Coils under the table holding Jenny emit a strong magnetic field that interacts with nanoparticles injected into the tumor in Jenny's mouth, causing the particles to heat up and destroy the tumor cells.

SHAPING THE FUTURE OF SURGICAL TREATMENTS

By Timothy Dean

In 1896, the first clinical x-ray in the United States was taken at Dartmouth. So it seems fitting that Dartmouth-Hitchcock is poised to lead the country into a new frontier of medical imaging with the completion later this year of the Advanced Surgical Center (AdSC).

"So far, imaging technologies such as MRI [magnetic resonance imaging] and CT [computed tomography] have mostly been used to diagnose things," explains spine surgeon Sohail Mirza, M.D., the chair of the Department of Orthopaedics. "By leveraging research in areas like nanotechnology, we're going to have a facility that actually lets us stretch into what we call 'therapeutic imaging,' using imaging to treat things." When the AdSC opens, it will achieve a series of firsts. "A few other institutions have similar facilities, but none are focused exclusively on research, as we will be," Mirza says. "None have the generation of MRI and the detailed imaging that we'll have. And none have a CT in addition to the MRI. The technologies complement each other, giving us tremendous detail of different structures. With MRI it's soft tissues; with CT it's bone."

The AdSC's unique design includes a suspended MRI machine that will move along a ceiling track into either of the suite's two operating rooms. "All of our imaging systems will be linked, so we'll have the ability to cross modalities which will make this an ideal setting for validating and benchmarking approaches, and developing translational technologies," Mirza explains. "For example, what we're able to confirm using MRI, CT, and, say, fluoroscopy [x-ray] or ultrasound in the lab, will help us validate lower-cost, simpler procedures that can be used in a community hospital setting."

When it is completed, the Advanced Surgical Center will offer Geisel and Dartmouth-Hitchcock researchers a unique space to improve surgical care.

A $9.3-million infrastructure grant from the NIH helped make the facility possible. Dartmouth's relatively small size, highly collaborative environment, and cross-disciplinary expertise were important factors in receiving the award, says Keith Paulsen, Ph.D., the Robert A. Pritzker Professor of Engineering at Thayer, who along with Mirza has led the AdSC project.

Dartmouth's grant proposal argued that research efforts could be optimized if a separate infrastructure was built to support them. "Today, with so much emphasis being placed on high clinical volumes, efficiency, and cost-containment, there are fewer opportunities to do research, especially in environments like the OR," says Paulsen, who has been a leading innovator of medical imaging technology and cancer therapeutics for over 20 years. "With this infrastructure, we see fertile ground for doing the kind of experimental work that needs to be done to speed up the translation of new concepts into clinical practice."