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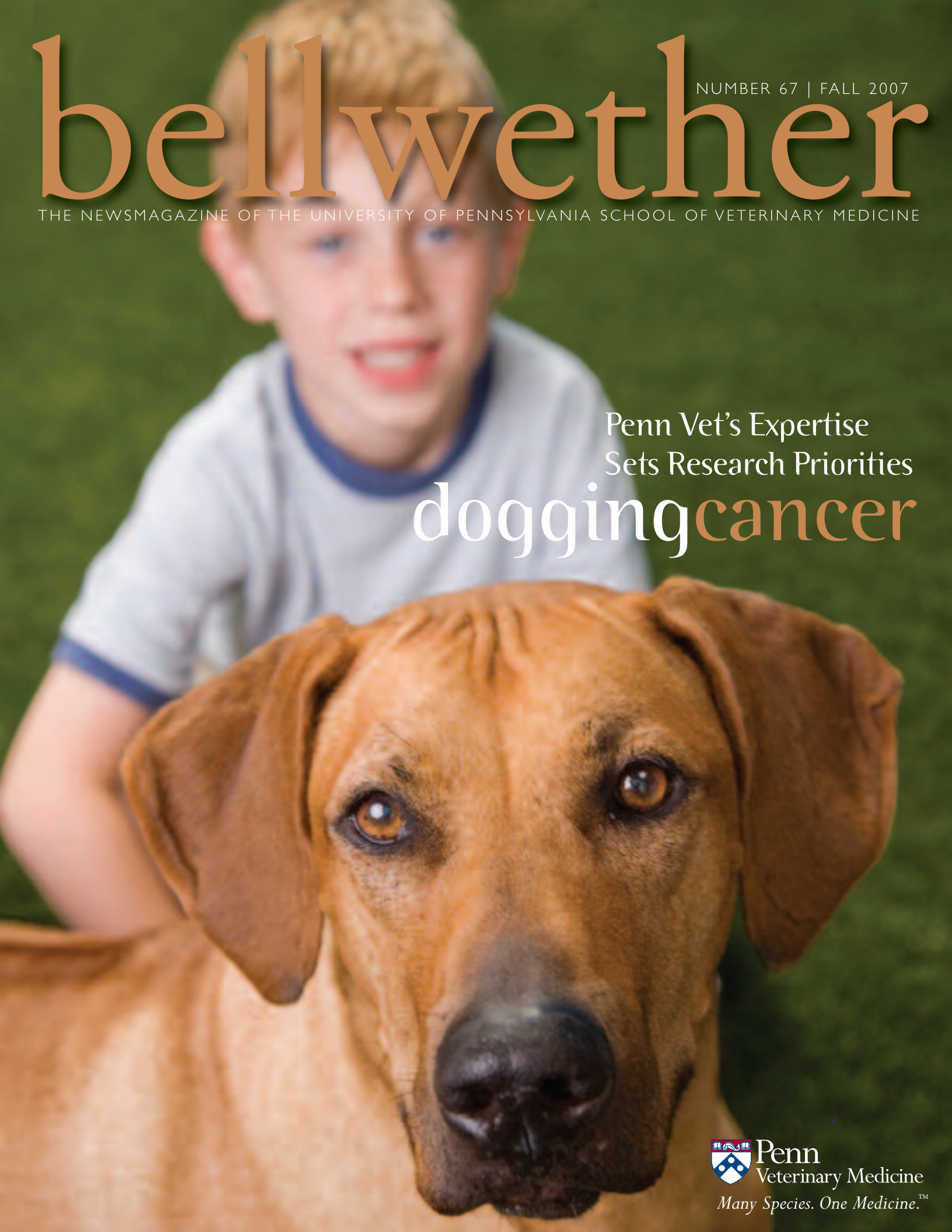
Dogging Cancer: Penn Vet's Expertise Sets Research Priorities

Susan I. Finkelsetin
University of Pennsylvania



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Penn Vet's Expertise Sets Research Priorities

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Penn Veterinary Medicine

Many Species. One Medicine.™

Penn Veterinary Medicine

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writers
SUSAN I. FINKELSTEIN
KATE JUDGE
GAIL LUCIANI
NANCY WEST

designer
ANNE MARIE KANE

We'd like to hear your praise, criticisms or comments.

