The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research: Workshop Summary

DETAILS

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Workshop Summary

Sharyl J. Nass and Heather Gorby, *Rapporteurs*

National Cancer Policy Forum

Board on Health Care Services

Institute of Medicine

The National Academies of
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Cover image contributed by Joe Mendoza/Colorado State University Photography. Angela's surgery for her bone cancer was first developed by Dr. Withrow in pet dogs with the same disease. This treatment advancement continues to help dogs and people with bone cancer.

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this report was overseen by **ELI Y. ADASHI,** Warren Alpert Medical School at Brown University. He was responsible for making certain that an independent examination

of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs and the institution.

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The Forum wishes to express its gratitude to the expert speakers whose presentations helped define the current challenges and opportunities for integrating comparative oncology trials within the cancer research continuum. The Forum also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda.

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Acronyms and Abbreviations

ATP	adenosine triphosphate
BTK	Bruton tyrosine kinase
CCOGC	Canine Comparative Oncology and Genomics Consortium
CML	chronic myeloid leukemia
COTC	Comparative Oncology Trials Consortium
CT	computed tomography
CTVT	canine transmissible venereal tumor
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DSMB	data safety and monitoring board
FDA	U.S. Food and Drug Administration
FDG	flourodeoxyglucose
FLT	fluorothymidine
F-TFB	F-tetrafluoroborate
GEMM	Genomic-Enabled Medicine for Melanoma (trial)
HCQ	hydroxychloroquine
HIPAA	Health Insurance Portability and Accountability Act

IACUC	institutional animal care and use committee
IND	investigational new drug (application)
IOM	Institute of Medicine
IRB	institutional review board
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PDX	patient-derived xenograft
PET	positron emission tomography
PI	principal investigator
PK	pharmacokinetic
TBR	target-to-background ratio
TCC	transitional cell carcinoma
TGEN	Translational Genomics Research Institute
TNF	tumor necrosis factor

WORKSHOP SUMMARY

INTRODUCTION

Traditional preclinical mouse models of cancer have been very useful for studying the biology of cancer. However, they often lack key characteristics of human cancers, such as long latency, genomic instability, and heterogeneity among the tumor cells and the surrounding microenvironment. Moreover, the complex biology of cancer recurrence and metastasis are not sufficiently recapitulated in mice. As a result, many novel drug candidates fail in human clinical trials despite evidence of drug efficacy in those preclinical models (Couzin-Frankel, 2013; DiMasi and Grabowski, 2007; DiMasi et al., 2013). Thus, researchers are seeking new approaches to augment preclinical knowledge before undertaking clinical trials for human patients.

Recently, there has been renewed interest in comparative oncology—the study of naturally developing cancers in animals as models for human disease—as one way to improve cancer drug development and reduce attrition of investigational agents. Tumors that spontaneously develop in pet dogs and other companion animals as a result of normal aging share many characteristics with human cancers, such as histological appearance, tumor genetics, biological behavior, molecular targets, and therapeutic response. They also exhibit acquired resistance, recurrence, and metastasis, similar to human cancers (Paoloni and Khanna, 2008; Paoloni et al., 2009b).

Cancer incidence has increased in pet populations in recent years due

to the pets' increased life expectancy, which itself is the result of better veterinary care. More than 1 million pet dogs are diagnosed with a wide variety of cancers in the United States each year, and pet owners are often highly motivated to seek out new treatment options for cancer in their pets. Although there is a range of therapeutic options available for pets with cancer, including surgery, radiation therapy, and chemotherapy, there are few established standards of care for the treatment of cancer in these pets. Clinical trials for pets with cancer provide potential alternatives for treatment with novel therapies in development.

The Comparative Oncology Trials Consortium (COTC)[1] was established to provide the infrastructure and resources needed to integrate clinical trials for pets with naturally occurring cancers into the development pathways for new drugs, devices, and imaging techniques for human cancers. Trials are conducted at 20 veterinary academic centers in the United States, with thorough owner education and informed consent, to investigate new diagnostic or treatment options for the benefit of both animal and human health (Gordon et al., 2009). There is a long history of studying cancer in dogs, and clinical trials for pet patients with cancer can serve as a useful intermediary between traditional preclinical studies and human clinical trials in the translational research pathway. Once a drug has been approved for use in humans, clinical trials for pet patients can also yield valuable insights into post-market challenges such as defining optimal dosage and treatment regimens (Paoloni and Khanna, 2008).

However, the cancer research community has not reached agreement concerning the value of these clinical trial data for advancing human cancer research or when and how best to integrate comparative oncology trials within the cancer research continuum. Thus, the Institute of Medicine's (IOM's) National Cancer Policy Forum, with support from a coalition of sponsors, hosted a workshop held in Washington, DC, on June 8–9, 2015, to examine the rationale and potential for integrating clinical trials for pet patients with naturally occurring cancers into translational cancer research and development. The workshop also highlighted potential opportunities to overcome existing challenges to that integration.

At the workshop, subject-matter experts and members of the public discussed topics that included

[1] See https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home (accessed August 13, 2015).

1. The limitations of current preclinical oncology models and resulting late-stage drug development failures and costs;
2. The opportunities to use data from trials for pet patients to select lead compounds, identify signals of toxicity and efficacy, and help develop dosing regimens for human clinical trials;
3. The way in which data from clinical trials for pet patients are viewed by the U.S. Food and Drug Administration (FDA) and drug sponsors;
4. Research needs, strategies, and resources to support greater integration of clinical trials for pets with cancer into translational research pathways; and
5. Challenges and potential solutions for facilitating that integration.

This report is a summary of the presentations and discussions at the workshop.[2] A broad range of views and ideas were presented, and a summary of the suggestions offered by individual participants is provided in Box 1. Additional details and context for these suggestions can be found throughout the workshop summary. The workshop Statement of Task and agenda can be found in Appendixes A and B, respectively. The speakers' presentations (in PDF and video formats) have been archived online.[3]

OVERVIEW OF THE RATIONALE FOR COMPARATIVE ONCOLOGY TRIALS

The workshop began with several presentations on the rationale for conducting comparative oncology clinical trials as a means of advancing both human and animal health and of advancing the drug development pipeline to produce new therapies for cancer. As background, Michael Kastan from the Duke Cancer Institute said that cancer is a common public health problem, with one out of every three women and one out of every two men developing cancer within their lifetimes. Approximately 1.4 mil-

[2] The workshop was organized by an independent planning committee whose role was limited to the identification of topics and speakers. The workshop summary has been prepared by the rapporteurs as a factual account of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the IOM. They should not be construed as reflecting any group consensus.

[3] See https://iom.nationalacademies.org/Activities/Disease/NCPF/2015-JUN-08.aspx (accessed November 6, 2015).

BOX 1
Suggestions Made by Individual Workshop Participants

Leverage the Advantages of Clinical Trials for Pet Patients in Translational Cancer Research

- Use data from clinical trials for pet patients to inform the design of subsequent clinical trials for human patients. (Timothy Fan, Daniel Gustafson, Anne Keane, Chand Khanna, Cheryl London)
- Use parallel data from human and pet patients to expand our understanding of cancer biology and gain more information than is possible from clinical trials in either species alone. (Mark Dewhirst, Lee Helman)
- Use clinical trials for pet patients to select the best compound and to prioritize the most promising combinations to advance in human clinical trials. (Anne Keane, Chand Khanna, Amy LeBlanc, David Vail)
- Learn from trials that enroll dogs with treatment-naïve disease because many human patients who enroll in trials have advanced, treatment-resistant disease. (Chand Khanna, Cheryl London)
- Develop trials for cancers that occur frequently in dogs in order to address high unmet needs for rare human cancers. (Daniel Tumas)
- Use genomic information from pet patients to identify cancer genes not yet identified in humans and to accelerate the development of targeted therapies to benefit both pet patients and humans. (Jessica Alföldi, Matthew Breen)
- Utilize imaging studies in pet patients to accelerate the development of imaging tracers and new drugs. (Peter Choyke, Amy LeBlanc)

Improve Clinical Trials for Pet Patients

- Use novel statistical design methods, such as Bayesian designs, for clinical trials in order to achieve meaningful results with fewer pet patients. (David Vail)
- Use genomics-guided drug matching to study the treatment potential of novel agents for the treatment of cancer in both humans and pet patients. (Jeff Trent)
- Combine functional imaging with genomics analyses. (Mark Dewhirst)

Promote Greater Integration of Clinical Trials for Pet Patients into the Drug Development Pipeline

- Increase the number of veterinarians specializing in oncology. (Amy LeBlanc, Cheryl London)
- Describe potential limitations and determine how to address these limitations in order to make trials for pet patients with cancer a useful tool in translational research. (Timothy Fan)

- Develop assays, reagents, and antibodies for particular genetic markers that are currently missing for clinical trials for pet patients. (Timothy Fan, Matthew Frank)
- Continue to molecularly validate canine cancer as a model for human cancer. (Amy LeBlanc)
- Perform a cost analysis to assess the return on investment for trials with pet patients, such as improved success in phase III human trials or dropping investigational agents at an earlier stage of development. (Carolyn Henry, Anne Keane)

Clarify Regulatory Oversight and Processes

- Develop Food and Drug Administration guidance specifically for clinical trials for pet patients. (Tanja Zabka)

Adopt Best Practices for the Ethical Conduct of Clinical Trials for Pet Patients

- Harmonize the consent process for pet patients with the informed consent process for human clinical trials where possible. (Rod Page)
- Carefully consider the needs of both the pet and pet owner and engage them as partners in the research enterprise. (Patricia Olson)
- Require review of a trial concept by a scientific committee in the approval process. (Rod Page)
- Develop a clinical trials registry for pet patients similar to the registry for human trials at www.ClinicalTrials.gov. (Rod Page)
- Adapt audit guidelines from the National Cancer Institute's National Clinical Trials Network for pet patients. (Rod Page)
- Adhere to the CONSORT guidelines for the reporting of clinical trial data. (David Vail)
- Establish a confidential process for reporting potential ethical or protocol breaches. (Rod Page)
- Establish a publication policy to increase the accountability of trials for pet patients and to provide open access to all primary data, including negative studies. (Rod Page)
- Use pet owner diaries and quality-of-life surveys as a way to monitor adverse events in clinical trials. (Christopher Loss)

Improve Communication Among Interested Stakeholders

- Build a communication plan to raise awareness in the pet owner community, improve networking capabilities, and promote existing opportunities. (Rod Page)
- Report results from clinical trials for pet patients in journals and at meetings focused on human medicine. (Anne Keane)
- Use commercial databases to communicate with the pet owner community. (Patricia Olson)

lion Americans will be diagnosed with cancer this year, with 600,000 dying from cancer. There are more than 14 million cancer survivors in the United States.[4]

Kastan emphasized that better oncology therapies with improved efficacy and less toxicity are needed. Cancer outcomes are improving for many types of cancer; however, the survival benefits from these improvements are often measured in months, and the short- and long-term toxicities from current cancer therapies are quite significant. The surgery, radiation therapy, and chemotherapy used to treat cancer today often leave cancer survivors with significant health problems, including cardiovascular disease, metabolic disorders, and the dysfunction of various organs (heart, liver, kidney, etc.).

Furthermore, the process for developing new cancer therapies is long and costly. Kastan said that it takes an average of 13 to 16 years and as much as $1.8 billion to bring a new therapeutic from target validation to the marketplace (Paul et al., 2010). Oncology drug attrition rates are also significantly higher than the attrition rates in other therapeutic areas, said Lee Helman from the National Cancer Institute (NCI) (Kola and Landis, 2004). About 59 percent of oncology drugs that enter phase III clinical trials fail, usually due to a lack of efficacy rather than to toxicity, he said. However, Carl Barrett of AstraZeneca added a note of optimism based on more recent trends; he said that five oncology agents were approved in the first 5 months of 2015, and there have been more than 30 different targeted therapies approved in the past 10 years.

"One Medicine" Concept

The "one medicine" concept is a core principle underpinning the inclusion of clinical trials for pet animals in the cancer research continuum, said Matthew Breen from North Carolina State University. The idea behind "one medicine" is that collaboration among multiple disciplines in animal and human health can contribute to producing the optimal health for both. The mouse is the traditional preclinical research model for cancer, but the induced or transplanted tumors studied in mice are not naturally occurring. Additionally, many preclinical cancer studies are conducted in immunoincompetent mice, while spontaneous canine tumors occur in animals with intact immune systems, making them more similar to human cancers. The

[4] See http://seer.cancer.gov/statfacts/html/all.html (accessed August 18, 2015).

types of cancers that affect people also naturally occur in pets, so knowledge gained from clinical trials for pet patients with spontaneous tumors can complement the traditional approach to preclinical cancer research prior to conducting trials for human patients. In particular, Breen said, certain dog breeds are highly affected by certain naturally occurring cancers, and this suggests that dog breeds have an inherited predisposition to those cancers. The fact that canine cancers show some breed predispositions provides a powerful research opportunity to identify the genetic factors that underlie these predispositions in dogs and simultaneously to contribute to advancing cancer research in humans. Additionally, these naturally occurring cancers develop in the same environment as those in humans.

