Short Communication

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Unleashing the power of comparative oncology models in nanomedicine research

Abstract: The pathway from discovery of novel candidate drugs, including nanomedicine compounds, to FDA approval is lengthy and may be difficult to navigate. Often times, investigational drugs are appropriately abandoned early in the development pathway due to preclinical failure. Other novel compounds may look quite promising in rodent models and preclinical trials, but prove disappointing when tested in human patients. In fact, only 5% of drugs entering Phase I human cancer clinical trials in the US are ultimately approved. Given the enormous cost, in terms of both financial investment and delay in progress toward improved patient outcome, there is a critical need for a more reliable and efficient process. One solution may be to improve translatability of our preclinical data by including trials in cancer-bearing pet dogs in the drug development pathway.

Keywords: canine; model; oncology; preclinical; translational.

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Introduction

The pace at which medical discoveries have translated into novel therapy options for cancer patients in the US has been frustratingly slow, with few drugs surviving the pathway to FDA approval. In fact, only one of every 5000–10,000 prospective new anticancer agents is eventually approved (1, 2). While many candidate drugs are appropriately withdrawn from the drug development pathway due to failures discovered in preclinical evaluation, many others show promise in rodent models that does not translate to success when applied to human patients. Of drugs that enter Phase I human cancer clinical trials in the US, a mere 5% will ultimately be approved (1, 2). Clearly, there is a critical need for improved drug screening and enhanced efficiency in the process of developmental therapeutics. What if the solution to this problem lay quite literally at our feet? Perhaps it does.

The role for companion animal models in cancer nanomedicine research

In their 2013 review article entitled, “Mind the gap: A survey of how cancer drug carriers are susceptible to the gap between research and practice”, Stirland et al. address the issue of the failure of preclinical drug performance in animals to be realized in the human clinical setting, stating, one of the difficulties with cancer in the clinical setting is its inherent heterogeneity and similarity to ‘self’, thus making it difficult to choose a ligand that will be universally expressed by cancer cells yet not expressed by healthy tissue. This is not as much of an issue in preclinical studies that use more homogeneous cancer cell lines and could explain the disparity in results when translating to the clinical setting (3).

These limitations of preclinical studies in rodent models are cited repeatedly in the literature, yet the potential for companion animal clinical trials to address this problem is rarely mentioned. Part of this exclusion likely relates to a lack of awareness of spontaneously occurring cancer in pet dogs and its similarity to human cancer. While other companion animals species may also serve as models of spontaneously occurring diseases in people, the domestic dog has been utilized most often in cancer studies due to the prevalence of cancer in this species; thus, this review focuses on canine companion animals.

The pet dog population in the US is estimated at 70 million dogs, with the total number of canine veterinary visits in 2011 reported at 130.4 million (4). Of the disease states that prompt veterinary visits, many share
a commonality with human health disorders, including cancer. While most people would not be surprised to learn that an estimated 1.6 million Americans will be diagnosed with cancer this year, a lesser known statistic is that cancer is the leading cause of death in dogs, with approximately 6 million dogs diagnosed with cancer each year in the US (5–7). In fact, nearly one in four dogs will develop cancer during their lifetime (8). Of the 10 most common cancers occurring in men and women, ALL have been reported to develop spontaneously in pet dogs (5).

Some canine cancers that have been studied as models of analogous human disease include breast, prostate, bladder, and head and neck cancer, as well as osteosarcoma, lymphoma, and malignant melanoma (9, 10). These naturally-occurring neoplastic diseases in companion animals offer significant advantages over more traditional in vivo models of induced neoplastic disease including similarities in terms of etiology, heterogeneity, biological and metastatic behavior, and clinical response to therapy than does a cancer induced in a laboratory animal with an incompetent immune system (9–12). Many of these advantages are outlined in Table 1.

The elucidation of the canine genome has provided the promise of selecting canine cancer models that can enhance our understanding of tumor etiology and behavior, as well as aid in the progress of a more targeted, personalized medical approach to cancer care (13). Mapping disease susceptibility by dog breed can provide valuable clues regarding underlying genetic causes. For example, if one identifies a dog breed that is uniquely susceptible to a specific tumor type, whereas another breed is rarely affected, comparing the genomics of the two breeds to the rest of the population may help define the underlying etiology, as well as provide insight as to how to manage or mitigate disease development and progression. The study of comparative oncology facilitates optimal disease model selection for preclinical trials in dogs such that results will be directly applicable to human clinical trial design. If veterinary patients can benefit from the resultant innovation, a win-win dynamic exists that will foster further transdisciplinary discovery and collaboration.

