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Development Strategies for Animal Medical Therapeutics

Alexander H. Morrison
Department of Medicine, Perelman School of Medicine, University of Pennsylvania

Nicola J. Mason
School of Veterinary Medicine, University of Pennsylvania

Yvonne Paterson
Perelman School of Medicine, University of Pennsylvania

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Summary

- The process of developing a new therapeutic is long, expensive, and risky.
- Current small animal models are often poor representations of human disease, contributing to the high rate of failure in human trials.
- Outbred dogs can be excellent models for researching human disease.
- Clinical trials in dogs are inexpensive and efficient compared with human trials.
- Advaxis, a clinical-stage biotechnology company developing cancer immunotherapies, provides one case study on how trials in dogs can help advance trials in humans.

Development Strategies for Animal Medical Therapeutics

Alexander H. Morrison, MD, MSTR,[1] Nicola J. Mason, PhD, BVetMed,[2] and Yvonne Paterson, PhD[3]

Topic Relevance by Timeline

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Introduction

The process of developing a new therapeutic is expensive, time-consuming, and uncertain. On average, it takes nine years (Kaitin) and costs more than $1 billion (DiMasi et al.; Adams and Brantner) to take a new therapy through clinical development. Despite this significant investment, only approximately 10% (Hay et al.) of Investigational New Drugs (INDs) submitted to the Food and Drug Administration (FDA) are ultimately approved, with the majority of failures due to a lack of efficacy. Therefore, investors in novel therapeutics are constantly looking for therapies that have the best chance of succeeding in clinical trials. For academic investigators trying to raise money for human trials of their novel therapeutic, generating early data that show their therapeutic

[1] Department of Medicine, Perelman School of Medicine, University of Pennsylvania
[2] School of Veterinary Medicine, University of Pennsylvania
[3] Perelman School of Medicine, University of Pennsylvania

has a greater than average chance of success can significantly improve their ability to obtain funding. Unfortunately, it is very difficult to generate truly differentiated data using current small animal models.

An emerging avenue for improving preclinical efficacy estimates is clinical trials on pet dogs. For certain diseases, pet dogs serve as an excellent disease model to efficiently and inexpensively reduce the risk of a new therapeutic. In this chapter, we present the rationale for using pet dogs, details on why pet dogs can be a good model, a brief overview of the logistics of running pet dog trials, and a case study on how this approach has been used to advance one immunotherapeutic into human trials.

Current Small Animal Models Are Often Poor Representations of Human Disease

For decades, mice have served as the foundation of preclinical research on human diseases. Mice are easy to manipulate genetically and have short lifespans, making them excellent tools for probing the biological mechanisms of disease. While this approach has driven the synthesis and development of many novel therapeutics, drugs that are effective in mice too often fail to work in humans. A number of reasons have been proposed as to why mouse findings do not translate to humans: (1) research mice are only ~85% similar to humans in the protein-coding regions of their genomes, (2) mice are often engineered to express target genes in nonphysiologic ways, (3) mice are inbred, (4) mice are raised in laboratory environments and thus not exposed to the same environments as people, and (5) mice can withstand dosages of drugs that would be extremely toxic in humans. Altogether, these issues limit the ability of murine models to predict the safety and therapeutic efficacy of novel agents in human patients. Nevertheless, it is nearly impossible to advance a therapy into human trials without positive evidence in mice.