Limitations of Traditional Drug Development Preclinical Research Models

Only 11 percent of oncology agents that demonstrate efficacy in mouse models are ever approved for humans use, said Beverly Teicher from NCI. One problem with the models, she explained, is that they lack key characteristics of human cancer, such as long latency, natural causation, genomic instability, tumor heterogeneity, and tumor microenvironment characteristics. The advantages and limitations of these murine models are summarized in Table 1.

Teicher said that differences between mice and humans have led to inaccurate predictions of drug activity in human cancer. In mice, she said, every study is done at the maximum tolerated dose (MTD) of a drug, which is generally defined as the dose resulting in a 20 percent loss of body weight. Another disadvantage of the mouse model is that human bone marrow is more sensitive to chemotherapy than mouse bone marrow, so mice can often withstand much higher doses of anticancer agents. An audience participant asked about the comparability of toxicity data between mice and dogs. Myrtle Davis from NCI explained that the decision to conduct studies in dogs or another non-rodent species would be agent-dependent. For example, she said, for targeted therapies it might not be possible to assess the appropriate endpoints. She added that mice are rarely used to generate safety data.

Teicher also discussed the importance of the tumor microenvironment in tumor progression. The tumor microenvironment plays a role in the initiation of carcinogenesis, malignant progression, and treatment response or resistance, but the mouse tumor microenvironment does not always

TABLE 1 Mouse Models in Cancer Research

Mouse Model	Description	Advantages	Disadvantages
Transplantable syngeneic tumor model	Injection of cells or explants from the same species	• Low cost • Reproducible • Immunocompetent host • Limited variety • Non-immunogenic • Long history/strong baseline data • Hosts readily available • Statistically valid numbers	• Rodent tumor cells • Old tumor cells lines • Subcutaneous implantation • Rodent target • Rodent host • Rodent immune system • Very quick growth
Human tumor xenograft	Injection of human cell lines, usually subcutaneous	• Human tumor cells • Reproducible • Wide variety • Long history/strong baseline data • Hosts readily available • Tumor growth easily followed • Statistically valid numbers	• More costly • Rodent stroma • Immunodeficient host • Non-natural tumor site (subcutaneous) • Old tumor cell lines • Limited genetic diversity
Disseminated disease models	Implanted human tumor xenografts	• Similar to clinical disease • Tumor growth in tissue of origin of primary tumor type • Good variety • Hosts readily available • Immunocompetent host	• Complex surgery • Costly • Rodent stroma • Old tumor cell lines • Immunodeficient host • Nonreproducibility of tumor growth rate • Statistics difficult due to low numbers

TABLE 1 Continued

Mouse Model	Description	Advantages	Disadvantages
"Labeled" tumor models	Implanted tumor that carries a foreign fluorescence protein	• Tumor response can be visualized with fluorescence or luminescence • Visualization of metastasis • Tumor measurement • Limited variety • Hosts readily available	• Genetically altered cell lines • Many clonal lines • Poor representation of disease • Rodent stroma • Immunodeficient host • Costly equipment • Statistics difficult due to low numbers
Patient-derived xenograft (PDX) models	Direct implantation of a tumor fragment from human patients	• Tumor cells recently from patient • Genetically similar to patient • Tumor measurement • Hosts readily available	• Large tumor specimen required • Slow growth • Immunodeficient host • Mouse stroma • Very costly • Statistics difficult due to low numbers • Not a validated predictor
Genetically engineered mouse models	Expression of target or label, spontaneous carcinogenesis	• Tumor arises in desired tissue • Well-defined lesion, defined mutations • Immunocompetent host • Tumor can be followed over a long time course	• Limited availability of hosts • Limited mutations not reflective of human disease • Rodent tumors • Rodent stroma • Slow tumor development • Very costly • Variable tumor stage • Tumor difficult to follow • Endpoint is usually survival • Statistics difficult due to low numbers

SOURCE: Teicher presentation, June 8, 2015.

correspond well with the microenvironment of a spontaneously developing human cancer. For example, the mouse subcutaneous space in which transplanted tumor tissue grows is different in a number of ways from the microenvironment in which spontaneous human tumors develop. Also, surgery is required to implant the tumor tissue in mice, which is followed by wound healing and a resulting cytokine cascade that can boost tumor growth. The immune signaling pathways also differ between the mouse and human, and in some instances interferons, interleukins, and growth factors are non-functional in the mouse. These differences between the mouse and human immune system motivated the development of mice with a humanized immune system, Teicher said (Brehm et al., 2010; Liu et al., 2014; Mestas and Hughes, 2004).

Furthermore, Teicher said, the pharmacokinetic and metabolic handling of drugs can vary significantly between mouse models of cancer and human patients. For example, one study showed that tumors in the brains and livers of mice were more resistant to the classic anticancer agent cyclophosphamide than transplanted subcutaneous tumors, and tumor cells in the circulating blood and the spleen completely disappeared in response to cyclophosphamide (Holden et al., 1997). She said that the subcutaneously transplanted tumors were probably more responsive than a naturally occurring tumor would be, and thus studies using that model may generate an overly optimistic prediction of the human response to a potential therapeutic. Tumor scale is also mismatched between humans and mice, as even a small tumor is unrealistically large with regard to mouse body mass. This is less of an issue in larger pet patients.

Similarities Between Human Cancers and Naturally Occurring Cancers in Pet Patients

Cancer is common in pets, Kastan said. There are more than 170 million pets in the United States (80 million dogs and 90 million cats), and approximately 47 percent of U.S. households own at least one dog. Each year more than 1 million dogs are treated for cancer in the United States, he said, and cancer kills 50 percent of all dogs over the age of 10. Many canine tumors have tissue origins similar to human cancers, including sarcomas, melanoma, lymphoma, and glioma. Canine tumors also share similarities with human cancers in histologic appearance, tumor genetics, biologic behavior, molecular targets, therapeutic response, heterogeneity, acquired resistance, recurrence, and metastasis, Kastan said.

Helman noted the advantages of studying tumors that develop spontaneously in older pet animals. Canine patients are relatively outbred compared with traditional laboratory animals such as the mouse, and their larger size along with the strong anatomical and physiological similarities between pets and humans makes treatment regimens more comparable. Furthermore, unlike many mouse models of cancer, pet animals have a competent immune system. Also, compared with trials for human patients, clinical trials for pet patients can often be completed in less time because spontaneous tumors in pet animals generally progress more quickly than in humans, which makes it possible to assess clinical outcomes and generate knowledge more quickly.

Helman noted that humans and dogs have lived and evolved together for thousands of years. Because they have evolved in the same environments, they tended to evolve similar traits—a process commonly referred to as "convergent evolution." This is worth noting because cancer develops from a combination of environmental exposures and genetic susceptibilities. In humans, there are familial cancer susceptibility syndromes. The canine equivalent is dog breed cancer susceptibilities, and learning about these susceptibilities should provide insight into how environmental exposures contribute to cancer development in humans, Helman said.

Helman concluded that comparative oncology studies in animals with naturally occurring cancers provide important opportunities to expand our understanding of cancer biology and to develop new therapies. He added that the integration of comparative oncology trials into the drug development process should be iterative, with clinical trials for pet patients informing human clinical trials and vice versa.

The Integrated Comparative Clinical Trial Approach

Clinical trials for pet patients with naturally occurring tumors are underutilized in the drug development process, Helman said. In the conventional cancer drug development pathway, phase I human clinical trials are used to assess toxicity and dose, phase II trials begin to assess anti-tumor response, and phase III trials are used to assess patient outcomes with the new agent versus the usual standard of care. Cancer drugs that demonstrate improved patient outcomes (such as better survival rates) in phase III trials successfully emerge from this pathway. However, considering how high the attrition rate is for new agents, Helman said, some adjustments to the traditional drug development process are needed. Much of the attrition is due to

the fact that cancer is a very complex disease and preclinical models fail to predict how a drug will perform in humans. Contributing to the problem, Helman said, is the fact that the traditional drug development pathway is largely a linear process with few iterative components. He advocated for an integrated approach to cancer drug development in which clinical trials for pet patients are conducted in parallel with human clinical trials to gain additional insight into drug activity, toxicity, regimen and schedule, biomarkers, and possible combination therapies (Paoloni et al., 2008) (see Figure 1).

Chand Khanna from NCI further discussed the added value of an integrated drug development pathway. He said that using the integrative approach makes it possible to identify early on those drugs that are less likely to succeed in early human trials (Gordon et al., 2009). Comparative studies that are undertaken concurrently or immediately before or after human phase I trials can help clarify pharmacokinetic (PK) and pharmacodynamic (PD) endpoints as well as dose, regimen, and schedule. This integrative approach can also decrease the cost and risk of drug development by reducing the number of agents entering each phase of drug development

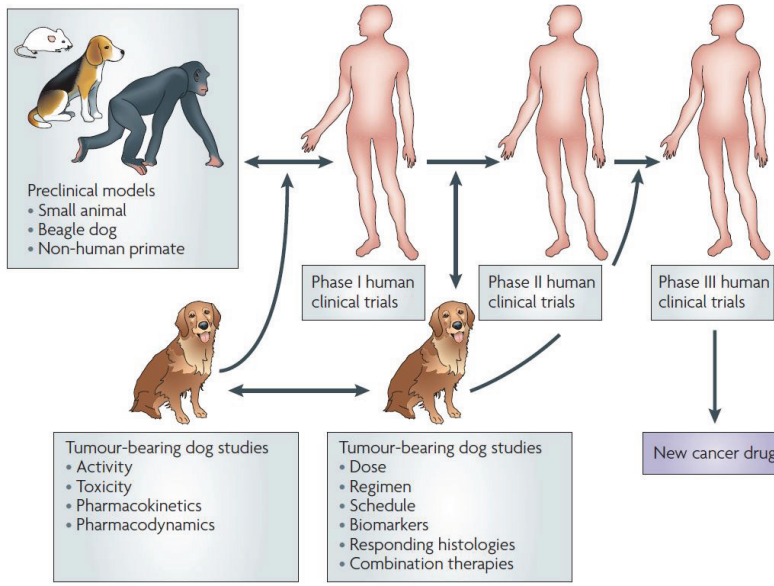

FIGURE 1 A comparative and integrated approach to cancer drug development.
SOURCES: Helman and Khanna presentations, June 8, 2015; Paoloni and Khanna, 2008. Reprinted with permission from Macmillan Publishers, Ltd.: Nature Reviews Cancer.

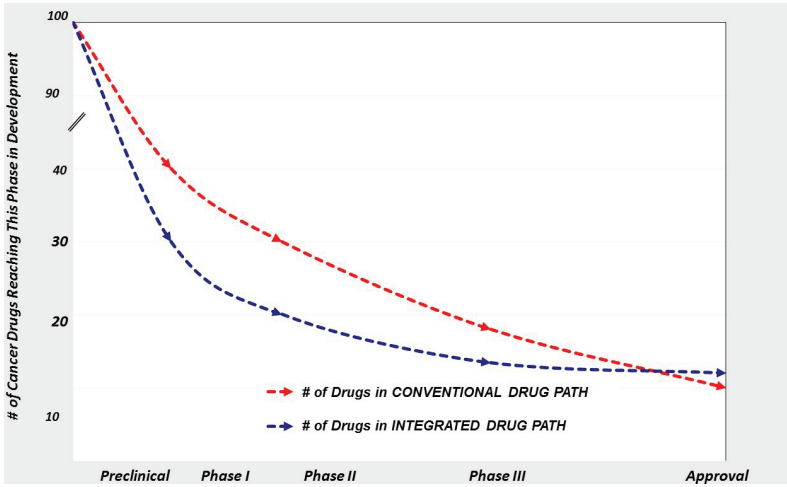

FIGURE 2 Projected value of an integrated drug development path.
SOURCES: Khanna presentation, June 8, 2015; Gordon et al., 2009.

and increasing the success of phase III clinical trials (see Figure 2). Khanna said that the largest opportunities for integrative approaches are between phase I and II human clinical trials and in contributing to better designs for phase II trials.

Examples of Clinical Trials for Pets with Naturally Occurring Cancers

Comparative oncology clinical trials have helped to inform human trials since the 1960s, Khanna said, and he cited the development of a regimen for bone marrow transplants for treating lymphoma as a classic example. NCI established the Comparative Oncology Trials Consortium (COTC) in 2003 to facilitate such trials, he said, and the COTC has infrastructure and resources in place that can integrate clinical trials for pet patients with naturally occurring cancer into the development of new drugs, devices, and imaging techniques for human cancers. The COTC also has a pharmacodynamics core that provides efficient access to laboratory and investigative platforms for studying the biology of cancer and drug–cancer relationships in pet patients. Khanna said that the COTC provides opportunities and resources within NCI and the broader research community to develop approaches for determining why drugs succeed or fail in human

clinical trials. This approach has been successful, he said, and several studies have been completed and published in peer-reviewed journals.

NCI sponsored a meeting in 2008 to provide clarity on how to conduct comparative oncology trials and to report the resulting data (Khanna et al., 2009). Khanna described the process of the COTC study development as follows. Clinical trials for pet patients are developed to address questions not fully answered through conventional preclinical models or human clinical trials. The study development process takes advantage of the fact that pet patients can be treated with various doses of a drug with concurrent measurement of PK along with the collection of tumor and normal tissue before and after exposure to the drug. These kinds of trials can also determine the validity or the applicability of various imaging approaches or biomarker tests. Questions that can be answered using this approach include those regarding safety, the relevant therapeutic dose, and the effects on biological targets or biological surrogate endpoints.

