CANCER

Perspectives from man's best friend: National Academy of Medicine's Workshop on Comparative Oncology

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Scientists gather to survey comparative oncology research and pinpoint potential contributions to human therapeutics.

Collective experience within the cancer drug-development community suggests that conventional animal models and early-phase clinical studies in patients fail to provide seminal therapeutic insights needed to enhance the low rates of overall success and to reduce the late-stage failures in cancer drug discovery efforts. Dogs develop a broad spectrum of naturally occurring cancers that share strong similarities with human cancers, and, like human patients, pets receive state-of-the-art medical care that can include experimental therapeutics, thus offering a singular opportunity for preclinical modeling (1). A growing alliance of scientists involved in cancer research and drug development has recognized the inclusion of dogs with cancer in a comparative and integrated translational drug development path as a possible means to markedly accelerate cancer drug discovery (2, 3).

The U.S. National Academy of Medicine's National Cancer Policy Forum, which operates at the intersection of scientific research, science policy, and strategy development for cancer treatment and prevention, convened a workshop to analyze gaps in the optimal setting for clinical studies that include dogs with naturally occurring cancers (Fig. 1). The workshop provided a framework within which potential or perceived deficiencies in the field of comparative oncology could be defined and explored. A goal of the workshop was to apply a gap analysis to fashion an agenda designed to advance the role of dogs in preclinical drug development. Sessions on seven distinct topics sought to address a potential or perceived gap in the effective delivery of comparative oncology. Here we discuss how insights gained from this gap analysis can drive the development of a strategic roadmap for the advancement of comparative oncology as a translational discipline.

WORKSHOP SESSIONS: GAP ANALYSIS

Is there sufficient understanding of comparative oncology's utility in biomedical translation?

Although the past decade has witnessed a modest advance in awareness of the biological insights provided by comparative oncology studies, by most measures, this knowledge has not translated widely among researchers in the field of cancer drug development. U.S. national meetings, including those of the American Society for Clinical Oncology (ASCO), the American Association of Cancer Research (AACR) and others, rarely include plenary sessions that discuss the merits and challenges of spontaneous cancer models in drug development. Federal funding opportunities and human cancer research foundations are generally not receptive to comparative canine oncology studies. Last, much of the lay public, including pet owners, have a poor understanding of the critical role of preclinical cancer models and the opportunity for their pets to play a role in advancing cross-species clinical discovery.

Additional professional and patient groups must be included in translational medicine research and development. For example, veterinarians and physicians within the pharmaceutical industry and clinical practice can contribute crucial knowledge, whereas physician and veterinary medical associations, aligned philanthropic groups, and educated and passionate pet owners could provide advocacy and support. As we convey the importance of comparative biology, we must emphasize that such studies ask basic questions that relate to drug development and thus are species agnostic. As a result, effectively designed comparative oncology studies should offer bidirectional benefit to both pet animals and humans with cancer. Although it is not the primary intent of comparative oncology research to lead to approval of a veterinary product, the data gained can effectively lead to such an outcome and serve to support the initiation of new studies that then lead to the approval of drugs for pet animals.

In the past five years, the interest in drug development for pet animals with cancer has dramatically expanded, with the full or conditional approval of six new treatments (toceranib phosphate, xenogeneic canine melanoma vaccine, monoclonal antibodies for B-cell and T-cell lymphomas, masitinib, and paclitaxel) for animals with cancer. In four out of six of these examples, the initial conduct of comparative oncology studies was designed first to help human patients but eventually led to approval of the same or similar drugs for use in animal patients. Thus the inclusion of dogs with cancer in clinical trials designed to assist in the development of human cancer drugs has helped current and future canine patients.

How can canine tumor biology and genomics inform cancer drug development?