The drug development and approval pathway for nanomedicine is somewhat unique in scope compared to traditional medical therapies. In a systematic review of the current nanomedicine pipeline including both commercialized and investigational nanomedicine products, Etheridge et al. identified 363 potential nanomedicine applications and products under review in 2010 and 2011 (14). Thirty-eight of these were previously approved products that were either being investigated for a new condition or that were serving as the comparator group for a new drug product, whereas the remainder were newly investigated nanomedicines. Of the products under investigation, roughly two-thirds were being evaluated for cancer therapy. These included both “hard” nanostructures such as gold and iron oxide and “soft” nanostructures including micelles, liposomes, emulsions, dendrimers, and other polymeric nanostructures (14).

Some of the properties for which nanoparticles are touted as carrying a potential advantage over traditional systemic cancer therapies are the very properties that may be best studied in cancer-bearing pet animals. Improved

### Table 1: Advantages of pet dog cancer clinical trials.

<table>
<thead>
<tr>
<th>General Advantage</th>
<th>Underlying principles</th>
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<tbody>
<tr>
<td>Cancer develops spontaneously, rather than being artificially induced</td>
<td>– Immunocompetent host – Shared environmental factors may underlie etiology</td>
</tr>
<tr>
<td>Diagnostic and staging methods are analogous</td>
<td>– Tumor is heterogeneous and tumor microenvironment is analogous – Advanced imaging methods such as ultrasound, PET/CT, MRI are available – Staging criteria in veterinary oncology are modeled after WHO criteria</td>
</tr>
<tr>
<td>Shortened life span compared to people</td>
<td>– Biomarkers may be similar – Shorter time frame for trial outcomes to be reached – Can study drug toxicity and disease behavior over lifetime of patient</td>
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<tr>
<td>More control over confounding variables than with human subjects</td>
<td>– Lifestyle choices – alcohol, tobacco, drug use – Diet – less variability – Hormonal status – can study disesease in neutered subjects</td>
</tr>
<tr>
<td>Ability to study therapy in minimal residual disease setting</td>
<td>– Natural post-surgical disease behavior can be studied – Monitoring for metastatic disease over lifetime is feasible</td>
</tr>
<tr>
<td>Genetic and pedigree information may be available</td>
<td>– Canine genome defined – American Kennel Club and other breed registration records retrievable – Standard-of-care not always defined – Much of the animal care is provided by the pet owner at home – Pet owner consents for the trial enrollee</td>
</tr>
<tr>
<td>Trial approval process is simplified</td>
<td>– Insurance claims usually not a factor – Can harvest ample variety and quantity of samples from live patient – Repeated biopsy of tumor and normal tissue can provide proof of target – Necropsy is not uncommon – Breed-specific funding to address breed-related diseases</td>
</tr>
<tr>
<td>Additional funding opportunities may be available</td>
<td>– Animal foundation funding – Veterinary scientific community</td>
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drug delivery to the cancer target, decreased toxicity to the patient, and sustained therapeutic drug levels are all potential advantages of nanoparticle therapy. Thus, the ability to assess pharmacokinetics, pharmacodynamics, tolerability, and the long-term effects of nanomedicines is essential and arguably most appropriately done using a syngeneic tumor-bearing animal that can be followed clinically for the natural course of its treated disease (15). This is in contrast to rodent models with artificially-induced or xenografted cancer that experience rapid disease progression, often precluding evaluation of long term effects on metastatic disease progression, drug resistance, and organ toxicity.