Khanna briefly described some examples of trials conducted through the COTC, including trials evaluating the targeted delivery of tumor necrosis factor (TNF)-alpha and the effects of a combination therapy of IL-2 and IL-12 immunoctyokines, trials modeling precision medicine, and preclinical comparisons that were used to select the lead compound for human clinical trials (an approach he referred to as "pick the winner" strategy). In the case of the TNF-alpha study, biopsies of both normal and tumor tissues were performed prior to and following dosing with a drug. With this approach, the researchers were able to confirm that the drug only targeted tumor tissue and not normal tissue, as was intended. Khanna said that this approach using serial biopsies would not have been feasible in a human clinical trial and cannot be done in laboratory animals because they do not have spontaneously developing tumors.

As an example of how the development of precision medicine can be facilitated with clinical trials for canine patients, Khanna described a study in which the researchers used genetic and molecular profiling to match dog breeds and tumor types with the optimal targeted therapeutics. He stressed again that this would be impossible to do in mouse models because of the lack of naturally occurring tumors.

Khanna also described an example of the "pick the winner" strategy for lead compound selection, in which three novel topoisomerase inhibitors were tested in canine patients with lymphoma. Clinical trials for pet patients can be helpful in distinguishing among multiple compounds in development in order to identify the optimal lead compound for human testing by assess-

ing efficacy, biomarkers, and PK, he said. Again, this would be difficult to do using conventional preclinical mouse models or in human clinical trials.

Khanna said that planned projects include a collaboration with the Morris Animal Foundation and others to study osteosarcoma in canine patients and to develop agents that target metastatic progression (Khanna et al., 2014). If these agents show efficacy in the study, they will then be tested in human clinical trials. If approved by FDA for human use, they could also become available in a variety of ways for veterinary use, resulting in benefits for both human and animal patients.

Risks and Challenges of Clinical Trials for Pet Patients

Khanna also described some of the key perceived risks and concerns related to clinical trials for pet patients. These clinical trials are longer in duration than most studies in traditional preclinical models, but the strategic inclusion of comparative oncology trials that are mindful of the specific goals of the drug development process will allow the timely integration of data to inform or complement human trials. Pets, like humans, are also more genetically diverse than laboratory research animals.

Another concern with comparative oncology trials is that the incidence of various types of cancer can differ between pet animals and humans, Khanna said. For example, sarcomas and lymphoid neoplasms occur more frequently in dogs than in humans, while breast, prostate, gastrointestinal, and lung carcinomas occur less frequently. As a result, it can take a long time to enroll sufficient numbers of canine patients into trials for breast cancer and other cancers that have a low incidence in dogs. On the other hand, it may be faster and easier to enroll pet patients in trials for sarcomas and lymphoid neoplasms than it is to conduct trials for human patients with those cancers.

Yet another issue, Khanna said, is that the target biology in pets may be different from humans and must be defined in advance of clinical trials. There are several resources available to aid in defining the cancer biology in pets, he said, including the Canine Comparative Oncology and Genomics Consortium (CCOGC).

Khanna also noted concerns regarding drug availability and budgeting requirements. Canine patients require larger doses of drugs than mice, which means that a larger supply of the drug is needed. The drugs used in clinical trials for pet patients do not have to meet good manufacturing practice standards, but the agents used in human clinical trials must meet these

standards, and this could influence decisions by regulatory bodies, he said. Regulatory authorities might require that the agents used in clinical trials for pet patients be as similar as possible to the agents administered to humans. A mechanism for reporting adverse events (including details concerning the severity, duration, and attribution) is also needed in these trials, he added.

Khanna also mentioned that biotechnology companies have concerns regarding FDA regulatory oversight and reporting. FDA has not issued formal guidance on clinical trials for pet patients, although there is non-FDA-issued guidance available in the literature (Khanna et al., 2009). Tanja Zabka, a veterinary pathologist at Genentech, suggested that having a third party interact with regulatory bodies might help in formulating an unbiased approach for integrating clinical trials for pet patients into the development pipeline. She said that from a pharmaceutical development perspective, there is "a lot of hesitancy in [enrolling] dogs in clinical trials because they are afraid to generate safety signals or new safety signals in patients." However, Douglas Thamm from Colorado State University said that pharmaceutical companies often conduct studies in normal dogs to generate safety data during the preclinical development phase. He said that there should be a process in place to ensure that these safety screens are done prior to drug administration to pet patients, but this is not currently a universal requirement.

Matthew Frank from the Stanford School of Medicine added that there are also various technical gaps to address, such as a lack of assays, reagents, and antibodies for particular genetic markers for comparative oncology trials.

CANINE TUMOR BIOLOGY

Canine Cancer Genomics

Heidi Parker from the National Human Genome Research Institute discussed the utility of studying different dog breeds to map traits that have proven difficult to examine through human studies. Many cancers show a strong breed predisposition; for example, bladder cancer is more common in Scottish Terriers. As a specific example of the value of genetic mapping, Parker described the case of canine transitional cell carcinoma (TCC) of the bladder. TCC of the bladder accounts for 2 percent of all canine tumors and can affect up to 20,000 pets each year; this rate is similar to that seen in humans. Scottish Terriers are 19 more times more likely to develop TCC than the average dog breed.

Parker described the process of identifying mutations that may contribute to the development of TCC. The complete transcriptome for multiple tumors was analyzed using a method of RNA sequencing known as RNA-seq. The goals were to identify RNA transcripts that might be present in these tumors but were not present in normal canine cells, to find genes that were expressed only in the tumors, and to identify somatic mutations in canine TCC. The data showed that there is a mutation in the canine BRAF gene that is identical to the BRAFV600E mutation in humans, which is common in melanoma. Functional experiments suggested that, as with human tumors, this BRAF mutation activates the MAP Kinase signaling pathway. This knowledge might enable the use of canine TCC as a powerful system to evaluate BRAF-targeted therapies or combination therapies, which could enhance the treatment of both human and canine cancers. The research team was also able to use next-generation sequencing to identify the mutation in 1 out of 1,000 alleles analyzed, Parker said, and this could be used to create a sensitive urine-based assay for cancer detection and diagnosis.

Parker also said that a transmissible form of cancer, canine transmissible venereal tumor (CTVT), has provided insights regarding how tumors escape immune detection. CTVT is a clonally transmissible cancer that is passed from one dog to the next. It is the world's oldest known continuously propagating cell lineage. CTVT affects dogs worldwide, but information from the genome of this tumor suggests that it originated from a single dog, Parker said.

Parker described the creation of a catalog of canine genomic variation that includes data from 186 diverse dog breeds and encompasses the vast majority of genetic variation in the modern dog. The researchers concluded that shared CTVT variants found in the catalog are likely inherited alleles from the founder animal and that CTVT variants not found in the catalog are likely due to subsequent somatic mutations. The results showed overlapping mutations at every step of somatic cell immunosurveillance, Parker said. The identification of these mutations points to genes that may have contributed to the ability of CTVT to avoid destruction by the immune system, thereby establishing clonal transmissibility. Understanding CTVT biology may shed light on host–tumor interactions in human cancer, she said, and sequencing is currently under way for a new CTVT-specific genome assembly.

Genomic Resources for Comparative Oncology Clinical Trials

Breen described the importance of tissue biobanks for cancer research. Canine genetic information derived from biological specimens with well-annotated patient data can play a key role in understanding a complex disease like cancer, he said. Genetic data provides crucial information for improving cancer detection, diagnosis, prognosis, intervention, treatment, and prevention. Furthermore, he emphasized, sharing these resources and information is necessary to promote canine cancer research.

Breen briefly detailed the key requirements of an effective biobank, including the need to have standard operating procedures. The procedures for specimen selection, handling, and storage have to be fit for purpose, with high-quality preparation and storage and efficient mechanisms for retrieval. It is also important that specimens and patient data be accessible for research over time, he said, and it is necessary to have a data-sharing plan for specimen use so that researchers can select the most relevant samples for their research purposes.

Breen briefly mentioned the Golden Retriever Lifetime Study,[5] which is currently in progress with support from the Morris Animal Foundation. One strength of this study, he said, is the breed specificity; the study will focus on one breed that is very popular in the United States, with plans to enroll 3,000 pets. Samples will be collected annually from pets enrolled in this study, starting at age 2 and extending through their lifetimes. A variety of different biological specimens will be collected as well as comprehensive patient information, including the dog's place of residence, diet, and environmental factors.

Canine Comparative Oncology and Genomics Consortium

Breen briefly described the CCOGC,[6] which was incorporated as a nonprofit organization in 2007 to facilitate strategic partnerships and collaborations across a variety of disciplines, with a focus on cancer in dogs. An initial priority for the consortium was the development of a biospecimen repository.

There were originally eight COCGC biobank sites, Breen said, six of which are currently active. They now contain more than 60,000 samples

[5] See https://caninelifetimehealth.org (accessed August 17, 2015).
[6] See http://ccogc.net (accessed August 17, 2015).

from approximately 2,000 pet patients; multiple samples are obtained from each patient, including tumor and normal tissue, frozen serum, plasma, whole blood, and urine. The types of cancer found in the sample collection include osteosarcoma, lymphoma, melanoma, pulmonary tumors, mast cell tumors, soft tissue sarcomas, and hemangiosarcoma. An important step in setting up the CCOGC was the development of standard operating procedures for the biospecimen repository. These procedures are intended to ensure that the samples are collected in a carefully controlled manner, and a quality control and quality assurance study of 331 specimens in the CCOGC found that the tumor DNA and RNA quality was indeed very good and that there was a high correlation between the cancer diagnosis on the sample label and the actual cancer found in the sample. The CCOGC has also cataloged specimens according to their level of heterogeneity and nucleic acid quality.

Breen also described how well-defined specimens from patients with cancer can accelerate cancer research to benefit both pet patients and humans. For example, he said, studies have shown that the gene expression profiles for canine and human osteosarcoma are indistinguishable, suggesting that findings from clinical trials for dogs with that type of cancer would be informative for human patients with osteosarcoma. He also described a study in which investigators used molecular cytogenics to identify inherited and somatic changes. Dogs have more chromosomes than humans, Breen said, but the total amount of DNA is similar—it is just packaged differently. The researchers studied the genomic reorganization that often occurs during the development of cancer to identify the genomic changes associated with cancer in both humans and dogs. One of the key questions they asked was whether there are evolutionarily related chromosome aberrations. The most common example of this is the Philadelphia chromosome, which is an aberrant translocation between human chromosomes 9 and 22 that results in the genes BCR and ABL becoming co-localized on a derivative chromosome known as the Philadelphia chromosome. The resulting BCR-ABL protein is a tyrosine kinase, and it is a particular characteristic feature of chronic myeloid leukemia (CML). The BCR-ABL inhibitor imatinib mesylate (Gleevec) was developed using this information. Breen said that although CML is rare in dogs, they found a similar chromosomal aberration that led to the BCR-ABL fusion gene, and those dog patients are now being treated with a tyrosine kinase inhibitor. This example leads to the question of whether genomic information from pet patients can be used to identify cancer genes that have not yet been identified in humans

and allow the development of targeted therapies to benefit both animals and humans, Breen said.

The contrasting architecture of the canine and human genomes offers tremendous potential for identifying and refining regions of significance, Breen said. For example, human meningiomas are known to have cytogenetic alterations on human chromosome 22, but there were a large number of candidate genes for meningiomas in dogs. By evaluating canine meningioma data, it was possible to reduce the canine candidate region of interest by approximately 25-fold (Thomas et al., 2009). Another example of the potential of canine genomic data to inform cancer in both pets and humans comes from a study of canine TCC bladder cancer (Shapiro et al., 2015). TCC is difficult to diagnose in pets and requires a biopsy to confirm. When whole-genome profiling was performed on a cohort of dogs with bladder cancers, the data showed that three particular chromosomal aberrations were increased, Breen said. Based on these three chromosomal aberrations, a cytogenetic assay with high sensitivity and specificity was developed for identifying the presence of TCC in symptomatic canine patients. Breen added that the assay is also being used to screen for the early presence of TCC in pets that are not symptomatic. The information from the canine analysis was subsequently used to identify candidate genes in humans as well, Breen said. The frequency of gene copy number aberrations across both species was identified with an informatics approach. Then cross-species filtering of genome-wide copy number data pointed to several genes as high-profile candidates for further analysis. Using this comparative approach, new information on the genomics of cancer can be identified and applied to the health of both species, Breen said.

CanFam 3.1 Canine Genome Assembly

Jessica Alföldi from the Broad Institute of Harvard University and the Massachusetts Institute of Technology discussed CanFam 3.1, the most recent version of the canine genome assembly. Released in 2011 after 6 years of work, CanFam 3.1 included 85 Mb of new sequence data to increase coverage of the dog genome from 99.2 to 99.6 percent. This version also closed 1,044 sequence gaps in the promoters/first exon regions of the chromosomes. This is the third most detailed mammalian gene ever assembled, behind only the mouse and human genomes, Alföldi said. She also described efforts to assemble high-quality genotyping data across a wide variety of dog breeds and wolves. There is currently no project under way to make further improvements to the gene assembly, Alföldi said, adding

that recent grant applications to create additional canine genome resources were not funded because a higher priority was given to the mouse, human, and non-human primate genomes.