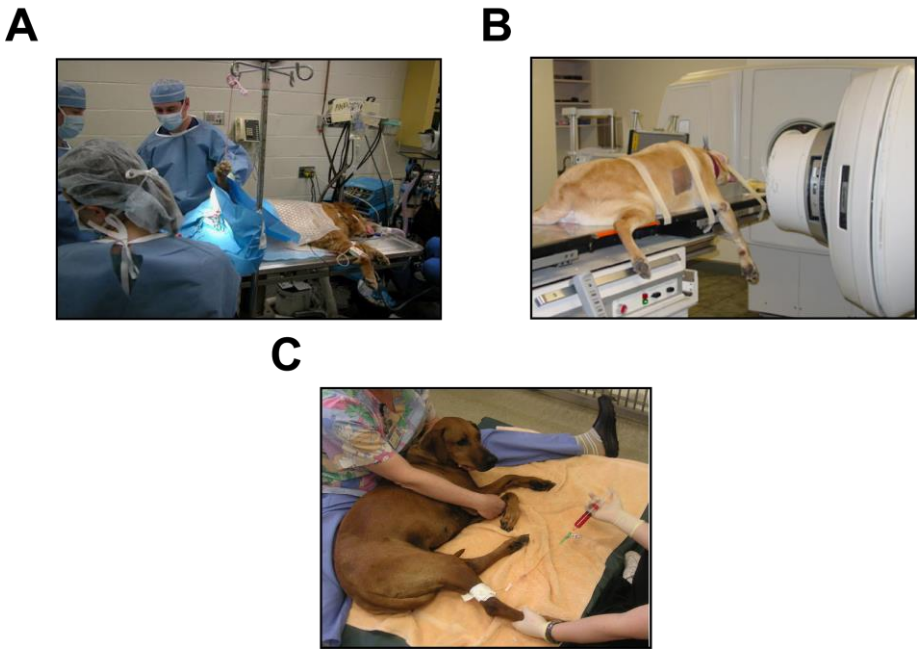
Outbred Dogs Can Be Excellent Models of Human Disease

Unlike laboratory animals, pet dogs spontaneously develop many of the same diseases that humans do, including narcolepsy, psychiatric disorders, osteoarthritis, and cancer (Lin et al.; Tang et al.; Kosinska et al.; Simpson et al.). Also, unlike laboratory mice, pet animals share the same environmental exposures as humans and have not undergone any artificial genetic manipulation. As such, pet dogs develop diseases with a very similar pathogenesis to those in humans. The most well-characterized similarities between dog and human diseases are in cancers, including melanoma, osteosarcoma, and lymphoma. In each of these cancers, dogs have been found to spontaneously develop tumors whose clinical presentation, biological behavior, and genetic aberrancies (mutations and chromosomal translocations) are very similar to their human counterparts. Thus

pet dogs with spontaneous diseases more faithfully represent the pathogenesis of human diseases than do laboratory mice.

Beyond having very similar disease pathogenesis, dogs as a species are in many ways more similar to humans than mice are. Dogs have a longer lifespan than mice, are phylogenetically closer to humans than mice are, and experience similar side effects and toxicities to drugs as humans do (Paoloni and Khanna; National Academies of Sciences, Engineering, and Medicine). In fact, laboratory dogs are already used in preclinical toxicity studies to help ensure new therapies are safe to test on humans. There are 70–80 million dogs in the United States, of which ~20% will develop osteoarthritis and ~25% will die of cancer. These canine patients require treatment, and studying the outcomes of their treatment can inform human clinical trials. In addition to the benefits they provide to humans, pet trials provide owners with free access to cutting-edge therapies for their dogs and the chance to improve the health and wellbeing of their pets. Pet dogs routinely receive the same breadth of clinical interventions as humans, including surgery, radiation, and chemotherapy (Figure 1), and so can serve as research subjects in trials for a broad range of therapies (see the chapter “Pre-clinical Animal Models”).

Figure 1. Multiple Types of Therapies Can Be Evaluated in Pet Dogs.



Legend: Images of pet dogs undergoing treatment with (A) surgery, (B) radiation, and (C) chemotherapy and immunotherapy.

Clinical Trials in Pet Dogs

Inexpensive and efficient compared with human trials

Not only do pet dogs recapitulate human diseases more accurately than murine models, but clinical trials in pet dogs are an efficient way to evaluate therapeutic safety, efficacy and inform human clinical trial design (Table 1). Unlike human trials, clinical trials in pets are governed primarily by the United States Department of Agriculture (USDA) under the Animal Welfare Act (AWA). Under this act, trials need the approval of only the Institutional Animal Care and Use Committee (IACUC). As such, trial approval can occur within months or even weeks, without extensive federal review. Moreover, because dogs have a shorter lifespan than humans and age five to eight times faster, their diseases often progress faster, allowing for a more rapid evaluation of treatment efficacy. Overall, this faster, shorter trial process makes trials in pet dogs significantly less expensive than human trials. Relative to mouse experiments, dog trials do require significantly more drugs and are more expensive to conduct. However, the improved efficacy signals from dogs can improve the chances of success for the even more expensive human trials that follow. Moreover, initiating dog trials before human trials might allow investigators to identify and appropriately adjust for safety signals in dogs prior to beginning human trials, thus increasing the likelihood of delivering a therapeutic dose and reducing the safety risk in human trials.

