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Veterinary Oncology: Taking Animal Research Out of the Lab

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Dr. Arta Monjazeb, a human radiation oncologist, and Dr. Michael Kent, veterinary oncologist, collaborate on clinical trials at UC Davis School of Veterinary Medicine to improve the lives of canine and human patients. Photo courtesy UC-Davis.

Fido is NOT a Lab Rat!

Well, Fido may actually BE a lab rat, in a manner of speaking. He may be one of hundreds of dogs participating in clinical trials of novel cancer treatments that certainly have application in animal

A Short History of Veterinary Oncology

Veterinary Oncology was first recognized as a specialty within veterinary medicine in the US close to 50 years ago. The Veterinary Cancer Society (VCS) was

medicine, but possibly in human medicine as well. Veterinary oncology is a field that extends animal research outside the vivarium deep into the public realm, with fascinating possibilities for human medicine.

Putting the "Veterinary" in Veterinary Oncology

Veterinary oncology in the US, EU, and Japan is one of the most rapidly-expanding disciplines within the field of companion animal veterinary medicine. In addition to its obvious applications to treating cancer in pets, there is the potential for wide application in human medicine. The connection between canine cancers and human cancers has long been established.[1] Pets as research subjects have several advantages over traditional "lab animals"—and sometimes human participants, too:

- The tumor models are better. Spontaneous tumors in dogs are more complex than tumors induced in the lab, and more directly representative of the variety and complexity of human tumors.
- Canines and humans show similar effects of aging on the immune system.

founded in 1976 as a professional organization dedicated specifically to veterinary oncology. The American College of Internal Veterinary Medicine (ACVIM) was founded as an umbrella group for specialties within veterinary medicine in 1973, and Medical Oncology was added as a specialty in 1988. In Europe, the European Society of Veterinary Oncology (ESVONC) was founded in 1982, and oncology was added to the European College of Veterinary Medicine – Companion Animals (ECVIM-CA) in 2009. Two additional leading veterinary oncology societies are the Associação Brasileira de Oncologia Veterinária (Arbrovet), founded in Brazil in 2004, and the Japan Veterinary Cancer Society (JVCS), founded in 2009.

The earliest work in veterinary oncology dates from the mid- to late-1960's, with work in the US and Europe on tumors in animals beginning to appear in the literature. In the late 1960's and early 1970's, regimens for bone marrow transplants in dogs were developed, and the mid-1970's saw development of

Michael Kent, MD, of the UC Davis Clinical and Translational Science Center, noted that "Like people, dogs are experiencing an increase of cancer incidence, and their owners are highly motivated to seek novel treatments."[2] Because of this motivation, patient compliance is better than in humans.

- Tumors are as easy to diagnose in dogs as in humans, and similar (or even the same) laboratory techniques and diagnostic tools can be used on both canine and human cancers.
- Immunotherapy is well-suited to companion animals as they have normally-functioning immune systems. Immunosuppressed animals are required to grow induced tumors, but as Henrik Rönnberg, CEO of AdvaVet, Inc., points out, therapies that challenge or modify immune responses can't be tested in animals that don't have working immune systems.[3]

Sequencing the dog genome has allowed molecular biological approaches to vaccines for canine lymphoma.

The World Health Organization (WHO) first published the International Histological Classification of Tumors of Domestic Animals in 1974, followed in 1980 by the TNM Classification of Tumors in Domestic Animals, significant for showing that spontaneous canine and feline tumors are relevant models to study human cancers.

Early studies of immunotherapy regimens in the mid-1980's showed promise for treatment of canine melanoma, leading to DNA vaccine evaluations in the mid-2000's that assessed the potential for translation to human patients.

The National Cancer Institute started its Comparative Oncology Program (COP) in 2003, which led to the establishment of the Comparative Oncology Trials Consortium (COTC), a network of 20 academic comparative oncology centers which conducts clinical trials of new therapies in dogs with

look for DNA changes that predispose the dogs to certain forms of cancer. Because of the close correlation between a number of human and canine cancer forms, there is considerable potential for successful canine gene therapies to cross over to human therapies and vice versa.