Please address your correspondence to:
Gail Luciani, Editor
University of Pennsylvania
School of Veterinary Medicine
3800 Spruce Street
Philadelphia, PA 19104-6010
(215) 898-1475
luciani@vet.upenn.edu

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about the cover:

Nine-year-old Kyra, a Rhodesian ridgeback, was diagnosed with canine lymphoma after her owner noticed a large lump on the back of her left leg. After 20 weeks of chemotherapy at the Matthew J. Ryan Veterinary Hospital, the dog's cancer went into remission. Kyra then became the first dog to participate in a clinical trial at Ryan—funded by the Alliance for Cancer Gene Therapy—that is testing a vaccine to sustain the remission. "We can get very valuable information about whether this is a very feasible strategy to vaccinate humans, specifically kids with cancer," said **Dr. Karin Sorenmo**, one of the trial's principal investigators, and chief of Ryan's Oncology Section.

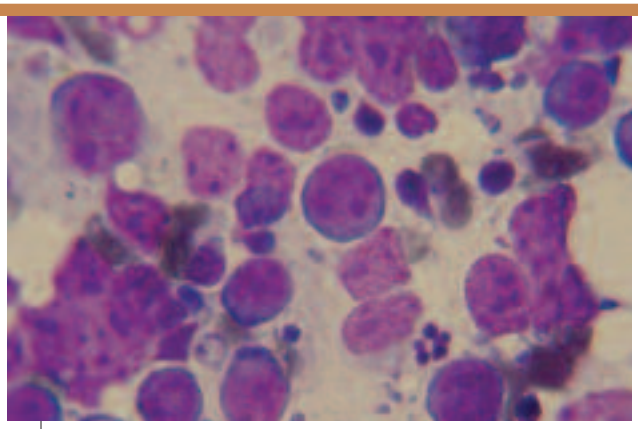
Penn Vet's Expertise Sets Research Priorities

dogging cancer

BY SUSAN I. FINKELSTEIN

"Finding a cure for cancer" and "putting a man on the moon" are phrases that convey achievement of seemingly impossible tasks: if we can put a man on the moon, then, well, we should be able to do just about anything. We got to the moon in 1969, but still are searching for the cure (more likely, cures) for cancer—a landmark in human progress that will change the world even more than did Apollo 11. But research underway at Penn Vet and elsewhere indicates we need not probe the cosmos for this particular milestone—in fact, we may not have to look any farther than our own feet in an easy chair or at the end of the bed. Dogs and cats with cancer may lead to a cure in people, and a branch of medicine called comparative oncology may be the vehicle to get there.

Of the approximately 65 million dogs and 32 million cats in the United States, the National Cancer Institute estimates that each year roughly six million dogs and about the same number of cats will be diagnosed with cancers that share many features with human malignancies—including osteosarcoma, prostate and breast cancers, non-Hodgkin's lymphoma, melanoma, soft-tissue sarcoma and



Cytology from a needle aspiration biopsy of a lymph node of a dog with lymphoma. The predominant cells are lymphoblasts. Slide was stained with a modified Wright's stain. / Joel Mills, DVM.

head and neck carcinoma. The sheer numbers of these cases and the many biological similarities between people and dogs make the latter especially ideal models for studying comparable human cancers.

Also, because animals age more quickly than people and have shorter lifespans, data from studies of new therapy methods and drugs are obtained more quickly when working with animals—knowledge that can be applied that much sooner to human treatments. And one hand (or paw) washes the other when results of large-scale research efforts for humans can also be administered to animals. Veterinary and medical oncologists, the pharmaceutical industry and academic research centers are all studying comparative oncology, the study of naturally occurring cancers in animals as models for human disease. Many areas of research offer promise: anti-cancer vaccines, bioengineering for new delivery systems, early detection.

Clinical Trials: A Critical Component

The University of Pennsylvania School of Veterinary Medicine is uniquely positioned to be a pioneer in comparative oncology. As one of the only vet schools closely integrated with a medical school, collaboration among researchers and clinicians from diverse backgrounds and interests is stronger than at other universities.

Clinical trials involving animals with spontaneous disease are perhaps the most important component of comparative oncology studies. Although considered "experimental," treatments used in clinical trials have been previously evaluated in laboratory animals, and their safety has been demonstrated in normal dogs and cats. The hope is that these new approaches will significantly benefit the patients receiving them or produce new knowledge for others with the same condition. In fact, many effective treatments are available today because of lab research and patient participation in clinical trials.

"Another Perspective"

Funded by the Alliance for Cancer Gene Therapy, an ongoing clinical trial that marks a joint effort of Penn Vet, Abramson Family Cancer Research Institute and Children's Hospital of Philadelphia involves dogs with lymphoma, an aggressive disease of malignant lymph glands and/or cells. Because canine lymphoma is a systemic disease—comparable to non-Hodgkin's lymphoma in people—chemotherapy usually is the recommended course of treatment. Seventy to 80 percent of dogs respond to chemotherapy at first, but the majority relapses, and the new tumors eventually become resistant to treatment. On average, survival time is one year.

