

By Manasee Wagh

NOTEBOOK

Gene therapy for Fido

A few months after arriving at Baylor College of Medicine in 1995, Ruxandra Draghia-Akli, an assistant professor, adopted an abandoned Jack Russell terrier she found at the cafeteria. Baylor, named for the school, is one of two dogs that Draghia-Akli has lost to cancer in the past six years, and watching his decline was taxing. "He couldn't breathe anymore, he had many metastases, and it was truly horrible to see him suffering," she says.



Plasmid GHRH delivery in a dog.
Courtesy of Patricia Brown

Draghia-Akli put Baylor to sleep in 2002, just as her colleagues were beginning to test a gene therapy approach aimed at reducing cachexia, a complication of cancer in which a catabolic state produces anemia, muscle wasting, and fatigue, which makes facing aggressive cancer therapies difficult.

About 10 years ago, she and her colleagues began developing growth hormone releasing hormone (GHRH)-encoding plasmids for use in gene therapy. In animal models, the reintroduction of anabolic hormones such as growth hormone and insulin-like growth factor 1 (IGF-1) had been shown to reverse catabolic conditions associated with cancer. The idea was to find out if establishing GHRH production in muscle cells might increase hormone production and give sick animals like Baylor a fighting chance.

At Houston's Gulf Coast Veterinary Specialists, veterinarian Kevin Hahn began testing the therapy on 20 sick dogs in 2001. From a Great Pyrenees to a Chihuahua, the dogs were on chemotherapy, radiation therapy, or both. Hahn was excited by the opportunity. If something has the potential to reduce an animal's suffering from a terminal disease, he says, "I would give anything to have it in my clinic and use it."

Using a device that looks like a portable defibrillator, they would push a cluster of needles into the dogs' inner thighs, inject up to a milligram of the plasmid, and introduce a light shock to maximize uptake by electroporation. Electroporation increases cellular uptake 100- to 1,000-fold according to Draghia-Akli. Thus, the injection point "serves as a mini factory of GHRH," she says.

A little more than two weeks after the procedure, tests showed a rise in IGF-1 between 20% and 120%. This correlated with reduced anemia (R. Draghia-Akli et al., *Mol Ther*, 6:830-6, 2002). According to Hahn, the treated animals also showed improvements in alertness, appetite, and energy, and were no longer anemic.

In eight weeks, 16 of the 20 treated dogs improved (four died or were euthanized), compared to 20 untreated controls receiving standard care. "It provided a phenomenal response in our patients," says Hahn. "There was an improvement in quality of life and quantity of time they had to live."

As studies were ramping up, the team had transferred the technology to **ADViSYS**, a Baylor startup company in The Woodlands, Texas. **ADViSYS**, which changed its name to VGX Immune Therapeutics due to a merger in February, has developed plasmids for dogs, cats, pigs, horses, and other animals.

In Australia, researchers have been testing the therapy for agricultural purposes. Young healthy pigs given the plasmid show increased weight gain in the first few months of life. For pregnant sows, the treatment induced long-term, regulated protein secretion that increased sow health and reduced offspring morbidity and mortality.

The animals aren't transgenic. Nevertheless, Ina Dobrinski, director of the Center for Animal Transgenesis and Germ Cell Research at University of Pennsylvania's School of Veterinary Medicine, says, "The regulatory background is that anything that comes into contact with foreign DNA would not be considered fit for human consumption." Draghia-Akli, who also serves as vice president for research at VGX Immune Therapeutics, argues that the DNA isn't exactly foreign and that the gene therapy regimen isn't much different from vaccines using DNA or attenuated viruses.

The company has been working toward approval for Australian pigs, but the focus in the United States is largely on the dogs. "I think this is going to be something that is going to make a difference for companion animals," she says. "In time we may be able to offer the same kind of therapy for humans."

Large-scale studies had been started with dogs in the United States in 2003 but were stopped midway due to funding issues. VGX Immune Therapeutics will be seeking approval according to Draghia-Akli, but not everyone is patient with the progress. In an E-mail Hahn writes: "It was the one project in my 20 years of oncology that made a huge difference in the quality of life of my patients, and it remains frustrating that it is no longer available."

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comment:

Gene therapy for Fedo

by Shamim A. Faruqi, Ph.D.

[Comment posted 2007-05-04 15:37:00]

The results are very encouraging and it should be published in the nations top ten newspapers. There shall be some philanthropist, I am quite sure, who shall be able to provide funds for such a remarkable breakthrough if not for human but certainly for dogs welfare. At the end game it shall also benefit man.

comment:

Gene Therapy for Dogs

by Zulema Seligsohn

[Comment posted 2007-05-04 16:49:31]

What a good idea by Dr. Faruki. There is more than one promising therapy languishing for lack of funding.

comment:

Putting together dog information network

by Thomas P. Caruso, PhD

[Comment posted 2007-05-07 20:58:30]

I am in the process of building a network that would allow more organized research with dogs with diseases that could serve as models for human disease. There are many opportunities beyond cancer, particularly in understanding gene associations with disease. I am rather excited to see this particular success, but disappointed that funding for studies with animals continues to be a problem.

Not only could the use of client dogs with diseases related to human disease help those dogs and eventually benefit humans, but also it could reduce the need for use of laboratory animal models.