RNA-seq data offer another resource for genomic studies in dogs, Alföldi said. In one study, researchers used tissue samples from 10 adult beagles to created three sets of RNA libraries: a library of messenger RNA, one that was a mix of messenger RNA and other transcripts, and a library of microRNA. The Ensembl[7] organization used the first two libraries for gene prediction and confirmation, and this information can now be used to find gene equivalents across species. The data are hosted by the Broad Institute and have been integrated into the University of California, Santa Cruz, Genome Browser.

Using the genome data, Alföldi said, researchers explored factors that might predispose certain dog breeds (greyhounds, Irish wolfhounds, and Rottweilers) to get osteosarcoma. The data showed that there were 33 different loci associated with a predisposition to osteosarcoma in one or another of these breeds. There was no overlap among the breeds in the loci identified because of the homogeneity of the dog populations, but the genes were all part of cell signaling pathways for osteoblast differentiation and proliferation, skeletal growth, and mesenchymal–epithelial cell transitions. These results demonstrated that is necessary to separate breeds when performing an analysis, she commented. One can identify risk factors with as few as about 100 cases and controls, she said.

Precision Medicine in Clinical Trials for Pet Patients

Jeff Trent from the Translational Genomics Research Institute (TGEN) spoke about the use of precision medicine in cancer clinical trials. TGEN has focused on the integrative genomic profiling of tumors, he said. In this type of profiling, deep exome sequencing[8] is used to identify low-frequency mutations in heterogeneous tumor samples, and RNA sequencing is used to confirm mutations, identify oncogenic fusions, and examine gene differential expression. TGEN uses a Dell Clinical Cluster[9] to integrate and mine both DNA and RNA data. He said it currently takes about 1 day to do

[7] See http://www.ensembl.org (accessed August 18, 2015).

[8] Deep sequencing refers to sequencing where the total number of reads is many times larger than the length of the sequence under study.

[9] The Dell Clinical Cluster is a high-power computing infrastructure able to perform 31 trillion calculations per second.

this, after which the analysis is combined with clinical information as well. Over several years, he said TGEN developed clinical collaborative applications for assessing and distributing data across a federated network that is hosted in a secure cloud-enabled Web-accessible framework. The network complies with the regulations for protecting the privacy of personal health information under the Health Insurance Portability and Accountability Act (HIPAA). This allows multiple physicians from different institutions to view the data in a HIPAA-compliant manner, he said.

As an example of this approach Trent described a large-scale human trial, the Genomic-Enabled Medicine for Melanoma (GEMM) trial, which is being conducted through the Melanoma Research Alliance, comprised of 18 participating sites. It took more than 3 years to get formal FDA approval to run the trial, he said. It is a randomized phase II trial that will study the efficacy of molecularly targeted therapy in patients with metastatic melanoma. There are currently eight drugs from six different pharmaceutical companies being used in the trial. This trial stresses the importance of collaboration in precision medicine, he added.

Recent work suggests that sporadic, naturally occurring melanomas in dogs have significant overlapping clinical and histopathological features with human melanomas, Trent said (Simpson et al., 2014). This presents an opportunity to explore canine melanoma for preclinical research.

TGEN has also developed a novel trial design for adjuvant therapy with correlative genomic analysis, which will include circulating DNA measurements and other features related to the predictive modeling of genomics-guided drug matching. The goal of this study is to determine whether early treatment of naïve cancers results in a different response compared with treatment of metastatic, late-stage tumors. Trent concluded by saying that genomics-guided drug matching is the best way to study the treatment potential of novel agents for the treatment of cancer in both humans and pet patients.

Breen also briefly discussed a collaboration with the COTC that was a proof-of-concept trial to determine the feasibility of collecting a tumor sample from canine patients and generating a prospective molecular profiling report within 1 week (Khanna et al., 2014). He said that the results of this trial showed that it is possible to conduct a molecularly guided analysis of tumors from pet patients with naturally occurring cancer in a clinically relevant setting.

OPPORTUNITIES FOR INTEGRATING BIOMARKERS INTO STUDY DESIGNS

Pharmacokinetics in Clinical Trials for Pet Patients

Timothy Fan from the University of Illinois at Urbana-Champaign discussed opportunities for testing novel therapies in trials for pet patients, emphasizing that data from those trials can provide evidence regarding drug toxicity and efficacy and can help in the development of dosing regimens for human clinical trials (see Table 2). He said that each of the various "hallmarks of cancer"[10] can serve as a potential drug target (Hanahan and Weinberg, 2000, 2011). As an example, he described a line of research focused on the evasion of apoptosis. Fan said cytotoxin therapy has long been the primary focus of cancer research, and in general, cytotoxins induce apoptotic cell death in rapidly dividing cells. However, if cytotoxins are to be effective, there must be a functional apoptotic cascade, and cancer cells are known to evade apoptosis because of defects in that cascade. Thus, increasing the dose of these cytotoxins is unlikely to yield significant improvements in treatment.

Fan reported that a library of molecules with pro-apoptotic activity was screened and a molecule labeled PAC-1 was identified as the most promising (West et al., 2012). PAC-1 was shown to activate a protein called procaspase-3 (a key regulatory protein in the apoptotic cascade [Roy et al., 2001]) and to induce apoptotic death of cancer cells in culture. Fan explained that cells with higher procaspase-3 concentrations are more sensitive to PAC-1 and that malignant cells preferentially overexpress procaspase-3 relative to normal cells, which presents an opportunity to target cancer cells with PAC-1. After it was shown that PAC-1 reduced the tumor burden in three different mouse models of cancer (Putt et al., 2006), researchers designed clinical trials for canine patients to investigate drug PK and toxicology and to assess therapeutic combinations. The first trial involved the administration of a PAC-1 derivative called sulphonamide PAC-1, or SPAC-1, which required cumbersome 24-hour intravenous infusions, Fan said. The results indicated that the single agent had only marginal anti-cancer activity and had substantial toxicity. Thus, Fan said, a decision

[10] The hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, and evading immune destruction.

TABLE 2 Examples of Clinical Trials for Pet Patients That Informed the Design of Trials for Human Patients

Agent	Current Stage of Drug Development	Findings from Clinical Trials for Canine Patients	How Data from Canine Trials Informed Trial Design for Human Patients
PAC-1 (procaspase-3 activator)	Phase I human trials ongoing	Patients tolerate therapy in combination with temozolomide	Assessed single-agent activity and toxicity for development of tolerable dosing regimen
GS-9291 (anti-proliferative nucleotide analog prodrug)	Phase I human trial completed; registration trial ongoing for veterinary use	Measured PK, toxicity, and demonstrated antitumor activity	Proof of concept; Refined dose schedule to minimize toxicity
Toceranib/sunitinib (KIT kinase inhibitor)	FDA-approved for veterinary use and human use	Confirmed target inhibition and tumor response	Proof of target; defined PK
Hydroxychloroquine (inhibitor of autophagy)	Phase I human trial completed	Demonstration of target inhibition; No correlation between accumulation in tumor tissues and plasma	Proof of target; refined measure of drug exposure
Ibrutinib (Bruton tyrosine kinase inhibitor)	FDA approved for human use	Demonstrated efficacy and surrogate endpoint	Validation of biomarker test for use in human trials; dose modulation
Ganetespib (HSP90 inhibitor)	Phase III human trials	Determined toxicity, biomarkers, and biologic activity	Proof-of-target for IND application; defined PK/PD relationship
KPT-335 (XPO1 inhibitor)	Phase I human trials ongoing	Identified adverse events, dose, and regimen	Determined dosing regimen and supportive care protocols

NOTE: FDA = U.S. Food and Drug Administration; IND = investigational new drug; PD = pharmacodynamics; PK = pharmacokinetics.
SOURCES: Fan, Gustafson, London, Thamm, and Tumas presentations, June 8–9, 2015; Barnard et al., 2014; Honigberg et al., 2010; London et al., 2003, 2011, 2014; Pryer et al., 2003; Rangwala et al., 2014; Reiser et al., 2008; Vail et al., 2009.

was made to not move forward with development of that particular compound as a single-agent treatment.

Fan said that the next step was to investigate whether PAC-1 could act synergistically with conventional cancer treatments (conventional chemotherapy agents, ionizing radiation therapy, and small molecule drugs) to boost apoptosis. In a preliminary study, canine patients with metastatic osteosarcoma were given oral PAC-1 in combination with temozolomide or doxorubicin. The treatment was well tolerated, so the researchers moved forward with a pulsatile oral delivery of the PAC-1 and temozolomide combination.

Fan added that PAC-1 readily penetrates the blood–brain barrier and thus has potential for treating cancer in the central nervous system. In a mouse model of glioma, survival times were increased with a combination of PAC-1 and temozolomide. Based on these promising early results, Fan said, two feasibility studies are planned for dogs with glioma, one using oral temozolomide plus oral PAC-1 and the other using radiotherapy plus oral PAC-1.

Fan concluded by summarizing the ways in which clinical trials for pet patients can be useful in drug development. In the examples he described, these trials were critical for assessing toxicity and single-agent activity and were necessary for the development of tolerable dosing regimens that could be used to inform the design of trials for human patients. The trials also provided preliminary evidence to support the use of combination therapies in human trials. Fan said that this work has contributed to the development of two phase I human clinical trials of PAC-1, one of them with a dose-escalation design for late-stage cancer patients, and a second trial in glioblastoma patients being treated once daily with PAC-1 plus temozolomide for 21 days.

Daniel Gustafson from Colorado State University described the process for carrying out PK studies in canine patients. Drug dispensing is done in a manner consistent with human medicine, he said, and time-course sampling can be done in individual pet patients. He added that sample collection is done by trained professional staff (just as in human trials), with clearly defined standard operating procedures for sample processing.

Gustafson described a study that assessed variability in PK with doxorubicin dosing in both human and canine patients. Patients were dosed with the MTD, and the PK variability observed in dogs was very similar to the variability observed in humans; thus, Gustafson said, such trials for canine patients provide a useful mechanism to explore dose scheduling and to inform human clinical trials. The utility of this model is currently being

explored in a study of dasatinib for canine patients with cancer to assess efficacy and toxicity at the target dose, he said.

Gustafson also described other early phase clinical trials to assess PK and PD in canine patients. For example, a phase I/II trial was undertaken to test a prodrug, GS-9291, in dogs with naturally occurring non-Hodgkin's lymphoma (NHL) in order to measure PK, toxicity, and antitumor activity (Vail et al., 2009). The results of the trial made it possible to define the exposure parameters in plasma and peripheral blood mononuclear cells (PBMCs) for the drug and active metabolites. Based on the results, the dose schedule was refined to minimize toxicity, Gustafson said.

Clinical trials for pet patients also allow the exploration of drug delivery and the assessment of toxicity in a manner that is similar to the process in human trials; it is not possible to do this in mouse models (e.g., comparing infusion versus bolus delivery), Gustafson said. It is also possible to assess such side effects as lethargy or weakness in pet patients that cannot be observed in mice. Clinical trials for pet patients also allow a graded and standardized toxicity assessment. As an example, Gustafson mentioned sunitinib for human patients and toceranib for pet patients, which are very similar molecules. The drugs produced some toxicities that were similar in the two species, such as weakness, vomiting, and neutropenia, and some toxicities that affected one species and not the other, such as diarrhea, hypertension, and skin toxicity (Faivre et al., 2006; London et al., 2003). Gastrointestinal toxicity is a common side effect in canine patients, he said. Canines have 30 percent more blood flow to the gastrointestinal tract, which increases exposure.

Gustafson then described an example of tissue sampling in canine patients that was used to assess PK/PD correlations. Drug levels were assessed in plasma and tumor tissue from dogs with NHL that had been treated with hydroxychloroquine (HCQ) (Barnard et al., 2014). Both agents accumulated in tumor tissue at levels that were approximately 100 times greater than plasma levels, and there was no correlation between levels of the drugs found in plasma and in tumor tissue. These findings demonstrated that plasma drug levels were not a good measure of tumor drug exposure for these agents, a conclusion that subsequently informed the design of human clinical trials. Furthermore, the trial showed that HCQ inhibited the targeted cell process, which was autophagy, or the degradation of dysfunctional cellular components. Data from both clinical trials for canine patients were published along with data from the human trials, as part of a series in the journal *Autophagy* (Rangwala et al., 2014).

Pharmacodynamics in Clinical Trials for Pet Patients

Douglas Thamm from Colorado State University further discussed the role of clinical trials for canine cancer patients in PD assessments. He noted several potential advantages of assessing PD endpoints in such trials, including a favorable body size, which allows safe, repeated tissue or blood sample collection; a commonality of imaging techniques; and a commonality of drug delivery methods (e.g., aerosolized lung therapy, isolated perfusion, or radiation delivery). Additionally, he said, studies with pet patients enable investigations of potential predictive biomarkers, including the correlations between clinical outcomes and surrogate endpoints. They can also facilitate assessments of PK/PD relationships and validation of tumor-specific drug delivery and target modulation through serial biopsy of the tumor tissue. Size limitations make it difficult, if not impossible, to investigate many of these endpoints in preclinical mouse models, he added.

