

Biotech for your companion?

With the market for companion animals and veterinary products booming, will the animal biotech sector finally receive the financial resources it has so long needed? Jim Kling reports.

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In March, United Kingdom-based animal health firm Merial received conditional approval from the US Department of Agriculture, in Washington, DC, for a canine melanoma vaccine. This represents the first therapeutic cancer vaccine approved in the United States for any species, human or animal. The vaccine—licensed from the San Diego-based biotech company Vical by Merial, a joint venture of Sanofi Aventis and Merck—is a DNA plasmid vaccine encoding human tyrosinase based on Vical's cationic lipid (1,2-dimyristyloxypropyl-3-dimethylhydroxyethyl ammonium bromide/dioleoylphosphatidylethanolamine; DMRIE/DOPE) DNA delivery technology.

The melanoma vaccine isn't the first new product to be introduced via the animal market. In 1998, the US Food and Drug Administration (FDA), in Rockville, Maryland, approved the blood substitute Oxyglobin (polymerized bovine hemoglobin), marketed by BioPure of Cambridge, Massachusetts, to treat anemia, which kills millions of dogs every year. And overall, the FDA has approved more than 700 drugs for companion animals—dogs, cats and horses—as of 2006.

It's no secret that pet owners are demanding better care and access to cutting-edge technologies for their animals. Both pharmaceutical and biotech companies are hearing the call (Table 1). Increasingly, drug companies are turning to the companion animal market early in product development—reversing the traditional route in which new drugs are approved first in humans and then later applied to animals.

“Our fastest-growing area (in the health sciences) is companion animal research,” says Barry Astroff, director of life sciences for Midwest Research Institute, a contract research organization based in Kansas City, Missouri. This trend has created a significant companion animal market: figures from the US Animal Health Institute show that biologics are the fastest-rising R&D sector in the animal health industry, and more than half of the roughly \$4 billion spent on animal care products in 2006 in the United States was for companion animals (<http://www.ahi.org/Documents/MarketSalesRelease2006.pdf>).

From scraps to niche products

Traditionally, companion animals—dogs, cats, gerbils, rabbits and their ilk—have settled for

hand-me-downs when it comes to therapeutic agents. Companies developing drugs for human use occasionally applied them to the companion animal market, almost as an afterthought. But that dynamic is changing.

With the current multibillion-dollar market for animal health products growing at a rate of 10% per year, drug firms are taking a closer look at companion animals as a potential source of revenue. Already, for Novartis in Basel, Switzerland, Pfizer in New York and Heska in Fort Collins, Colorado, animal health care brings in over \$1 billion in annual sales. What's more, some completely new therapies are reaching the pet market before an equivalent therapy is available for humans.

The attraction is due in part to pet owners becoming increasingly proactive about their furry companions' health. In the United States alone, pet lovers spend over \$19 billion on veterinary care; increasingly, they're no longer content to take their pets to general practitioners, preferring instead to lavish dollars on the burgeoning number of veterinary specialists—oncologists, ophthalmologists, orthopediatricians, you name it. “Pets in our society are part of the family. In most cases, people spend more money for pets than they do for their own health,” says Yuri Melekhovets, laboratory director of Toronto-

based HealthGene, which markets veterinary DNA diagnostics. Another reason for growth in the companion animal market may have to do with improved nutrition. “You've got companies pouring tens of millions of dollars into nutrition, and as a result animals are living longer, and they have different health needs. They're getting diseases that they never had before,” says Astroff.

Increasingly, biotech companies are looking proactively towards the veterinary market in order to develop the veterinary applications alongside the human products. Animal products can produce cash flow in the form of revenue or licensing deals, and they can also provide valuable experience with issues like manufacturing. For example, Vical is working on human versions of the canine melanoma vaccine, as well as other, similar products. “That experience will be very helpful as they look at other DNA vaccines,” says Peter Hanson, executive director for pharmaceutical R&D at Merial.