The trial's principal investigators are **Dr. Karin Sorenmo**, chief of the Ryan Veterinary Hospital's Oncology Section and associate professor of oncology; **Dr. Nicola Mason**, assistant professor of immunology, and Pamela Cole Chair in Companion Animal Medicine at Penn Vet; and the Abramson Institute's Dr. Robert Vonderheide, assistant professor of medicine. Its purpose is to assess the potential benefits and side effects of a novel type of immunotherapy (a cancer vaccine) used after remission is achieved with standard chemotherapy. The vaccine is designed to stimulate the immune system to recognize and attack the cancer anywhere in the body, preventing relapse of the original malignancy. With this, researchers hope to prolong the time during which the

Oncology staff prepare to administer chemotherapy treatment to Kyra.

patient is disease-free, increase the percentage of long-term lymphoma survivors and facilitate further development of this vaccine strategy in children patients.

"It brings another perspective to the practice of oncology," said Dr. Sorenmo, referring not just this study, but to veterinary clinical trials generally, "and it's exciting to be part of something that reaches beyond treating dogs and cats, even though I think that is worthy in and of itself. We are not merely a means for researchers to figure out how to treat humans with cancer, but treatment of animals themselves is worthy as well."

Ryan's Oncology Section is also a member of the National Cancer Institute's Comparative Oncology Trial Consortium (COTC), a new-drug development consortium based on collaborative relationships with accredited schools of veterinary medicine throughout the country. As part of the COTC, Penn Vet was involved in another, recently closed trial for dogs with various non-operative malignant tumors that were treated with "tumor necrosis factor" (TNF), a cytokine naturally produced in response to infection, inflammatory conditions and tumors.

"The purpose of this trial in to see if it's still safe when we give it multiple times, but also to determine if it results in shrinkage of the tumor," Dr. Sorenmo explained. "I think that the decision to take this to human clinical trials will be very much dependent on the results of this dog trial."

Other Trials

Down another third-floor corridor of the Ryan Veterinary Hospital, faculty from various sections and services (principal investigators: **Dr. Deanna Worley**, surgery resident, and **Dr. John Lewis, V'97**, assistant professor of dentistry and oral surgery; co-investigators: **Dr. Alexander Reiter**, assistant professor in dentistry and oral surgery; **Dr. David Holt**, section chief and professor of surgery; **Dr. Stanley Blazejewski, V'80**, dentistry and oral surgery resident; **Dr. Dorothy Cimino Brown**, assistant professor of surgery; **Dr. Carrie Tupper, V'03**, oncology resident; **Dr. Tiffany Scanlon, V'01**, pathobiology lecturer; and **Dr. Tom Van Winkle**, professor of veterinary pathology and chief of the Small Animal Necropsy Service) are involved in a clinical trial using procedures commonly performed in human oncology to evaluate lymph-node drainage patterns in dogs with oral malignant melanoma, the most common malignant oral tumor in dogs (funded by the Barry and Savannah French-Poodle Memorial Fund and by Penn's Veterinary Clinical Investigations Center). Doctors combine surgical removal of regional lymph nodes with injection of a dye to identify the sentinel lymph node, which is the first node or nodes receiving drainage from a tumor.