Thamm offered an example of how clinical trials for canine patients have informed human clinical trials. Preclinical research on predictive biomarkers had suggested that an inhibitor of the Bruton tyrosine kinase (BTK) could be useful for the treatment of lymphoma (Honigberg et al., 2010). However, there was no in vivo preclinical model of lymphoma for testing the efficacy of the inhibitor. The availability of pet dogs with naturally occurring lymphomas and sustained B cell receptor signaling made it possible to demonstrate drug efficacy, he said. Trials for canine patients also allowed the validation of a biomarker test for use in human clinical trials. Through a series of paired pre- and post-treatment tumor biopsies as well as pre- and post-treatment PBMC samples at two different drug doses, researchers were able to demonstrate a correlation between measurements in PBMCs and measurements in tumor tissue, suggesting that this assay would be a useful surrogate endpoint in human clinical trials. The researchers were also able to assess efficacy and refine the distinction between the MTD and a biologically effective dose. After the drug had been administered to a small cohort of canine patients, it was determined that a lower dose than initially planned was capable of modulating the target, which led to a lower dose of the agent being used in early-phase clinical trials for human patients (Honigberg et al., 2010). In this way the data from the clinical trials for canine patients accelerated the drug development process for humans. In addition, the investigators at potential sites for human clinical trials were more willing to participate in subsequent trials because of the evidence of the efficacy from the trials for canine patients. The BTK inhibitor used in these trials was approved for use in humans as ibrutinib, Thamm reported.

However, despite this ultimate success, there were some initial challenges, Thamm noted. Before conducting the clinical trials, it was necessary to determine if there was a canine BTK homolog, whether canine B cell lymphomas expressed BTK, and whether BTK was active in canine B cell lymphoma. Furthermore, one of the goals of the trials for canine patients was to validate an antibody for detecting BTK phosphorylation, but the antibody was not cross-reactive in canines, so this objective could not be met.

Thamm also elaborated on the successful validation of the targeted delivery of TNF-alpha, which had been mentioned by Khanna (Paoloni et al., 2009a). TNF-alpha is a potent cytokine with anti-tumor activity, but its use has been limited by the fact that it can cause severe systemic toxicity. The agent investigated in the canine patients was designed to circumvent the systemic toxicity by using a virus to target delivery of the TNF-alpha gene to a protein that is present on the surface of rapidly dividing tumor endothelium. The clinical trial for canine patients assessed toxicity and the localized delivery of the targeted agent. The results of the study in canine patients demonstrated that the agent had tumor-selective delivery to tumor vasculature and that the response to the drug was correlated with TNF-alpha gene expression in the tumor. Necropsy samples also demonstrated a selective delivery of the agent to the tumor but not to normal tissues.

Thamm also described the successful development of toceranib, a molecule that is FDA-approved for veterinary use and is similar to sunitinib, which is approved for use in humans. Toceranib is a receptor tyrosine kinase inhibitor. Mutations of the c-kit gene are present in 20 to 40 percent of all canine mast cell tumors, a frequency that is similar to how often activating mutations are present in human gastrointestinal stromal tumors, Thamm said. Clinical trials for canine patients used molecules that were similar to, but not identical with, the lead compound for humans (sunitinib) (London et al., 2003). Proof-of-target studies were performed in canine patients to gather data on safety, tolerability, PK, and target modulation (Pryer et al., 2003). These studies confirmed target inhibition and demonstrated that tumor response to the treatment correlated with significant downregulation of KIT protein phosphorylation in the tumor. An adaptive clinical trial is currently under way for studying c-kit mutation and drug localization status as response predictors in canine mast cell tumors that have been treated with toceranib or vinblastine.

Thamm said that one of the barriers to advancing clinical trials for dogs is the fact that there is no comprehensive characterization of the genetic

mutations present in canine cancer. Study sponsors usually have a molecular target that needs to be validated in clinical trials, but canine cancer types with that specific mutation of interest may not have been identified. It would be useful to have a large database of canine cancers so that investigators could understand which cancers could be targeted by investigational drugs, Thamm concluded.

IMAGING TECHNOLOGY IN CLINICAL TRIALS FOR PET PATIENTS

Challenges and Opportunities in Using PET Imaging in Clinical Trials

Peter Choyke from NCI discussed positron emission tomography (PET) imaging in clinical trials for pet patients. In general, radioactive tracers used in PET imaging depend on a high target-to-background ratio (TBR), he said, adding that data from mouse studies generally provide overestimates of the tracer target affinity and underestimates of background. Imaging background is related to PK, and the PK of rodents is very different from that of larger mammals. Thus, larger mammals will provide a more realistic estimate of TBR in humans, he said. Some of the challenges in pet patients relate to the co-administration of general anesthesia with the radioactive tracer during scanning and the handling of radioactive waste during and after a scan. There are also technical considerations that arise in imaging trials in pets. These include the fact that the equipment is typically dual use—PET scanners are generally not dedicated to canine use—which makes it necessary to separate the scheduling of pet and human patients, usually by 1 or 2 hours. There are also requirements for specialized staffing, including PET technologists, veterinary staff, and imaging specialists. There is also the concern about radiation safety; pet patients eliminate unpredictably, and this waste is radioactive. When human patients get PET scans, the radioactive waste (which generally has a short half-life) enters the municipal sewer system where it is very diluted and thus does not pose a safety a concern. For pet patients, temporary housing is usually provided until most of the tracer is cleared from the animal's body. However, he added that while most tracers are cleared very quickly, others can take days to leave the animal's system.

Choyke next discussed types of PET imaging agents. Receptor-specific imaging agents are highly targeted but can be slightly more difficult to work

with in canine patients, he said, because the receptors in dogs are not identical to those in humans. Thus, the radiochemistry for the human version does not work for the canine version, and the agent must be reworked to accommodate the differences between the canine and the human receptor. For these reasons, other tracers are more commonly used in imaging of pet patients.

Choyke described several examples of studies with commonly used PET imaging agents. By using ^{18}FDG (flourodeoxyglucose), which is a marker of metabolism, he said it was possible to examine tumor regression in a pet patient with B cell NHL after treatment with conventional chemotherapy. This is an excellent example of PET imaging for veterinary use, he emphasized. Another useful agent for both human and pet clinical trials is fluorothymidine (^{18}FLT), which is a marker of cellular proliferative activity. ^{18}FLT can be very specific for cancer and can allow differentiation between tumor and non-tumor tissue, he added.

Choyke also said that the PET imaging agent ^{18}F-tetrafluoroborate (^{18}F-TFB) has mainly been used in animals, but it may also be useful in human clinical trials. ^{18}F-TFB images the sodium/iodide symporter (NIS) protein, so the agent is very useful for imaging in the salivary glands, thyroid, and stomach, where the symporter is very active. One worrisome side effect of radiation therapy is the destruction of the salivary glands, he said, and ^{18}F-TFB may facilitate studies of interventions to protect the salivary glands during radiation.

Choyke also discussed ^{18}F-CP18, which is currently in development as an imaging agent for monitoring apoptosis. There have been some small and preliminary studies in non-human primates and a clinical trial with a few human volunteers, he said. Those studies indicated that the agent is rapidly excreted and has low background, and no safety signals[11] were identified. However, whether it can be used to effectively measure apoptosis in humans has not been determined. Choyke suggested that this is one example of how PET imaging studies in pet patients could accelerate the development of imaging tracers and drug development.

[11] The Council for International Organizations of Medical Sciences defines a safety signal as information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

There are a number of questions remaining regarding the development of imaging agents in clinical trials for pet patients, Choyke said. For example, there is a lack of clarity about how FDA might consider data from pet patients, and it is unknown whether metabolic differences between humans and animals will make the data unreliable as a marker of efficacy.

Challenges and Opportunities in Using MRI Imaging in Clinical Trials

Functional imaging data from pet patients can help optimize the design of human clinical trials, said Mark Dewhirst from Duke University. He discussed the utility of magnetic resonance imaging (MRI) in clinical trials for canine patients and the historical perspective of imaging tumor biology. Some of the first two-dimensional models of canine tumors were developed by calculating temperature distributions using heat transfer modeling with computed tomography (CT) scans, he said (Dewhirst et al., 1987). Studies in canine patients were also used to map temperature distributions within tumors treated with hyperthermia. Clinical guidelines for the use of hyperthermia treatment for cancer were informed by studies in canine patients with soft tissue sarcomas, he added (Dewhirst et al., 1990).

In humans with high-grade soft tissue sarcoma, Dewhirst said, metastasis occurs in 40 to 50 percent of patients, and there is currently no accepted biomarker to assist in treatment decisions. To develop potential biomarkers, researchers investigated physiologic and metabolic parameters related to overall survival and metastasis-free survival in canine patients with soft tissue sarcomas. This kind of study is not possible in human patients, Dewhirst emphasized. A form of functional MRI was used to collect metabolic information in a phase II clinical trial in which canine patients were administered high and low thermal doses plus radiotherapy. Several variables were associated with metastasis-free and overall survival in the canine patients, including tumor grade, tumor volume, phosphodiester/adenosine triphosphate (ATP) ratio, and extracellular pH (Lora-Michiels et al., 2006). Intra- and extracellular pH was measured in tumors from canine patients with soft tissue sarcomas, and the data showed that intracellular pH was higher (more alkaline) than the extracellular pH (Prescott et al., 2000). This was the first study to demonstrate this effect in a spontaneous tumor, Dewhirst said. Subsequent research in human trials also found that the metabolite ratio of phosphomonoesters to phosophodiesters was also associated with metastasis-free survival in human sarcoma, he added.

Dewhirst also described dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), which has been used in canine patients with soft tissue sarcoma to predict the therapeutic outcome after treatment with hyperthermia and radiotherapy (Viglianti et al., 2009). The DCE-MRI parameters predicted the clinical outcome in this study, Dewhirst said. A small preliminary study in human patients found similar results, but there were too few patients for a statistically valid conclusion.

Dewhirst next explained how diffusion-weighted imaging in canine patients was used to evaluate pathophysiologic response to thermoradiotherapy (Chi et al., 2011). Diffusion-weighted imaging measures the mobility of water in tissue. There was a detectable change in the diffusion coefficient in response to treatment, which indicated tumor regression. Gene expression analysis was also performed on a series of serial tumor tissue biopsies collected over time. Changes were seen in the expression of genes related to inflammation and tissue remodeling, and these changes were predictive of the treatment outcome, he said. Dewhirst explained that many of the factors that predicted metastasis-free and overall survival were similar between human and canine patients.

These kinds of studies could be applied to the investigation of many agents in order to get parallel data for human and pet patients, Dewhirst said. He noted that image data were key to thermal therapy modeling and for establishing the principles for clinical trial quality assurance. Functional imaging data obtained during therapeutic trials on pets have been used to guide and augment results from parallel human trials. A combination of functional imaging and genomics data revealed therapeutic targets and provided important prognostic information that could not be gathered from genomic analyses alone, he said.

LESSONS LEARNED FROM COMPARATIVE ONCOLOGY CLINICAL TRIALS

Single-Institution Clinical Trials

The advantages of single-site trials include flexibility and the ability to alter protocols rapidly in response to findings, while the disadvantages may include an inadequate representation of different breeds and the underrepresentation of certain adverse events, said Cheryl London from Ohio State University. There is usually a dedicated commitment by the site principal investigator (PI), which can aid rapid enrollment and allows the PI to

observe toxicities firsthand while treating affected pet patients. The model also allows for rapid changes in study protocol in response to clinical toxicities or observed responses because there is only one institutional review board (IRB) overseeing the trial. The possible drawbacks to the single-site trial include the fact that the patient population at the trial site may not be representative of the disease under study and that there may be several different trials competing for patients within that single site. Furthermore, rapid enrollment can sometimes result in toxicities that are not noticed before a larger number of patients have been treated. And in a single-site setting, London said, it can be challenging to enroll large numbers of patients with a specific type of cancer in a timely manner.

London described several examples of new drug candidates that were tested in single-study site trials for canine patients. The first example was ganetespib, a HSP90 inhibitor that is currently in phase III human clinical trials. A compound known as STA-1474, which is a highly soluble prodrug of ganetespib, was investigated in a phase I clinical trial for canine patients to determine clinical toxicities, establish surrogate biomarkers, and provide preliminary evidence of biologic activity before an investigational new drug (IND) application was submitted to FDA (London et al., 2011). Results suggested that sustained blood levels of ganetespib were associated with measurable responses to therapy. Subsequent studies in mice confirmed that longer drug exposures were associated with a more efficient inhibition of HSP90 activity in tumor cells. In a subsequent trial for canine patients with mast cell tumors, different dosing regimens were studied to identify a regimen that would result in biologic activity and sustained downregulation of HSP90 proteins similar to the results from an 8-hour infusion protocol. This study helped to define the PK/PD relationship and facilitated subsequent human clinical trials of ganetespib, London said.