Like Vical, Juvaris BioTherapeutics, based in Pleasanton, California, is also poised to move its technology into the companion animal market ahead of the human one. Colorado State University researcher and Juvaris cofounder Steven Dow used an immune stimulant based on Juvaris immunotherapy technology—a mixture of the cationic liposomes formed from DOTIM (octadecenoyloxy(ethyl-2-heptadecenyl-3-hydroxyethyl)imidazolium chloride) and cholesterol, together with a noncoding plasmid DNA—to treat pet dogs with naturally occurring hemangiosarcomas. In one study, dogs treated with an allogenic tumor vaccine (prepared using extracts of canine hemangiosarcoma cells and the liposomal immune stimulant) along with



Doggie donor. A German shepherd receives a medal after donating blood for the canine genome project. The completion of the canine genome has provided more grist for the companion animal drug mill.

Table 1 Selected biotech companies producing animal therapeutics

Company	Focus
Juvaris (Pleasanton, California)	Canine cancer vaccine
MetaMorphix (Beltsville, Maryland)	Canine DNA identification and parental testing
Peptech Animal Health (North Ryde NSW, Australia)	Birth control products for horses, birth control and testosterone control products for dogs
VetCell BioScience (London)	Veterinary applications of stem cells
Bioniche Animal Health (Belleville, Ontario)	Anticancer immunotherapeutic agent
HealthGene (Toronto)	Veterinary DNA testing
VetGen (Ann Arbor, Michigan)	Genetic disease testing
Vical (San Diego)	DNA delivery technology. Melanoma vaccine licensed to Merial has received conditional FDA approval
Accera (Broomfield, Colorado)	Product to slow cognitive decline for dogs. Signed deal with Nestle Purina PetCare
Sentrx Animal Care (Salt Lake City, Utah)	Wound care products
Velcera (Yardley, Pennsylvania)	Drug delivery formulation that is delivered via spray to the animal's gums. Licensed to Novartis Animal Health

chemotherapy outlived control animals receiving chemotherapy alone. At 200 days, none of the control animals were alive, whereas after 600 days, the treatment group had a survival rate of 40%¹. Other work using the immune stimulant platform in combination with allergen extracts had been successful in treating dogs with allergic dermatitis². The company will soon announce an alliance to take immunotherapeutics and vaccine adjuvants into the animal market.

Accera, in Broomfield, Colorado, hadn't even considered the companion animal market until Purina, of St. Louis, approached them after hearing about results from Accera's lead orally available Alzheimer's drug, Ketasyn (medium-chain triglycerides that are metabolized by the liver to β -hydroxybutyrate). In a phase 2a clinical trial, the drug improved memory and cognition in people with Alzheimer's disease. The company focuses on drugs that alter lipid- and glucose-metabolism defects associated with Alzheimer's disease and other neurodegenerative conditions. And it happens that dogs suffer from a similar condition known as canine cognitive dysfunction, which mimics the pathological and physiological outcomes of the human condition: this includes plaques and tangles in the brain as well as outward symptoms of wandering, lack of recognition of people and memory impairment. Purina sponsored a large-scale study in dogs at the University of Toronto using a dog model of Alzheimer's. The drug produced cognitive improvement and also caused behavioral changes, such as increased activity during the day. "They become more puppy-like," says Steve Orndorff, president and CEO of Accera.

Purina plans to incorporate the compound into one of its dog food products and signed a commercialization agreement with Accera in

January. Purina will take over development and manufacturing costs of the product, which is expected to go to market in June 2008.

For the moment, though, Accera is keeping its focus on human therapeutics. "For us, this was just a one-off opportunity, something that was a nice demonstration of the technology," says Orndorff. The trial provided data to support the company's work on the human side, in terms of safety, efficacy and mechanism of action (imaging studies showed increased blood flow to the brain). "There were a lot of advances that we couldn't have made without spending a lot [of] money and time elsewhere," says Orndorff. "It provides a level of validation for your product that can come years before you ever get it into humans." This helps when talking to investors, he adds. "I can point to this and say, 'We've got product sales. It works in dogs, and dogs have a similar condition to humans.' That resonates with investors and it reduces the perceived risk."

It also provides revenue. "It's not often that you can find another company that's willing to invest in a preclinical model. Pharmaceutical firms rarely reach back that far. We didn't have to raise money from other investors, and we didn't dilute out our shareholders," says Orndorff.