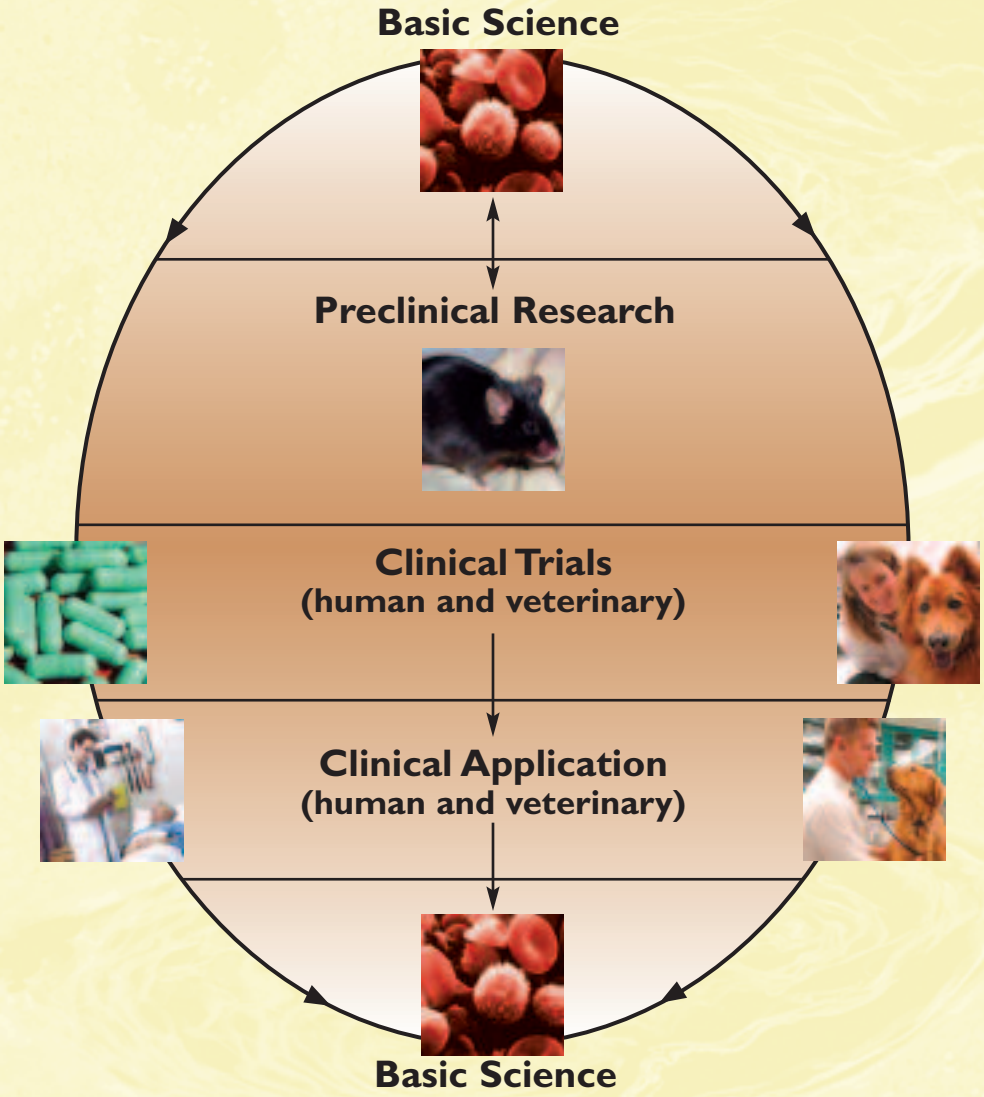
To perform a sentinel lymph node biopsy, surgeons first inject blue dye near the tumor several minutes before the actual biopsy. Then, during the biopsy, surgeons inspect the lymph nodes for staining. One or several nodes may take the dye, and these are designated the sentinel lymph nodes, which are then removed. Surgical excision of the primary site of oral malignant melanoma occurs after removal of the nodes. This method has been used in human medicine to better determine drainage patterns and extent of disease.

Another clinical trial involves staff from several Ryan departments collaborating with the Lankenau Institute for Medical Research (principal investigator: **Dr. Lewis**; co-investigators: **Dr. Reiter**; **Dr. Sorenmo**; **Dr. Erica Krick, V'02**, oncology lecturer; **Dr. Tiffany Scanlon, V'01**, pathobiology lecturer; and **Dr. Fran Shofer**, epidemiologist statistician). This time, the team is studying the use of a new chemotherapy drug in cats with inoperable oral squamous cell carcinoma (SCC) (squamous cells are in the skin's outer layer and cover some mucosal surfaces).

From left to right: back row: Dr. Karin Sorenmo, Dr. Robert Vonderheide and Angharad Waite; middle row: Roxanne Bachman, CVT, Dr. Nicola Mason and Dr. Beth Overley; front, kneeling: Michael Wexler and Amy LaBlanc,CVT; dog: Kyra Eisenhower.

Every week, the Ryan Veterinary Hospital sees cases of feline SCC, the most common oral cancer affecting cats, accounting for up to 80 percent of all feline oral tumors. An aggressive malignancy, it is uniformly fatal as the tumor invades local structures of the mouth, causing pain, lack of appetite and weight loss. Conventional treatment

The Cycle of Translational Medicine



Basic Science. Basic cancer research focuses on increasing understanding of mechanisms that control cell reproduction, for example, studying normal and diseased blood cells. This scanning electron microscope image from the National Cancer Institute shows normal circulating human blood.

Preclinical Research. During preclinical drug development, scientists evaluate the toxic and pharmacologic effects of the drug or treatment through in vitro and in vivo laboratory animal testing.

Veterinary Clinical Trials. Veterinary clinical trials involving pets with spontaneous disease often are part of developing new medications, procedures or therapies.