London also discussed another example of a single-site trial with KTN0158, a humanized monoclonal antibody that binds to the human and canine KIT protein, but not to rodent KIT. Preclinical studies were performed in healthy dogs to assess the likely adverse events before starting phase I clinical trials for canine patients with mast cell tumors. The same PI performed both the preclinical and the phase I studies. Additional adverse events were noted during the preclinical study, which resulted in protocol changes for the phase I trial. Better trial design should improve the quality of the data from subsequent trials, she added.

London also discussed preliminary work done with a small molecule inhibitor of the STAT3 (signal transducer and activator of transcription 3)

protein, known as LY5. Studies in mouse models of cancer demonstrated that LY5 had anti-tumor activity, and studies in canine patients showed good oral bioavailability of the agent. Future clinical trials are planned to define the MTD, PK/PD relationship, biologic activity, adverse event profile, and dosing regimen of the compound. This is an example of drug development studies being conducted in parallel in three different groups: mice, healthy dogs, and canine cancer patients.

London next described an example that illustrated the potential disadvantages of a single-site study with rapid patient recruitment. A clinical trial of a drug called RV1001 enrolled canine patients with newly diagnosed and relapsed T and B cell lymphoma too quickly and, as a result, did not make allowances for important toxicities that developed 1 to 3 weeks after drug administration. Enrollment was rapid, and all patients were enrolled within 4 weeks. Grade 3 and 4 hepatotoxicity occurred in all treatment groups within 1 to 3 weeks of drug administration. Interim PK analysis demonstrated that hepatotoxicity was associated with drug accumulation. An immediate dosing adjustment to only 5 days per week reduced the hepatotoxicity. However, a slower enrollment would have resulted in fewer pet patients receiving the toxic dose, she said.

Finally, London described phase I and II clinical trials for canine patients with lymphoma that were treated with KPT-335, a novel inhibitor of the XPO1 (exportin 1) protein. Clinical trials with KPT-335 were performed in canine patients with lymphoma in support of human clinical trials to assist with the identification of an adverse event profile and dose/regimen. Initial data from a phase I trial suggested that dosing 3 days per week could be well tolerated, but subsequent data from a phase II trial for canine patients showed that this dosing schedule was not well tolerated, and the regimen was changed to 2 days per week. Subsequent human trials used canine data to determine the drug regimen and supportive care protocols to address toxicities, she said.

London also briefly discussed patient recruitment in trials for pets with cancer. In the past, direct outreach to veterinarians has not been useful for recruiting patients, she said. London described a large marketing campaign aimed at increasing public awareness about clinical trials for pet patients that resulted in increased trial participation by directly informing pet owners.

Multi-Institution Clinical Trials

Amy LeBlanc from NCI discussed the operational structure of the COTC and how that structure meets the needs of the drug development community. The COTC is a component of the NCI comparative oncology program, and, as such, it can leverage existing NCI resources, including data management and community visibility. A dedicated not-for-profit clinical trial support system, the COTC has many member sites within veterinary academic centers throughout the United States.

LeBlanc described how trial budgeting operates under a standardized structure and fee schedule, with separate budgeting for correlative analysis. The study sponsor is responsible for the provision of the agent and any assays performed directly by the sponsor. The study protocol and consent documents are produced collaboratively by the study sponsor and NCI, and each site maintains documentation of approval from an institutional animal care and use committee (IACUC). Study sites are not permitted to deviate from the approved protocol, LeBlanc said. Each trial has a separate database maintained by the COTC and an independent data safety and monitoring board (DSMB) that includes a chair and four members from non-participating sites, if possible. The DSMB members meet quarterly to discuss all adverse events with site investigators and study sponsors, LeBlanc added. Kurt Weingand from Midwestern University reported that the American Veterinary Medical Association recently discussed the possibility of creating veterinary-specific IRBs; these IRBs would also interface with IACUCs. In the long term this could help protect pet patients and their owners and also help promote safety, he said.

LeBlanc explained that COTC trials are developed in response to specific unmet needs in human drug development. Clinical trials for pet patients should be uniquely designed to study questions that are best answered in pet patients, and only in pet patients, she said. Examples include questions about tumor biology, drug targets, PK/PD relationships, and biomarker validation; the selection of lead compounds, dose, and schedule; and the evaluation of combination therapies. Efficacy is often not the primary endpoint in these trials, she emphasized. She added that most preclinical models for studying cancer are helpful, but no single model will provide all of the information needed to move an agent forward in development. A focus on tumor biology and drug targets, rather than just looking at histology, is useful in designing clinical trials for pet patients, she said.

LeBlanc detailed a clinical trial for canine patients that administered

three different molecules in a "pick the winner" strategy. Data from animals that responded to the drug in an early cohort suggested a possible dose–response plateau, and one of the compounds had a much greater drug accumulation than the other two. However, there was no appropriate biomarker for this compound, so research to address that limitation is currently under way. LeBlanc said that this is a good example of how these kinds of trials can be useful in identifying a lead compound because preclinical studies in mice had not been able to discern a meaningful difference among these three compounds, while the results from trials for pet patients suggested that one of the compounds was indeed better.

LeBlanc also discussed the value of the COTC to the wider research and development community. The COTC provides centralized trial management at no cost to the sponsor, she said. Clinical trials for pet patients can be useful for carrying out PD studies in naturally occurring cancer, and they can provide access to patients with both treatment-naïve and drug-resistant disease, she emphasized. The COTC also provides a connection to a comparative oncology-imaging center with the ability to recruit dogs for imaging studies, she added.

LeBlanc also described some of the challenges that the COTC faces. Time management is important in executing a large number of agreements for clinical trials, and intellectual property rights agreements can be difficult to execute, she said. However, these difficulties are minimized, she said, by the fact that COTC member sites are not allowed to deviate from the protocol and generate their own data; the study sponsor/drug provider ultimately owns the data.

LeBlanc said that there are many advantages to a multi-site consortium, including the fact that researchers have access to a large number of pet patients with a specific, but uncommon, disease. This also helps to eliminate any possible geographical or investigator bias, she said. The COTC provides access to variety of resources for running clinical trials for pet patients, including genomics resources, and it makes it possible for early-stage investigators to leverage the resources needed to conduct large clinical trials. The consortium also integrates NCI resources, including preclinical drug discovery tools and methods (e.g., in vitro and in vivo mouse models), into the development path of novel anti-cancer agents, she said.

Leblanc said that the COTC's current capabilities include measuring the safety and efficacy of an investigational agent in pet patients and determining whether a tumor's histology or grade will predict its response to an agent. She also offered a list of questions that could be addressed in clinical

trials in pet patients that cannot be effectively answered in other animal models or in human trials at this time. These include determining why an agent succeeded or failed in human trials, whether an agent can prevent the onset of metastatic disease in the adjuvant setting, whether the agent can be safely combined with the standard of care, and whether there are shared actionable targets between human and canine cancers, irrespective of histologic diagnosis.

LeBlanc also suggested that new initiatives extending beyond clinical trials will be needed to move more clinical trials for pet patients forward. Ongoing molecular validation of canine cancer as a model for human cancer is needed, she said, including further investigation of the various oncology agents and imaging agents that are in development.

Barrett asked about the typical duration of treatment response in pet patients receiving standard of care, and how an exceptional responder would be defined in trials for pet patients. London said that for some diseases, there is a substantial body of evidence on expected outcomes that can be conveyed to pet owners and used for comparison to identify exceptional responders. LeBlanc added that post-treatment survival times in dogs are not necessarily comparable to humans, because dogs have a shorter lifespan. In addition, she said a complete response for even a short period of time could in some cases be viewed as an exceptional response that warrants further study.

CLINICAL TRIAL DESIGN

Clinical Trial Designs That Meet the Needs of Pet Patients and Their Owners

David Vail from the University of Wisconsin–Madison discussed the design of clinical trials for pet patients. Human patients who enter phase I clinical trials generally have already been treated with standard-of-care therapies, often with three or more different agents, he said. The patients also usually have an advanced disease. In contrast, animals that enter trials often are newly diagnosed and have not yet been treated for cancer. There is usually no standard of care for animals with cancer, or the standard of care is inadequate, so enrollment in a trial of an investigational drug may be an appealing option to pet owners. The costs of care can also be a motivating factor for trial enrollment, he said; in clinical trials the costs are covered by the study sponsor, so there may be some financial incentive for owners to

enroll their pets in trials. However, he added, pet owners are also motivated by altruism to provide information that may help future pet patients.

One goal of a phase I clinical trial for pet patients is to determine the MTD, Vail said, and there are many concerns with trials that are designed to assess that endpoint. For example, he said, the dosing often starts low and escalates, so efficacy is usually low in early cohorts, while later cohorts are more likely to be affected by toxicity. There are strategies that can be used to address some of these concerns, such as owner education and informed consent, treating a very small number of pet patients in the low-dose cohorts, allowing sufficient time for adverse events to occur before escalating the dose, and covering the cost of managing any potential adverse events.

Vail said that phase II trials are designed to characterize the clinical and biological activity of investigational agents, such as which tumor types or targets respond to the agent. Some of the concerns regarding phase II trials are similar to those for phase I trials. For example, when these trials start, there is little or nothing known about chronic effects or low-incidence adverse events related to the treatment. The phase II trials require larger numbers of patients than the phase I trials, and often surrogate endpoints are assessed rather than tumor response or patient survival. Investigators can address these concerns with owner education and informed consent, Vail said, and they can use statistical methods to help reduce the numbers of patients needed in their studies. He offered several examples of such approaches, such as the "pick the winner" strategy used in phase I and phase II trials of multiple agents. Another strategy is to enrich the trial enrollment with patients who are relatively homogenous with respect to predictive factors and to randomize only those patients who are likely to respond or benefit. A good example of this concept, Vail said, was the development of trastuzumab for women with HER2-positive breast cancer. By using enriched designs, researchers were able to move more quickly from phase II to a phase III trial in which an effect was seen with only 469 patients treated in the trial, compared with the more than 23,000 patients who would have been needed without enrichment (Slamon et al., 2001).

In phase III clinical trials, Vail said, the goal is to compare the effect of treatment with the natural history of the disease or to determine if the new treatment is better or less toxic than the standard of care, often with the intention of seeking FDA approval for the drug indications. Some of the concerns related to phase III clinical trials center on the use of placebo, denying the standard of care, and the need to enroll large numbers of patients. To alleviate some of these concerns, Vail said that the following

strategies can be implemented: owner education and informed consent, the use of best supportive care as the placebo, and study designs with early stopping rules, or other adaptive trial designs such as Bayesian designs, where statistical inferences are made using accumulated data, historical data, and data from other trials, which allows the treatment of fewer patients to get useful results (Buzdar et al., 2005). Vail added that as a result of bidirectional clinical trials for pets and human patients, several oncologic therapeutics, including toceranib and masitinib (Marech et al., 2014), have been FDA-approved for use in animals.

Trial reporting is another way to ensure that clinical trials for pet patients are ethically sound, Vail said, noting that the current standards for reporting trials are known as CONSORT.[12] The more information is available to the decision maker (patient or caregiver), he said, the more informed the choice will be of whether that trial is appropriate (Schulz et al., 2010). Vail concluded by saying that communication and information sharing should be a bidirectional process between pet patient owners and researchers.

Best Practices for the Ethical Conduct of Clinical Trials for Pet Patients

Rod Page from Colorado State University reported on the outcome of a meeting he helped organize[13] in 2014 on the ethical conduct and oversight of clinical trials for pet patients, in which the participants developed a set of best practices for clinical trials for pet patients. He said that the participants at that meeting agreed on the following principles:

- Clinical trials must preserve well-being, provide the best supportive care, and provide relief from pain and other distressing symptoms.
- All clinical trials should be peer reviewed for scientific and therapeutic merit, feasibility, sound design, and the absence of redundancy.
- The consent process must be honest, thorough, and well communicated, and the pet owner must have adequate time to consider participation without real or perceived coercion or conflict of interest.

[12] Consolidated Standards of Reporting Trials. See http://www.consort-statement.org (accessed August 17, 2015).

[13] With support from The Shipley Foundation and the Flint Animal Cancer Center.

- Accountability and oversight of research conduct by all those involved must be maintained.

Page noted that the Office of Research Integrity has established guidelines on the oversight of research in pet patients (HHS, 2007), and he said that continued improvement of education in clinical trial conduct and oversight is critical to both animal health and the appropriate translation of such data to human health.

Page also described best practices for the clinical trial approval process at a single institution (see Figure 3) (Baneux et al., 2014). IACUC approval is needed for any procedure beyond a normal patient workup. A research committee may also need to review the trial, depending on the details of that particular trial. A clinical trial approval process that requires both types of reviews would improve the clinical relevance of all studies, Page suggested.

Next Page discussed the informed consent process, which is an ethical obligation on the part of the researchers and aims to ensure that owners understand the trial goals and what is going to be done to their pet. Where possible, the informed consent process for pet patient trials should be harmonized with the informed consent process for human trials, he said, noting that there are several resources from FDA and NCI that can be used as guidance and templates in the development of informed consent processes for pet patient trials (HHS, 2013, 2014a,b). Page suggested that the informed consent process should do the following:

- Identify the consenting team;
- Clarify the study purpose;
- Thoroughly describe the study design and interventions;
- Identify the funding sources and disclose any conflict of interest;
- Discuss compensation and consider vulnerability;
- Describe advocacy and client support; and
- Document comprehension and retention.