And yet, the challenges

Despite these successes, the companion animal market is not a quick road to profit, says Merial's Hanson. "Many times companies underestimate what's involved and assume that we can be on the market in six months or a year." Not so. Safety and efficacy trials in the target species take time, as does navigating the regulatory path (Box 1). "It's still a long-term investment," he says.

Additionally, the veterinary market presents its own unique challenges. One stems from the

fact that, outside of the major pharmaceutical companies' animal divisions, there is a lack of clinical rigor when it comes to the development of drug products for companion animals. This came as a surprise to Richard Koehn when he took over the reins of Sentrx Animal Care, based in Salt Lake City, Utah, where he is now president and CEO. "I was stunned by the lack of scientific rigor in the development of many veterinary products," he says. "There are exceptions in the vaccines and antibacterial products that are sold by the animal divisions of large pharmaceutical companies, which undergo the same kind of development as the human versions. But the veterinary market is populated by a large number of companies that I would characterize as more like human nutraceutical companies than human biotechnology companies. Most of the products have not been clinically evaluated."

Koehn believes the problem stems from the paucity of funding in the sector. Animal health has never had an agency to fund and drive research in the way the US National Institutes of Health (NIH), in Bethesda, Maryland, accelerates human healthcare research. Research performed at veterinary schools is privately funded. "There's been an absence of a research culture in the field," Koehn says.

That, in turn, has made vets more price sensitive, as they aren't used to paying the high prices that products going through clinical trials must command. This can present problems for companies trying to convince vets that they need these higher-priced products. Sometimes vets aren't even aware that there is a health issue at all. Koehn cites the example of postsurgical abdominal adhesions, in which life-threatening internal scars form. Sentrx's product—chemically modified glycosaminoglycans that are cross-linked to form a matrix—can help to prevent adhesions, but many vets believe that this problem doesn't exist in dogs. "I began talking to a variety of vets, and the story was that dogs don't get adhesions. I thought, 'How can this be?' Rabbits get them, humans get them, even rats get them. As it turns out, if you do the experiment, 100% of dogs do get them," he says. What is absent in the field of veterinary medicine is a clinical syndrome associated with postsurgical adhesions.

Modeling cancer

Although companion animals have developed into a viable market in their own right, they have also gained considerable attention as animal models for human diseases. Most animal model work focuses on dogs. In 2004, the US National Cancer Institute, in Bethesda, Maryland, founded its Comparative Oncology Program (COP), which studies naturally occurring cancers in pet dogs as a model for human

cancers. “Although the work is based on the idea that pet owners are highly motivated to seek out new treatments for dogs, and the work we provide is in the service of companion animals, the basis of the work is really to improve the development of human drugs,” says Chand Khanna, director of the program.

The program was instituted in large part in response to the recognition that mouse models of cancer have severe shortcomings. Implanted tumors are biologically homogeneous, and oftentimes the way tumors grow in rodents is much different from the way they grow in humans or other animals. “By using naturally occurring tumors, we can see a more typical pathologic spectrum,” says Hanson.

Martin D. Cleary, president and CEO of Juvaris, agrees. “History says that if a tumor is implanted in a mouse, the results mean almost nothing. Naturally occurring tumors are a much larger challenge than implanted tumors.”

The COP is set up to assist with integrating results from studies in companion dogs into the overall development and design of human trials and is developing a variety of tools to enable this process. It has created canine tissue microarrays, with sample sets from dogs with lymphoma, nasal carcinoma and osteosarcoma. Most of the tissue samples also have information about clinical outcomes associated with them. Other initiatives include a project to validate antibodies for cross-reactivity with canine tissues, the development of a canine microarray to characterize gene expression in ten normal canine organs and the development of optimized proteomics protocols.

The usefulness of dogs extends beyond the physiological characteristics of naturally occurring tumors. Canine physiology, metabolism and drug distribution are all similar to those of humans. The genetic diversity is also a more realistic model of human patients. “You have a diverse population of patients, and that’s a good thing and a bad thing. If you want to study a specific (disease or process), the mouse allows you to do that. If you want to find out if the outcome is generalizable, the dogs are very necessary,” says Khanna. Because dogs are also more similar to humans in the way they metabolize drugs, their reactions are more predictive of potential toxicity. “If a compound is well tolerated in dogs, there’s a good chance it will be similarly well tolerated in humans,” says Hanson.