Human Clinical Trials. Often conducted in four phases, clinical trials involving people are conducted with volunteer patients, usually to evaluate a new treatment, under strictly controlled conditions. Each trial is designed to answer scientific questions and to find better ways to treat individuals with specific diseases.

Veterinary Application. Successful outcomes from clinical trials are made available to veterinarians for treating pets, and therapies from human medicine can be applied to veterinary medicine.

Human Application. Successful outcomes from clinical trials are made available to physicians for treating people, and therapies from veterinary medicine can be applied to human medicine.

(surgery, radiation and chemotherapy) have been of limited benefit to most cats with large SCC tumors.

Recent research in mice, however, has proved highly promising. Administering an enzyme-inhibiting substance called 2-**Di**Fluoro**M**ethyl**O**rnithine (DFMO) to SCC-bearing mice produced very positive results, and even apparent cures in a high percentage of them. Although DFMO has not yet been used in cats, safety, toxicity profiles and drug dosages higher than those in the current study have been well documented in other species. Penn Vet clinicians are using gradually increasing doses of DFMO to determine if the drug is well tolerated and effective in cats (three cats are treated at an assigned dose rate, and the next three cats are treated at a higher dose if the previous dosage was well tolerated).

Basic Research: The Foundation of Discovery

Before clinical oncology trials can even be considered, however, scientists often spend years performing basic, or "bench," research in the laboratory, studying communication between and workings of cells, and how their functions are affected by different conditions and drugs. Clinical trials—often divided into several phases themselves—follow lengthy preclinical research in which new drugs may be tested on laboratory animals to indicate the maximum doses, toxicities and anti-cancer potential. It is basic research, however, that provides the broad base of knowledge that has and will continue to make breakthroughs possible. X-rays, penicillin, the polio vaccine and genetic engineering are just a few of the numerous examples of celebrated medical advances that evolved from preliminary basic research.

Because cancer is a disease of the cell, basic cancer research has focused on increasing understanding of mechanisms that control cell reproduction. But cancer research also involves larger and smaller processes than the cell. To learn how tumors grow and spread, researchers must know how cells interact—and to identify and classify anti-cancer drugs, they need a thorough knowledge of fundamental chemistry and the newest approaches to designing and combining drugs. In oncology, basic research has focused on expanding knowledge of the molecular biology of both normal and malignant cellular growth and regulation. Given the complexity of cancer, successfully combating it requires interaction among scientists investigating cancer at all levels.

Some of the basic comparative oncology research currently underway at Penn Vet includes ways to target blood vessels that feed tumor cells, proteins that regulate the ability of cells to move, and the signaling of cells in inflammation and cancer. [See www.vet.upenn.edu/bellwether for details.]

Banking on a Cure

At the intersection of basic and clinical research is the School's new Tumor Tissue Bank (TTB), housing tissue specimens from clinical trial participants and other patients from the Ryan Veterinary Hospital. The TTB will serve basic scientists in a wide range of research applications—from genomics and proteomics to creating vaccines for cancers—and will act as a repository of canine and feline primary tumor tissue and related biofluids, like serum and plasma. It will be linked to a searchable database that will form the basis of a university core facility aimed at providing resources for basic and translational comparative oncology research.

"We already have a number of samples and have developed stable cell lines of low passage number from them," said Dr. Mason, who will direct the TTB with **Dr. Sam Long**, assistant professor of neurology and neurosurgery.

Historically, lack of access to tumor tissue has been a bottleneck for cancer research. Penn Vet's TTB will provide a comprehensive collection of cancer specimens with related clinical information that will enable researchers to address unanswered questions concerning the prognosis and treatment of cancer. As a multi-user resource, the TTB will be available to a wide range of cancer researchers at Penn and elsewhere.

"Researchers at Penn's veterinary and medical schools are already using some of the developed lines to investigate roles of certain signaling pathways in tumor development and to assess levels of expression of tumor antigens that may be targeted using novel immunotherapeutic approaches," stated Dr. Mason. "Work with these samples will lead to a greater understanding of cancer biology and allow great strides to be made in the field of translational cancer research."

New Knowledge

"The growth of our science and education will be enriched by new knowledge of our universe and environment, by new techniques of learning and mapping and observation, by new tools and computers for industry, medicine, the home as well as the school."

So said President John Kennedy in a 1962 speech on the nation's commitment to explore space—and so could be said of modern science's charge to reduce cancer's deadly toll. During the next decade, Penn Vet's brightest researchers may help uncover "new knowledge" that will allow doctors to detect and block many cancers at the earliest stages. It may very well be that our pets will be cancer-free before we are, through basic studies and clinical trials—yet one more contribution animals would make to the quality of our lives.