Page explained that there are many tools available, such as videos and interactive apps, to aid the consent process, including for non-English speakers or those with less education. These techniques, which were developed for human trials, could be applied to the consent process for pet patients as well.

Page made several suggestions for the post-approval monitoring of trials. This is a new concept for clinical trials in pet patients, he said, and

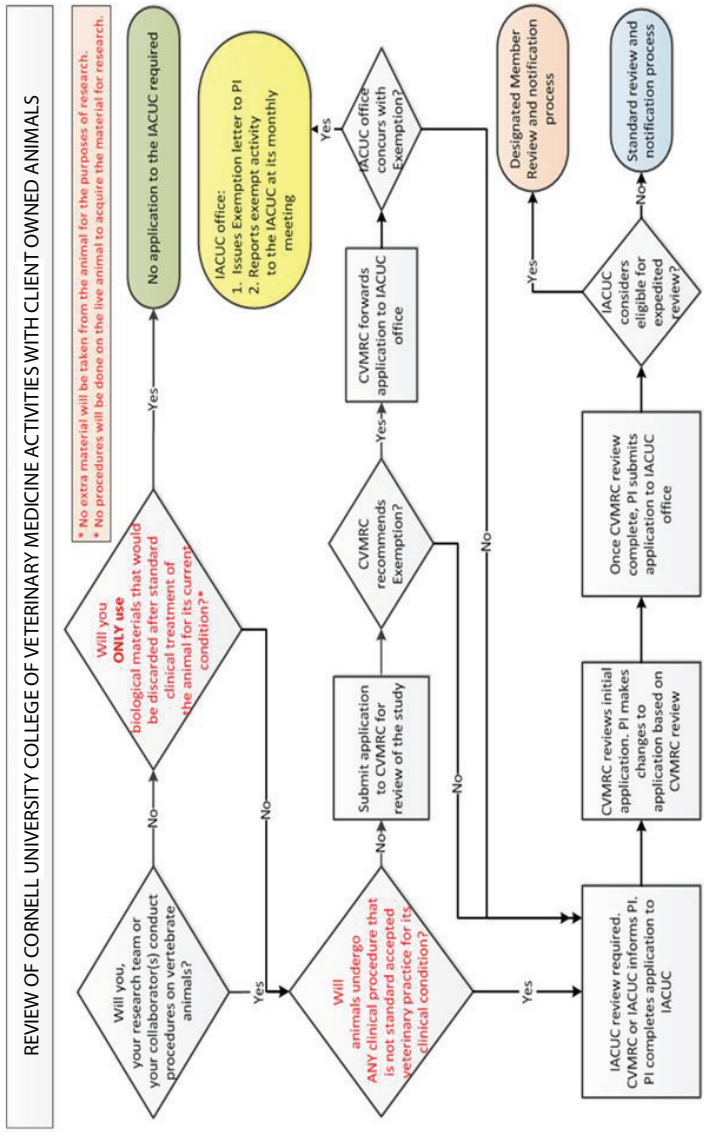

FIGURE 3 Clinical trial approval process at the Cornell University College of Veterinary Medicine.
NOTE: CVMRC = clinical veterinary medical research committee; IACUC = institutional animal care and use committee; PI = principal investigator.
SOURCES: Page presentation, June 9, 2015; Baneux et al., 2014. Reprinted with permission from Oxford University Press.

it will require additional education and training programs. He suggested that the NCI's National Clinical Trials Network[14] audit guidelines should be adapted for pet patients (NCI, 2014). Page also suggested establishing a confidential process for reporting potential ethical or protocol breaches.

Page also made several suggestions regarding reporting and publication. He said that improved data management systems should be created, and that it would be helpful to develop a clinical trials registry for pet patients that would be similar to the registry for human clinical trials (www.ClinicalTrials.gov). In addition, Page suggested that an improved publication policy should be put in place to increase accountability of trials for pet patients and that investigators should provide open access to all primary data, including those from negative studies (McGrath et al., 2015). Michael Lairmore from the University of California, Davis, School of Veterinary Medicine reported that the American Veterinary Medical Association is considering the creation of a clinical trial registry for pet patients.

In closing, Page had some suggestions for improving the clinical trial process, including the adoption and adaption, through regular review and revision, of clinical trial best practices. He also said that research should be encouraged on the process of conducting clinical trials for pets, with a focus on improving comprehension among pet owners, increasing enrollment and retention, and understanding the role of quality-of-life data reported by pet owners. Finally, Page said, all stakeholders should be educated about the clinical research process; in particular, this topic should be addressed by professional training programs for those in veterinary medicine and research.

Considerations of Pet Owners and Pet Patients in the Conduct of Clinical Trials

Patricia Olson, an independent consultant and former president and chief executive officer of the Morris Animal Foundation and advisor to the American Humane Association, discussed the importance of strategic, collaborative, and humane research that considers the needs of pet patients and owners. Increasingly, she said, pets are viewed as family members. A 2011 poll by Harris Research found that 69 percent of survey respondents had a dog, and 92 percent of those respondents considered the pet to be a family member. A majority of respondents allowed their pets to sleep in their beds, and some frequently purchased holiday present for their pets.

[14] See http://www.cancer.gov/research/areas/clinical-trials/nctn (accessed August 17, 2015).

A recent issue of the journal *Science* described some of the deep connections between canines and humans, Olson said. Canines were the first domesticated animals, for example, and humans and dogs have evolved shared hormone signaling and brain networks that encourage their interaction. The hormone oxytocin facilitates social connections between humans and dogs, and when humans view their dogs, the same common brain network for emotion is activated when mothers view images of their children (Grimm, 2015).

Olson next discussed attitudes toward the role of pet patients in research. In general, she said, women are less inclined to be in favor of animal research, and they outnumber men in animal protection movements. Positive attitudes toward research are dependent on the type of research, she added. For example, research studies that might help the pet patient are looked on more favorably than those that will not.

Olson said that trials for pet patients should be designed to advance disease prevention as well as to develop new therapies. She also mentioned several ethical considerations that should be discussed before launching a trial, including the appropriateness of delayed conventional therapies, limits on tissue and blood collection, and whether pet patients are likely to benefit from clinical trial research.

Olson suggested that pet patients should be considered similar to pediatric patients, noting that both need independent advocates to provide informed consent. She added that pet owners are a vulnerable population; a distressed and worried owner may not be the best independent advocate for the pet patient. Means should be found to communicate with diverse populations, she said, and she noted that stores selling pet products have large databases of information on pets and pet owners. These databases might be useful for finding improved methods of communication with the owner community, she said. She concluded by saying that pet owners can become partners in the research enterprise through careful consideration of their needs and expectations for their pets.

REGULATORY OVERSIGHT AND REPORTING REQUIREMENTS IN CLINICAL TRIALS FOR PET PATIENTS

The FDA Animal Rule (21 CFR 314.600 and 21 CFR 601.90) provides limited guidance regarding the use of clinical trials for pet patients during the drug approval process, said John Leighton from FDA's Center for Drug Evaluation and Research (CDER). These rules allow animal testing

as a surrogate for human clinical studies of efficacy when human efficacy studies are neither ethical nor feasible. FDA can approve a product after adequate and well-controlled animal studies establish that a given product is reasonably likely to provide clinical benefit when administered in humans, he said, as long as human safety studies are also conducted.

Leighton described the reporting requirements for adverse outcomes from a regulatory perspective and discussed how FDA handles a safety signal in clinical trials for pet patients. He said that unless there is an IND for the agent in place for human use, there are no reporting requirements for CDER. However, if the agent is under investigation for approval as a veterinary medicine, then reporting should be done with the Center for Veterinary Medicine under an IND for that purpose.

He also noted that clinical trials for pet patients are conducted under Good Clinical Practice Guidelines, not under Good Laboratory Practice Guidelines. As such, they are conducted without concurrent normal controls. There may be a control group that receives the standard of care, but toxicity studies required for an IND application usually are conducted in healthy animals with concurrent controls. Therefore, adverse events from the disease may be mistakenly recorded as adverse effects from the drug, he said. However, he emphasized that any safety signals would be evaluated using the totality of the data and "human clinical data would trump any animal data."

Leighton added that FDA has not taken regulatory action, such as a clinical hold or additional monitoring, in response to a safety signal observed in a clinical trial for pet patients. "I have never seen an adverse outcome from a safety signal in a companion animal study. We have heard this over and over again, that the FDA is going to take a negative perception to any safety signal, and in 15 years I have never seen it," he said.

Nonetheless, Tanja Zabka from Genentech said that it would be helpful to the field if FDA provided written guidance on clinical trials for pet patients. It is very difficult to convince drug developers that safety signals in pet patients will not affect a clinical trial for humans, she said.

Christopher Loss from the FDA Center for Veterinary Medicine noted that FDA guidelines do not require the use of a placebo in clinical trials. "Industry chooses to go with the placebo," he said, "mainly because . . . there is no good standard of care for some of these cancers we're talking about, and the ones [for which] there are standards of care, the efficacy is not truly known." Industry might be uneasy about comparing a potential therapeutic to the standard of care when the efficacy of the standard is

unknown, he said, but he added that modern trials usually include a stopping rule, so if disease progression is seen, the trial is stopped and patients are given the standard of care. Other options for comparison include historical controls or the natural history of the disease in a specific population, he said. However, such comparisons are difficult to carry out because the natural history of many cancers in pet patients is unknown. Loss also suggested that every clinical trial for pet patients should include both owner diaries and quality-of-life surveys. This would be another way to monitor adverse events in these clinical trials, he said.

STATUS OF CLINICAL TRIALS FOR PET PATIENTS

Wendy Levin from Fate Therapeutics offered some thoughts on incorporating clinical trials for pet patients into oncology drug development. In precision medicine, she said, there is no MTD for many targeted therapies. In developing dosing regimens for later-phase clinical trials, it may be more useful to rely on a biologically active dose than an MTD, she said, noting that in the case of targeted therapies, more is not always better. Levin explained that higher dosing can often lead to more toxicity and less efficacy, and thus PK/PD modeling may be the most useful study design in these situations. Validating and qualifying a biomarker early in the drug development pathway, using a preclinical study or a trial for pet patients, can accelerate the process, she said, and this additional data can increase enthusiasm among clinical investigators for conducting trials. This approach to drug and biomarker development is an iterative process, she noted, going from the bench to the clinic and back again as more information is gathered.

Levin also described a concern regarding the endpoints in clinical trials. Frequently, she said, there is a disconnect between the response rate and survival for targeted therapies, especially in hematologic malignancies. It might be possible to use clinical trials for pet patients to identify these kinds of issues early in the development process, she suggested.

Daniel Tumas from Gilead Sciences described several approaches that might increase the chances of success in drug discovery and development for both human and pet patients. These include investigating cancers in pet patients that are similar to and predictive for human cancers, especially those with high unmet needs; proof-of-concept studies for novel therapeutics; and the rational evaluation of novel combinations. He noted that some cancers that occur frequently in pet patients are uncommon in humans but do present a high unmet medical need for those diagnosed with the disease.

Tumas described a clinical trial in which a targeted agent was tested in canine patients with hematological malignancies. GS-9291, an antiproliferative nucleotide analog prodrug, had not shown efficacy in mouse models, but laboratory studies showed that the drug did have an effect on canine lymphocytes (Reiser et al., 2008). As a result, canine NHL was determined to be a relevant model for the evaluation of GS-9291 as an investigational agent, and a proof-of-concept study to assess therapeutic index was conducted. The key endpoints of the clinical trials for canine patients were PK; efficacy and activity in NHL, acute lymphoblastic leukemia, multiple myeloma, and cutaneous lymphoma; the evaluation of different doses, schedules, and combinations; the evaluation of post-response relapse; and a safety assessment (intensive monitoring) (Vail et al., 2009). Canine patients with NHL responded to GS-9291, and this provided the proof-of-concept that was critical for launching a phase I study for human patients, Tumas said. He explained that the trial was important because it not only evaluated efficacy, but it also assessed the acute response to the drug and its chronic tolerability, which provided insights into potential safety issues that could arise in human patients.

This molecule did not succeed in the human phase I study, Tumas said, perhaps because the human patients had more advanced disease. However, this molecule, now known as VDC-1101 (rabacfosadine), has been out-licensed and has progressed into animal clinical trials for regulatory approval for veterinary use. Thus, he emphasized, this experience offers an example of a clinical trial for pet patients that helped inform clinical trials for human patients and also advanced a potential therapeutic for pet patients with cancer.

Barriers to Clinical Trials for Pet Patients

Anne Keane from Achaogen discussed potential barriers to conducting clinical trials for pet patients and offered suggestions for overcoming them. Within an individual drug development company, she said, there are cross-functional teams that work together to develop a molecule, and there is intense competition among teams for resources. As a result, she said, there is some hesitancy to devoting the time and resources necessary to conduct clinical trials for pet patients. Demonstrating that these kinds of trials also help to move a compound forward in development would encourage industry to engage in more clinical trials for pet patients, she said.

Keane noted that launching a trial for human oncology patients is a

time-consuming process, with patient enrollment often occurring quite slowly, and any delay in the timeline increases costs. She said that FDA data indicate that more than 70 percent of trials take more time to complete than planned. Keane added that enrollment in pediatric studies can be particularly slow because there is only a small number of pediatric cancers diagnosed each year.