Table 1. Comparison of Research Trials for Evaluation of New Therapeutics.

Type of Trial	Cost	Speed	Safety predictive of Phase III human?	Efficacy predictive of Phase III human?	Inherent commercial potential	Comments
Small animal (e.g. lab mouse)	$	Weeks to months	Poor	Fair	None	• Ideal for mechanism or target discovery • Poorly predictive of results in humans
Pet dog	$$	Months	Very good	Good	Moderate	• Cheaper than human studies • Good predictor of human safety and efficacy • Commercial potential in pet dogs
Human (Phase I)	$$$	Years	Excellent	Very Good	None	• Standard for early safrty assessment • Efficacy not always predictive
Human (Phase II/III)	$$$$	Years	Excellent	Excellent	High	• Gold standard for clinical approval • Time consuming and expensive

Additional considerations

The timing of trials in pet dogs is critical to minimizing risk in human trials. Any adverse event or safety outcome found in a dog trial that was initiated after submission of an IND to the FDA must be reported to the FDA (see the chapter “FDA Drug Regulation: Investigational New Drug Applications”). Because dog trials are often non-randomized and performed with sick dogs, there

is a risk that adverse events associated with the natural progression of the disease might impact the therapy's perceived safety in humans. Therefore, for optimal benefit, dog trials should be started prior to human trials, allowing investigators to identify and appropriately adjust for safety signals in dogs without placing ongoing human programs at risk.

Commercial benefits

Clinical trials in dogs are not only tools for developing more efficient and easier-to-fund human trials. If designed properly, clinical trials in pet dogs can be used to commercialize therapeutics in dogs. To have this opportunity for small molecules, investigators must file an investigational new animal drug (INAD) application with the FDA's Center for Veterinary Medicine (CVM) and ensure agreement with regulators on trial design and reporting (see the chapter "FDA Drug Regulation: Investigational New Drug Applications"). These requirements will slow the trial timeline, but the upside of following them may be worthwhile for certain therapies. New veterinary biologics are currently governed by the USDA and thus do not require FDA approval to have commercial potential.

Case study: Advaxis

Advaxis, a clinical-stage biotechnology company that focuses on developing cancer immunotherapies, has used studies in pet dogs to enhance the development of a *Listeria monocytogenes*–based platform technology (Wood and Paterson). The company developed a *Listeria*-based immunotherapeutic that expresses HER2/neu (ADXS31-164) and initially generated extensive preclinical data in murine cancer models. As further proof of therapeutic efficacy, Advaxis funded an investigation of whether ADXS31-164 could delay or prevent metastatic disease in pet dogs with osteosarcoma. Canine osteosarcoma has the same clinical, biological, and molecular features as pediatric osteosarcoma, including the expression of the HER2/neu protein, which makes it an excellent model for evaluating the safety and therapeutic effects of treatments. The trial, carried out at the University of Pennsylvania School of Veterinary Medicine, tested the ADXS31-164 vaccine in dogs. The results showed that this immunotherapeutic approach prolonged median survival and disease-free survival and was safe and well tolerated (Mason et al.). These data have contributed to the ease with which the company has moved forward and raised money for human trials of the vaccine targeting HER2/neu in human cancers, including osteosarcoma.

Conclusion

Clinical trials in pet dogs represent a relatively fast and inexpensive way to (1) better characterize which investigational therapeutics will be successful and (2) improve the design of human trials. While dogs are not a perfect model for all human diseases, there are many diseases in which dogs are an excellent model. In these diseases, trials in pet dogs provide an excellent way to improve confidence in potential new therapies and increase the success rate of clinical trials. Investigators

trying to advance a new therapy to clinical trials should work with their veterinary colleagues to understand whether pet dogs are a good model for the disease being studied and, if so, consider testing their therapy on pet dogs as a bridge or supplement to human trials.

Resources

1. The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research: Workshop Summary (National Academies of Sciences, Engineering, and Medicine)
2. Guiding the Optimal Translation of New Cancer Treatments from Canine to Human Cancer Patients (Khanna et al.)

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