A Little Complexity is a Good Thing

One of the primary advantages of housing and using lab animals in the vivarium setting is the increased ability to control environmental factors as well as the characteristics of the animals themselves. External factors such as disease, predators, random stressing events, temperature and humidity, variability in food and feeding, etc. can be eliminated or tightly controlled. Controlling such factors allows the researchers to focus on the specific inputs and responses, be they behavioral or physical, short-term or longitudinal—without having to account for irregularities or variations these factors could introduce into the results.

On the other hand, companion animals with spontaneous disease or tumors, in clinical (i.e., non-laboratory) settings, live in and are studied in uncontrolled conditions. While eliminating the potential influences of these conditions is nearly impossible, it is generally not necessary or desirable.

For instance, a canine trial conducted in a clinical setting with a wider range of genotypes in the population makes early detection of pharmacogenomically-important variations in drug tolerability (i.e., drug responses based on the genetic makeup of the animals being tested) easier than it would be in a more homogeneous population of lab animals. This more closely aligns with conditions in human trials, making the companion animal studies potentially useful precursors to the human studies, especially because of the established similarities between canine and human cancers.

cancer that may directly or indirectly lead to further development of these therapies for use in human cancer patients. Tumor tissue biobanks provide data and/or tissue for comparative purposes, or to identify genotypes of interest. The Canine Comparative Oncology and Genomics Consortium (CCOGC) and the Pfizer-CCOGC Biospecimen Repository, created in 2012, provides a range of sample types and data for over 2,000 canine patients.

Diagnosis, sampling, data gathering, and treatment are generally done at veterinary hospitals or specialized veterinary oncology hospitals, with trial design, treatment prep, data analysis, archiving, etc., done in a laboratory that is not collocated with the clinic.

Examinations are usually done in the clinical setting. Most clinics have at least some laboratory capabilities, which allows for some sample analysis as well as preparing the samples for transport to the lab. Also, as noted earlier, most veterinary hospitals have in-house imaging capabilities, and data from digital cameras, measuring devices, and imaging can be captured and transmitted directly to the researchers. Collaboration is enhanced because the data can be quickly and widely shared among members of the research team.

Treatment is generally done in the clinical setting as well. It is more convenient for the owners to have diagnosis and treatment at the same facility, and most veterinary hospitals have more than adequate resources available to support most treatment modalities.

Because the patients are animals with whom the treating veterinarians may form attachments, randomized, single-, and double-blinded studies which separate the attending veterinarians from the researchers are used to prevent intentional or unintentional biases from influencing the test results. In single-blind studies, the researcher knows which animals are receiving treatment, and which are being given placebos, but the veterinarian and owner do not. The veterinarian administers the treatment to the animals, while the researcher generally prepares the treatments, randomizes them for administration to the animals, and analyzes the results. Double-blind studies use a third party to do the preparation and randomization, so that neither the researcher nor the veterinarian and owner know which animals are receiving treatment and which are being given placebos.

In trials involving only oral or injection/infusion medications, a single-blind trial is usually sufficient to ensure fair results. Double-blind trials are appropriate for trials that compare oral medications to injection/infusion medications. Researchers administer the medications, so they know which animals are getting pills and which are getting injections, but they would not know which animals were getting placebos. The animals' legs are all shaved in the same spot for infusions and blood draws so that

neither the veterinarians nor owners know which treatment which animal is getting.

Treating Dogs Like People

Like cancer in humans, cancer in dogs is treated through a wide range of modalities, often in combination. Developments in molecular biology, immunology, pharmacology, and radiation therapies in the last several years are more directly focused on their potential for use and/or adaptation for human cancer patients.

Chemotherapy is commonly used to treat lymphomas, with both multi- and single-drug protocols. While multidrug protocols are considered more effective, single-drug protocols using the commonly-used drug doxorubicin are generally less expensive, easier to administer, and well-tolerated.[4] Dog models have long been used in lab studies of doxorubicin-induced cardiotoxicity—a serious side effect that currently has no effective treatment—due to the similarities in how canine and human hearts respond to doxorubicin-based cancer protocols. Recent work by AdvaVet, an American subsidiary of Swedish pharma company Oasmia Pharmaceutical AB, combines doxorubicin with a nanoparticle-based delivery system that reduces toxicity for treatment of lymphomas in dogs, with indications that it may be able to inform development of a similar product for human use.