Keane said that these challenges require that changes be made in the drug development pathway if the development of drugs is to be accelerated. The role of phase I trials has greatly expanded, she said, and it is important to identify target populations for pivotal trials because the current preclinical models are not very predictive. However, phase I trials generally still recruit a broad spectrum of patients with many different types of advanced solid tumors, which dilutes the ability of the trial to identify the correct target population. Response rates from phase I trials may determine whether a compound progresses, Keane said, so the results need to be extraordinary. Moreover, she said, compounds that do progress beyond phase I still have a high risk of failure (see Figure 4), especially if critical phase II refinement work (patient population, dose, dosing regimen) is shortchanged.

Clinical trials for pet patients can enhance and accelerate drug development efforts by contributing unique information that cannot be obtained from traditional preclinical models or trials for human patients, Keane said. For example, studies with canine cell lines and pet patients with cancers with documented relevance to human cancers could be added to screening panels for all compounds, she said. Clinical trials for pet patients can also be used to help select the best compounds and to prioritize the most promising combinations to advance into human clinical trials. These kinds of trials can also thoroughly describe PK/PD and imaging endpoints that can inform human dosing, she added, so that potential safety signals can be identified early and addressed with mitigation strategies.

Keane also gave an example of how clinical trials for pet patients were introduced at one pharmaceutical company (Genentech). A cross-functional team was created to design and execute pilot studies in cooperation with molecule teams, and a monthly speaker series helped raise awareness of the utility of clinical trials for pet patients. This process also helped to identify barriers within the company to implementing such trials, including a lack of familiarity with veterinary medicine, concern over safety issues that could derail development, the perception that there is a lack of regulatory guidance, and concerns about the ability to recruit adequate numbers of

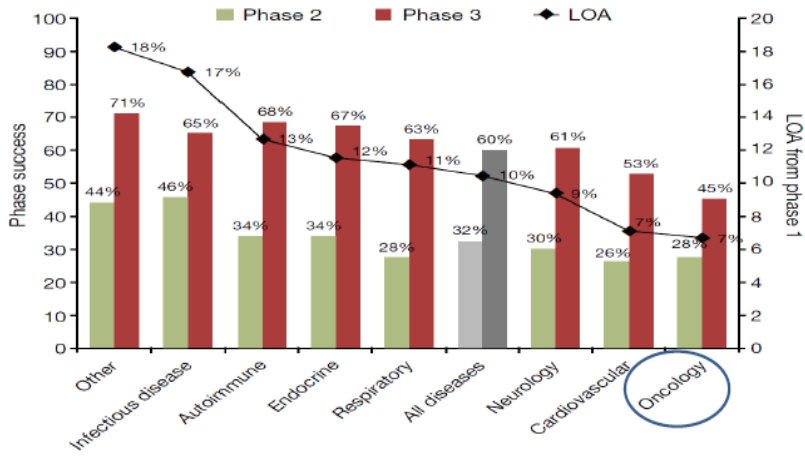

FIGURE 4 Clinical development success rates for investigational drugs. Phase success and letter of approval (LOA) from phase I by disease for all indications. The bars represent phase II and phase III success rates, and the line represents LOA from phase I. SOURCES: Keane presentation, June 9, 2015; Hay et al., 2014. Reprinted with permission from Macmillan Publishers, Ltd.: Nature Biotechnology.

pet patients. There are ongoing efforts at Genentech to educate staff and identify new collaborations for this field, she added.

Keane also detailed some strategies to mitigate such challenges. The lack of familiarity with trials for pet patients can be overcome with various educational approaches, such as speaker series, she said. She also suggested that results from clinical trials for pet patients should be published in human medicine journals and presented at national meetings focused on human medicine to raise awareness of the utility of the model. She also noted that there is some guidance on the best way to translate new cancer treatments from pet patients to human patients (Khanna et al., 2009).

Keane concluded by saying that integrating clinical trials for pet patients into the pharmaceutical development pipeline would improve the development process, but that this change will take some time and effort.

Carolyn Henry from the University of Missouri suggested that it would be useful to perform a cost analysis to assess the return on investment for trials with pet patients. For example, the costs of drug development might by reduced if the success rate in phase III human trials was improved or if investigational agents were dropped at an earlier stage of development before failing in late-stage trials. Keane agreed.

Research Needs

Several speakers and participants suggested that a more detailed characterization of the canine genome would help researchers understand the similarities and differences in cancers found in pet patients and in humans. Breen stressed that there is a great deal of opportunity to use clinical trials for pet patients to validate targeted agents and to gain understanding of how these agents work in order to design more effective human clinical trials, but the necessary information on what specific agents might target canine cancer is often lacking. Likewise, the specific assays and reagents that would make such trials possible are also often not available at this time, Fan said.

CLOSING REMARKS

After the final discussion panel, Deborah Knapp from Purdue University summarized her perspective on the workshop presentations and discussions. Cancer is still a large burden for both human and pet patients, she said, and one that is likely to worsen as the human population ages. "There is a huge need for complementary systems to complement the current structure in cancer research," she said, "and dogs that have naturally occurring cancer or who are at risk for naturally occurring cancer can certainly help." She emphasized that clinical trials for pet patients have been established on a solid foundation of more than 30 years of research through the work of scientists and veterinarians and that the field is well positioned to continue to move forward.

Knapp reiterated that there are specific forms of naturally occurring cancer in dogs that mimic what is seen in humans. "There have been substantial inroads into developing the tools, acquiring the samples, and in analyses that are showing and defining molecular and genetic characteristics within and across cancer types in dogs," she said, "and dogs do harbor chromosomal and mutational events that occur in human cancer." Some of these mutations may be passenger mutations and some of them may be driver mutations, she said, and it is possible that as the cancer evolves in a given individual, these may flip back and forth.

Knapp stressed that clinical trials for pet patients can be done in an ethical and a compassionate manner and that they can result in benefits for both pet patients and humans. An individual patient has the potential to benefit from an experimental therapy, she said, if there is no defined standard of care available or accessible or if the standard of care was not effective

for the patient. Moreover, she said, the information gathered from these trials will "help other dogs with cancer and . . . we will obtain information that could inform some future strategic way to manage human cancer."

Clinical trials for pet patients can also help define and test primary and secondary prevention strategies, Knapp said. Because pet patients have shorter lifespans than humans, the results from prevention trials on pets can be obtained more quickly. These studies can identify the most promising prevention strategies for testing in humans, she said, and they can be particularly relevant for less common cancers in humans, where there may be a limited number of patients.

Knapp also summarized some of the challenges for clinical trials for pet patients. A complete characterization of the disease is often lacking in pet patients. This characterization should include complete pathological and clinical behavior characteristics in addition to defining the molecular and genetic events that are important in those cancers, she said. In addition, there is a lack of knowledge among researchers regarding the potential role and value such trials have to offer in translational cancer research, and there are unsubstantiated concerns among drug sponsors that findings from clinical trials for pet patients could adversely affect a new drug application for human use.

Len Lichtenfeld from the American Cancer Society also provided his perspective on the workshop. Clinical oncology has progressed substantially in the past 40 years, he said. There are now many targeted cancer therapies available for clinical use, with hundreds more in the development pipeline, and recent successes with immunotherapy for some types of cancer have reinvigorated that line of investigation. But, he said, in spite of these successes there is still much more work to be done if we are to "make this cancer's last century." He noted that while the drug development pathway is changing—for example, more information is now being gathered in larger phase I clinical trials, which look for signals of targeted drug response as well as signs of toxicity—more could be done to accelerate the pace.

Lichtenfeld said that before the workshop he had been unfamiliar with clinical trials for pet patients, but shortly after receiving an invitation to participate, his own beloved family dog, Lily, was diagnosed with cancer. He said that that personal experience, along with all the informative presentations and discussions over the course of the workshop, had given him a deeper appreciation for the ways that clinical trials for pet patients offer opportunities to enhance and accelerate progress in cancer research. He reviewed some of the opportunities discussed at the workshop, including

the generation of data to inform and improve early-stage clinical trials for human patients, to identify lead compounds and prioritize combinations for testing, and to re-examine older drugs or investigational agents that did not demonstrate efficacy in unselected patient populations.

However, he noted, there is currently limited capacity for these kinds of trials in the United States, and many stakeholders are unfamiliar with the concept. He said he was encouraged by the strong commitment of the veterinary community to bring together stakeholders from many fields to learn, discuss, and raise awareness of the potential for clinical trials for pet patients and by ongoing campaigns to build public awareness. But, he added, additional investments will be needed to build capacity and facilitate these types of trials.

Lichtenfeld ended by saying, "The answers to our puzzles may be walking right beside us. . . . As we leave this room, let's commit to taking a look at those potentials, determining what they are, and making that happen."

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Appendix A

Statement of Task

An ad hoc committee will plan and host a 1.5-day public workshop that will feature invited presentations and panel discussions. Workshop participants will examine the rationale and potential for integrating clinical trials for pets with naturally occurring cancer into translational cancer research and drug development.

Participants will be invited to discuss topics that may include

- An overview of the limitations of current preclinical oncology models and resulting late-stage drug development failures and costs;
- Strategies to support the incorporation of data from clinical trials for pets with cancer in drug development pathways;
- Gaps in the evidence base to support integration of such trials in the drug development continuum and ways to address those gaps;
- Challenges and potential solutions to greater integration of such trials in cancer drug development pathways; and
- Opportunities for further collaborations and information exchange between human and veterinary oncologists.

The committee will develop the agenda for the workshop sessions, select and invite speakers and discussants, and moderate the discussions. An individually authored workshop summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

Appendix B

Workshop Agenda

June 8, 2015

7:30 am **Registration**

8:00 am **Welcome from the National Cancer Policy Forum**
Sharyl Nass, Institute of Medicine
Director, National Cancer Policy Forum

Overview of the Workshop
Michael Kastan, Duke Cancer Institute
Planning Committee Chair

8:15 am **Session 1: Overview and Value of Trials That Include Pets in Translational Cancer Research**
Moderator: Michael Kastan, Duke Cancer Institute

Overview of current challenges and opportunities in oncology drug development
Lee Helman, National Cancer Institute

Strengths and limitations of traditional preclinical models
Beverly Teicher, National Cancer Institute

Advantages and experiences with trials that include animal patients
Chand Khanna, National Cancer Institute

Group Discussion

10:10 am **Break**

10:20 am **Session 2: Canine Tumor Biology and Genomics Informing Cancer Drug Development**
Moderator: Deborah Knapp, Purdue University

The current state of canine tumor genetics and scientific limitations
Heidi Parker, National Human Genome Research Institute

Use and availability of canine cancer tissue banks in translational research
Matthew Breen, North Carolina State University

Genomic resources for canine cancer research
Jessica Alföldi, Broad Institute of the Massachusetts Institute of Technology and Harvard University

Biology and informatics needs
Jeff Trent, Translational Genomics Research Institute

Group Discussion

12:15 pm **Lunch Break**

1:00 pm **Session 3: Effectively Integrating Biomarkers into Study Designs**
Moderator: Carl Barrett, AstraZeneca

Opportunities for preclinical evaluation of novel therapies
Timothy Fan, University of Illinois at Urbana-Champaign

Pharmacokinetic (PK) assessment
Dan Gustafson, Colorado State University

Pharmacodynamics (PDs) and potential predictive biomarkers
Doug Thamm, Colorado State University

Group Discussion

2:30 pm **Session 4: Effectively Integrating Imaging Technologies into Study Designs**
Moderator: Peter Choyke, National Cancer Institute

Role of trials that include pets in the development of new imaging modalities
Peter Choyke, National Cancer Institute

Role of magnetic resonance imaging in studying tumor physiology: A clinical perspective
Mark Dewhirst, Duke University

Group Discussion

3:30 pm **Break**

3:45 pm **Session 5: Mechanisms for Comparative Oncology Trials**
Moderator: Lou DeGennaro, Leukemia & Lymphoma Society

Single-institution studies
Cheryl London, Ohio State University

Multi-institution studies
Amy LeBlanc, National Cancer Institute

Group Discussion

4:45 pm **Wrap Up Day 1**

June 9, 2015

7:30 am **Registration**

8:00 am **Session 6: Addressing the Needs of Pet Animals and Their Owners**
Moderator: Michael Lairmore, University of California, Davis

Trial design and appropriate oversight
David Vail, University of Wisconsin–Madison

Best practices for conduct of clinical trials for animal patients
Rod Page, Colorado State University
Patricia Olson, Independent Advisor on Animal Health and Welfare

Group Discussion

9:45 am **Break**

10:00 am **Session 7: The Status of Comparative Oncology in Drug Development**
Moderator: Perry Nisen, Sanford-Burnham Medical Discovery Institute

Panelists:
Anne Keane, Achaogen
John Leighton, Food and Drug Administration
Wendy Levin, Fate Therapeutics
Daniel Tumas, Gilead Sciences, Inc.

Group Discussion

11:30 am **Workshop Wrap Up**
Deborah Knapp, Purdue University
Len Lichtenfeld, American Cancer Society

12:00 pm **Adjourn**