Enhanced permeability and retention (EPR) is a phenomenon first described in the 1980s by Hiroshi Maeda whereby macromolecular anticancer therapies selectively extravasate and are retained in solid tumors (16). The EPR effect has been exploited in the clinical development of nanotechnology for cancer therapy. If the EPR hypothesis holds true, nano-sized drug carriers should provide an advantage over traditional therapies in that drug concentration within a tumor should be increased, thus improving efficacy while protecting the rest of the body from the drug and reducing toxicity. This is frequently the case for laboratory animal models used in preclinical studies, but has often failed to materialize in clinical settings (17–22). Perhaps the intermediary step of nanoparticle therapy evaluation in tumor-bearing pet dogs could mitigate the time and expense lost on unsuccessful human clinical trials. Preferential tumor targeting can be confirm via pre- and post-drug administration biosampling methods such as biopsy of normal and tumor tissue, as well as by radiolabeling candidate drugs and studying biodistribution via nuclear scintigraphy. What many researchers do not realize is that the identical imaging modalities available in human medicine are also found in many referral and academic veterinary medical centers.

One unique concern related to the use of nanomedicines is that of persistence in the body and what long-term effects could emerge. Whereas traditional cancer therapies are metabolized and excreted from the body, nanoparticles may persist for months or years. Given that human patients eligible for cancer clinical trials often enroll with very advanced and life-threatening disease, long-term effects of nanoparticle persistence may not be realized in the lifetime of the patients receiving them. In contrast to rodent or laboratory animal studies, companion animal cancer clinical trials permit longer term (life-long) follow-up of treated animals and provide the opportunity to assess for the effects of nanoparticle persistence in tissues. Because standard-of-care therapy is not always established for certain canine diseases, dogs may be enrolled in clinical trials at an earlier disease stage. Financial, as well as altruistic incentives often prompt pet owners to seek clinical trial participation, as does the opportunity to provide cutting-edge therapy to pets that are increasingly viewed in many parts of the world as true family members.

### Progress and the path forward

There are a number of real-life examples whereby implementation of veterinary oncology clinical trials in cancer-bearing pets has enabled researchers to gain valuable data to inform clinical trial decisions for subsequent human nanomedicine investigations (23–26). Relevant outcomes of veterinary preclinical trials may include proof-of-principle data to support further investigation, PK and PD data to guide dosing decisions, and elucidation of tumor targeting efficacy and drug safety. Access to these resources may be gained via contact through searchable veterinary clinical trials databases and through veterinary specialty organizations engaged in research (27–29). Examples are provided in Table 2. As awareness of these models grows, it is hoped that those conducting medical research will utilize

<table>
<thead>
<tr>
<th>Organization</th>
<th>Contact website</th>
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<tr>
<td>Veterinary Cooperative Oncology Group (VCOG) and the Veterinary Cancer Society (VCS)</td>
<td><a href="http://www.vetcancertrials.org/">www.vetcancertrials.org/</a></td>
</tr>
<tr>
<td>FETCH a Cure</td>
<td><a href="http://www.fetchacure.org/resource-library/clinical-trials/">www.fetchacure.org/resource-library/clinical-trials/</a></td>
</tr>
<tr>
<td>Morris Animal Foundation</td>
<td><a href="http://www.morrisanimalfoundation.org/vet-clinics/our-research/">www.morrisanimalfoundation.org/vet-clinics/our-research/</a></td>
</tr>
<tr>
<td>National Cancer Institute, Center for Cancer Research</td>
<td><a href="https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Clinical+Trials">https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Clinical+Trials</a></td>
</tr>
<tr>
<td>Veterinary Cancer Society American College of Veterinary Internal Medicine European College of Veterinary Internal Medicine – Companion Animals (ESVIM-CA)</td>
<td><a href="http://www.vetcancersociety.org/www.ACVIM.org">http://www.vetcancersociety.org/www.ACVIM.org</a> <a href="http://www.ecvim-ca.org/home">www.ecvim-ca.org/home</a></td>
</tr>
<tr>
<td>European Society of Veterinary Oncology (ESVONC)</td>
<td><a href="http://www.esvonc.org/">http://www.esvonc.org/</a></td>
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spontaneously-occurring companion animal models of human disease to speed progress and improve efficiency of biomedical research and clinical application of innovations.

References


Bionote

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of Veterinary Medicine and the School of Medicine. A graduate of Auburn University and board certified in Veterinary Oncology for over 20 years, Henry has been a faculty member at Washington State University (1993–1997) and MU (1997–present). She is Associate Director of Research for Ellis Fischel Cancer Center (the first academic certified member of the MD Anderson Cancer Network); Associate Dean for Research and Graduate Studies at the College of Veterinary Medicine; and the Provost-appointed One Health Facilitator.