Canine and human medical imaging are both done via X-ray Radiography; Ultrasound; Computed Tomography (CT); nuclear medicine, including Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET); and Magnetic Resonance Imaging (MRI). Low doses of radiation are used primarily for diagnostic purposes. CT and MRI are often used in conjunction with nuclear medicine modalities to build more complete images of the areas of interest.

Imaging equipment and techniques for canine nuclear medicine are very similar to—and in many cases the same as—equipment and techniques used for humans. While "veterinary" imaging equipment is becoming more widely available, use of equipment designed for human use is common. Most veterinary hospitals have digital X-ray, ultrasound, and CT capabilities, and most with CT have MRI capability as well. Due to its high cost, PET imaging is not widely available in veterinary hospitals, nor is it frequently used—it is often done off-hours in human hospitals, on human equipment. Picture Archiving and Communication System (PACS) software is used to store, retrieve, present, and share images produced by this equipment.

In the past, canine radiotherapy was primarily palliative, aimed at controlling growth of tumors and cancers to limit pain in the animal. However, in more recent years the focus of radiotherapy has shifted toward curative treatments designed to eliminate the tumors and cancers.

Intensity-Modulated Radiation Therapy (IMRT), Image-Guided Radiation Therapy (IGRT), and Stereotactic Radiotherapy (SRT) are more recent developments that more sharply focus the radiation on tumors, minimizing damage to healthy tissue. IMRT uses multiple beams that can be varied in intensity to give different doses to different areas of the tumor. IGRT uses imaging modalities during treatment to adjust the location and intensity of the radiation as the tumor changes size, shape, and location as the treatment progresses. SRT uses multiple beams of radiation directed at small tumors with well-defined edges that cannot be removed surgically, such as brain tumors. SRT also has the advantage of reducing the number of treatments required—where a conventional radiotherapy regimen might require 15 to 20 treatments, SRT can reduce that to 3 to 5 treatments, due to the higher doses of radiation used.[5]

Immunotherapy has its roots in the late 19th century, when William Coley, MD, experimented with injecting mixtures of live and inactivated Streptococcus pyogenes directly into his patients' tumors. "Coley's Toxins" had some success in achieving complete remission of a number of cancers, but between the lack of understanding how and why the treatment worked and the risks of deadly infection, surgery and radiotherapy became the standard cancer treatments during the 20th century.[6]

Immunotherapy today is a big tent, encompassing vaccines, genetic modification, tumor markers, "precision medicine," and so on. Many of the protocols used for canine immunotherapy have their roots in human medicine, and vice-versa.

Sequencing of the dog genome in 2007 has led to an increased the focus on studying cancer forms in dogs because of their close correlation to their human counterparts, and Next Generation Sequencing is making it more economically feasible to detect specific genetic features or defects that may correlate with increased risk for the cancer(s) being studied. For example, a recent study shows a correlation between increased risk of developing malignant mammary tumors in English Springer Spaniels and a gene that is also linked to drug resistance in human breast cancer, suggesting that canine mammary tumors

may also be useful as comparative models for future genetic and clinical studies of breast cancer.[7]

Man's Best Comparative Medicine Model

Veterinary oncology is a branch of animal research that has been hiding in plain sight for 50 years. By treating people's dogs in veterinary clinical settings, the public is involved in the research in a very personal way. Whether they realize it or not, the treatments that help their pets may eventually help humans as well. "Man's best friend," indeed—and much more!

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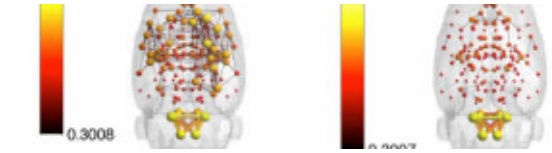

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