Strong similarities in cancer biology between dogs and humans include patterns of response or resistance to conventional therapy, as well as metastasis and recurrence (4). At the histological level, numerous specific cancers are functionally identical in dogs

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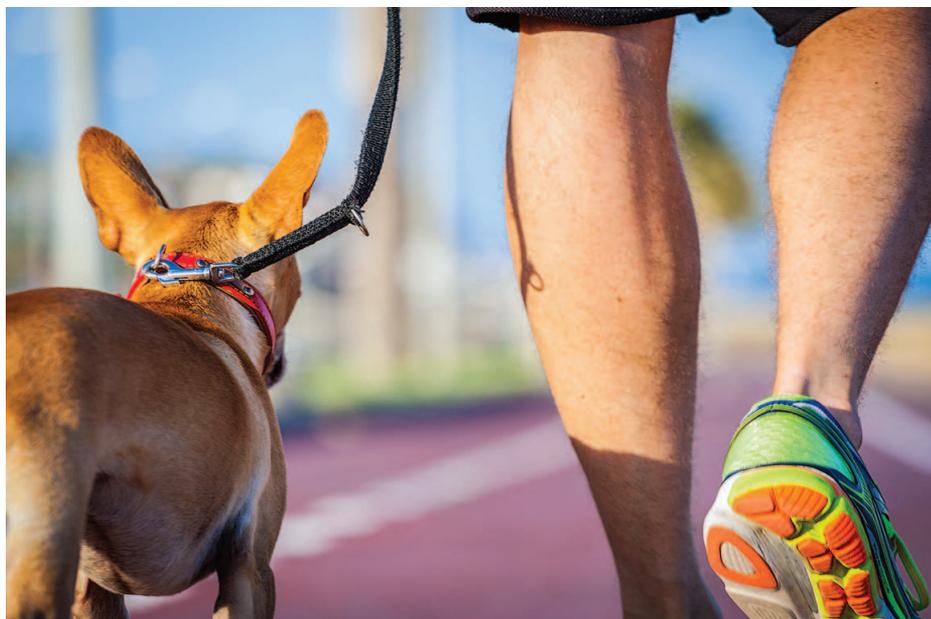
Fig. 1. Conquering cancer: Walking the path together. The workshop, held in June 2015 in Washington, D.C., was entitled "The role of clinical studies for pets with naturally occurring tumors in translational cancer research" and had as its key goal to carry out a gap analysis of comparative oncology research. (http://iom.nationalacademies.org/Activities/Disease/NCPF/2015-JUN-08.aspx).

and humans (osteosarcoma, mucosal melanoma, non-Hodgkin lymphoma, bladder cancer, and others) (*4–7*). Genome-wide studies have revealed similarities in gene dosage between corresponding cancers in dog and human, suggesting a conserved pathogenesis that might pinpoint key driver genes. Dog and human tumors also display similarities at the level of transcription and, on occasion, are considered to be indistinguishable between species.

However, at this time, our knowledge of genetic alterations that drive human cancers far exceeds that of the same alterations in canine cancers. Whereas more than 30,000 human cancers have been genomically profiled, genomic sequence data have been published for fewer than 50 canine cancers. Using strict quality control procedures, a multi-institutional collaboration has collected and banked ~60,000 tissue samples from canine cancers and matched normal tissues for comprehensive genomic and molecular analysis (*8*) [The Pfizer-Canine Comparative Oncology and Genomics Consortium (CCOGC) Biospecimen Repository; www.ccogc.net]. The success of the human Cancer Genome Atlas project (TCGA) may provide valuable lessons to facilitate the completion of a similar process in dogs, including a process that delivers high-quality, publicly available data in a reasonable period of time. An attractive alternative to the

analysis of previously banked tissues is the prospective analysis of tumor samples from canine patients entered in clinical trials, such that functional data on specific individuals (for example, exceptional responders or nonresponders) provide a functional perspective on any defined genomic variants.

Genomic data generated from dogs require modifications to standard informatics pipelines used for human samples. Specialized analysis tools that recognize unique elements of the canine genome would maximize our understanding of the canine versus human genetic backgrounds and enhance the correlative utility of genomic information. Expansion of our understanding of the genetic landscapes of canine cancer is widely considered to be the single largest current gap in comparative oncology today and likely precludes a more widespread use of the comparative oncology drug-development approach. Although several groups are actively involved in "-omics" characterization of canine cancer, we need more sophisticated and validated methodologies, reagents, and tools to optimally develop empirically driven therapeutic approaches based on genetic information.