Dogs are also useful for other disease areas. Accera’s Orndorff believes that dogs are a better model for Alzheimer’s disease than the more widely used rodent models. Their clinical study did not involve research animals, but rather retired hunting dogs that had been returned to breeders. “Research animals are dumb. They haven’t been in a learning environment, so they

Box 1 Regulations for Rover

Most small-molecule drugs for animals fall under the purview of the FDA’s Center for Veterinary Medicine (CVM). In contrast, biologics—including viruses, serums, toxins, vaccines and immunogenic components—are handled by the veterinary biologics staff at the Animal and Plant Health Inspection Service of the US Department of Agriculture.

Veterinary drugs are subject to safety and efficacy standards similar to those for human drugs, although trials are generally much smaller—with animal participants typically numbering in the hundreds.

A New Animal Drug Application (NADA) must include supporting safety and efficacy data, along with a report of adverse events, information on the drug’s chemistry, composition, manufacturing methods, facilities, proposed labeling and analytical methods.

In 2003, the US Congress passed the Animal Drug User Fee Act. Like its counterparts for human drugs and medical devices (PDUFA and MDUFA), the bill authorizes the FDA to collect fees for certain animal drug applications and other activities.

have a very limited ability to learn new tasks,” says Orndorff.

Animal trials can be faster than their human counterparts. “Some studies have been done in as little 3–6 months. Human trials can take 2–3 times the calendar time,” says Orndorff. That’s partly because of the time it takes to recruit human patients and partly because regulatory oversight is less onerous for animal trials. “There are regulatory reviews on animal tests, but they tend to go faster.”

Finally, trials can also be sped up, because the compressed life span of animals means that disease progression may be faster.

Diagnostics too

Companion animal biotechnologies aren’t limited to therapeutics. Dog breeders have been targeted by companies offering DNA diagnostic tests as well. Purebred dogs all went through a genetic bottleneck at some point in their history, and that can leave them susceptible to recessive genetic disorders, such as hemophilia in German shepherds or basset hound thrombopathia. With the help of genetic tests, dog breeders hope to eliminate some of those problems. They are mostly tools to help breeders weed them out, according to Rob Loechel, who is a consultant with VetGen in Ann Arbor, Michigan, which offers a variety of disease and trait tests for dogs and a test for polycystic kidney disease test in cats.

Genetic tests don’t just focus on disease. Breeders are also interested in tests that focus on traits, such as coat color. For example, bully whippets, which are muscle-bound versions of the racing dog known as the whippet, are homozygous for a mutation in the myostatin gene. Initially, breeders wanted to eliminate the mutation, but then they discovered that animals that carry only one copy of the gene are faster than normal dogs. “That adds a whole new twist. Now there might be

people trying to keep this thing around,” says Loechel.

Loechel expects more advances in companion animal genetics. “The field in general is picking up because the canine genome [sequence] was completed several years ago and now there are some new, more advanced screening tools available that are letting researchers find mutations much faster than they used to,” he says. In April, researchers announced that a gene fragment that suppresses the insulin-like growth factor-1 gene controls the size of dogs, which can vary from 2 pounds to 200 pounds³.

“Cats are only a few years behind. They just finished their genome project and they’re starting to develop the same sorts of tools,” says Loechel.

The forecast

Companion animal health care seems likely to continue to improve, with more new therapies and reformulated human therapies aimed at this growing market. “All human drugs went through animal studies at one point in their evolution, and I suspect a lot of companies are going back and digging through that data to see if it can be applied to the companion animal market,” says Koehn.

As biotech companies struggle for funding and corporate partners, it seems natural to inquire with pet care companies like Purina and Merial to see if an emerging biotech product could provide a new source of revenue and proof-of-concept in the companion animal market. “A huge chunk of the investment has already been made. To flip it over to the veterinary side is inexpensive, and it’s free money,” says Astroff.

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