Recent advances in tumor immunotherapy justify, as a high priority, the development of reagents that support and accelerate the use of this approach in tumor-bearing dogs. Spontaneous cancers in immune-

competent dogs present the same challenges to successful immunotherapy as those that are confronted in human cancer patients but poorly modeled in immune-deficient mice (such as cellular trafficking, immune editing, antigen escape, and an immune-suppressive tumor microenvironment). For the dog to inform human trials in immune therapy, we need to expand the canine immunological toolbox through development of reagents that enable more complete assessments of immune-target distribution, tumor-infiltrating immune cell subsets, T cell specificities (tetramer development), and functional immune responses.

Can preclinical study designs for pet dogs integrate biomarkers, pharmacokinetics, and pharmacodynamics?

New therapeutics are now often advanced into clinical development with an accompanying biomarker of effective drug exposure. Such biomarkers require preclinical validation, with increasing emphasis on validation of a circulating or bio-fluid surrogate to replace the need for sequential tumor biopsy before and after drug exposure. Preclinical studies of dogs with cancer are ideally suited for the development, validation, and testing of such tumor and circulating biomarkers (a so-called "liquid biopsy") wherein minimally invasive procedures can be routinely carried out to obtain biological samples. Because brief sedation or general anesthesia is a common component of conventional veterinary care (for example, physical examination or diagnostic imaging), it is both efficient and feasible to include serial biopsy end points into comparative oncology studies so as to rapidly validate a circulating end point against contemporaneously collected tumor tissue. Despite the fact that such biopsy-associated end points are now more common in human clinical trials, the simplicity and feasibility of acquiring such end-point studies in dogs should be prioritized as a means to ensure the success of similar studies in human patients.

How can studies in pet dogs most effectively integrate imaging technologies into study designs?

Noninvasive imaging techniques that can detect, describe, and monitor cancers before, during, and after therapy are used in both the clinical and research settings. There is an increasing demand for imaging agents that provide both anatomical and biological data

in a single study, which plays a role in the development of therapies that target specific cellular processes. Recent years have seen a dramatic increase in sophisticated anatomical and molecular imaging equipment. Growing expertise also exists at veterinary academic centers that are actively engaged in comparative oncology clinical trials.

Veterinary academic centers routinely have access to cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Many also have access to molecular imaging modalities such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and PET/CT. This access and expertise can yield pathophysiological insights from imaging end points in clinical trials and also can be leveraged for the development of new imaging agents. The physical size of dogs supports the use of clinical imaging systems that are directly translatable to the human cancer clinic. Emphasis should be placed on the use and evaluation of new "hallmark tracers" that evaluate cellular processes, such as metabolism [^{18}F-fluorodeoxyglucose (^{18}FDG), ^{18}F-glutamine], proliferation [^{18}F-fluorothymidine (^{18}FLT)], hypoxia [^{18}F-fluoromisonidazole (^{18}F-MISO), ^{64}Cu-ATSM], and apoptosis (^{99m}Tc-annexin V). These tracers allow interrogation of processes critical to tumor cell behavior yet do not rely on specific cellular markers or cell-surface molecules that might be distinct between species. Such tracers can be validated in their own right and also applied to a clinical trial in which a new agent is evaluated. Similarly, because of concerns over the handling and release of radioactive animals and exposures to radioactive wastes, emphasis should be placed on the study and development of radiopharmaceuticals that contain short-lived radioisotopes such as ^{18}F, ^{99m}Tc, and ^{68}Ga (9).

There is also a rationale for including MRI studies, as this technology is capable of acquiring data relevant to angiogenesis, drug transport, and cell killing. Dynamic contrast-enhanced MRI (DCE-MRI) end points have been shown to correlate with treatment outcome and predict for metastasis in canine patients with soft-tissue sarcoma. On the other hand, changes in the diffusion coefficient of water have been linked to acute genomic changes in tumors in response to therapy. The blending of functional imaging with genomics holds promise for assisting in target discovery and validation of target inactivation. Further, parallel studies in humans and canine

patients with the same diseases can further validate the value of imaging end points, particularly in settings in which parallel canine studies can provide long-term clinical follow-up that is often not possible in early-phase human trials.

What mechanisms are available to best conduct comparative oncology studies?

In 2004, the U.S. National Cancer Institute (NCI) launched the Comparative Oncology Program in an effort to improve the cancer translational drug development process. To date, the program has completed 12 multicenter clinical trials in pet dogs with spontaneous cancers, conducted through its clinical trial network, the Comparative Oncology Trials Consortium (NCI-COTC) (http://ccr.cancer.gov/resources/cop/COTC.asp), which consists of 20 academic veterinary teaching hospitals across the United States and Canada (2). Since the launch of this cooperative group, individual veterinary academic institutions have, under a single institutional lead investigator, initiated several small-scale (one to three sites) comparative oncology clinical trials to address similar questions in cancer drug development. These efforts can complement the larger-scale efforts conducted through the COTC mechanism, wherein six to eight or more academic sites participate in a single clinical trial that often includes multiple phases (dose escalation followed by cohort expansion) and may also evaluate multiple candidate agents simultaneously or specifically evaluate therapies for rare veterinary cancers (e.g., brain tumors). Given the end point, intensity, and time constraints of a development path, the optimal number and mechanism for trial delivery can be determined. The intensity of care needed for most successful comparative oncology studies suggests that academic centers in veterinary schools are best positioned and prepared to successfully recruit and manage patients for these studies.

Are the needs of companion animals and their owners being met with current clinical trial conduct and oversight practices?

It continues to be in the interest of all individuals associated with clinical trials in humans and pet animals to provide the highest levels of medical care to trial participants. Clinical trial design, conduct, and oversight practices are well described and implemented within both COTC studies and those conducted by

individual academic and private-sector investigators (1–3). Institutional mechanisms to ensure compliance with existing federal regulations regarding ethical use of companion animals and the necessary training to ensure ongoing compliance for such clinical studies are in place. It is essential that pet owners are clearly informed as their animals participate in a clinical trial, including those that are not expressly designed to explore the efficacy or development of animal drugs. As for any decision related to the medical care of a companion animal, pet owners should have access to professionals not directly involved in the clinical trial (e.g., counselors, primary care veterinarians, etc.) to provide knowledgeable, unbiased support for the decision-making process. Attention to animal welfare is critical to ensure a robust and sustainable enrollment process. The notion that pet owners should be considered vulnerable participants in this process was proposed at the workshop; however, this qualification has been neither widely debated nor adopted by the comparative oncology research community. A great need exists for a centralized clinical trial registry that would provide easy access for pet owners and veterinarians to open clinical trials for pets with cancer and other diseases. Currently several institutionally supported websites provide information on open clinical trials for cancer but do not provide uniform information with regard to eligibility, study procedures, financial support, sponsorship, or trial objectives.

What is the current status of comparative oncology in drug development?

The primary perceived limitations to the expansion of comparative oncology from a pharmaceutical industry perspective are (i) a lack of understanding of the genomic landscape of canine cancers; (ii) limited species-specific reagents and technologies to advance our immunological understanding of canine cancers for immunotherapeutic manipulation and integration with human studies; (iii) an inability to quantify or convey the value of comparative oncology studies; and (iv) the perception that the conduct of studies in tumor-bearing dogs that yield new or unexpected safety data might result in consequences from regulators who are overseeing parallel human clinical studies. To address issue (iii), a recent manuscript now provides additional clarity on the value of comparative oncology studies (10).

The fourth issue was discussed extensively during the workshop. The discussion herein and the public written transcript of the workshop—including direct comment from the U.S. Food and Drug Administration (FDA)—now provide unequivocal clarity on this perceived concern. Indeed, John Leighton of FDA's Center for Drug Evaluation and Research (CDER) clarified that data from comparative oncology studies would be reviewed within the context of a diseased-animal model. Therefore, these data would be considered as supplementary data and, accordingly, regulators would make appropriately cautious judgments about any new or unexpected results from these diseased-animal models, compared to data from rigorously designed and highly controlled conventional toxicology studies. This clarity alone was widely considered to be the most important outcome of this workshop. It was also clearly pointed out that the finding of unexpected toxicity in studies of tumor-bearing dogs has been and is expected to continue to be a highly uncommon occurrence. Furthermore, there is clear guidance on the mechanisms and procedures associated with the reporting of data from such comparative oncology studies, both before and after an investigational new drug application is filed with FDA.

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