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Abstract: Despite recent advances in biomedical research, translating preclinical findings into effective therapies remains a major challenge—particularly for complex diseases. Spontaneous diseases in companion animals, especially dogs, offer a powerful yet underutilized bridge to human medicine. Naturally occurring cancers, neurodegenerative disorders, and cardiovascular, renal, and ocular diseases in dogs closely resemble their human counterparts in pathophysiology, treatment response, and environmental exposure. These models allow for the evaluation of novel therapies, including immunotherapies and gene-based treatments, in immunologically relevant systems. Integrating patient-derived organoids and physiologically based pharmacokinetic modeling further enhances mechanistic understanding and translational accuracy. To fully leverage this potential, investment in infrastructure, biobanking, and interdisciplinary training is essential. As One Health gains momentum, spontaneous canine models emerge as scientifically robust and ethically sound tools for more predictive, cross-species drug development.

Keywords: One Health; comparative medicine; canine models; In Silico In Vitro modeling

Introduction

Despite significant progress in drug development, translating preclinical findings into effective human therapies remains a persistent challenge (Waring et al., 2015). High attrition rates in Phase II clinical studies, particularly for complex diseases such as cancer and neurodegeneration (90% attrition or more), underscore the limitations of conventional animal disease models (Schneider et al., 2018). Rodent systems, although fundamental to basic biomedical research, often struggle to replicate the complexity of human pathophysiology. This includes immune responses, heterogeneous diseases, and interactions with the environment (Gordon et al., 2009). The "One Health" approach, which emphasizes the interdependence of human, animal, and environmental health, offers a compelling framework to address these knowledge gaps (AVMA, 2008). Among the most promising, yet underutilized, resources in this framework are spontaneous disease models in companion animals, particularly dogs.

Dogs naturally develop a wide range of diseases that closely resemble those seen in humans in terms of pathophysiology, clinical presentation, and treatment response. Among others, these include cancers, cardiorenal metabolic diseases, ocular diseases, and age-related cognitive decline (Khanna et al., 2006; Head, 2013; Mochel and Danhof, 2015; Garden et al., 2018; Schütt et al., 2016, 2018; Sebbag and Mochel, 2020). Living alongside humans, dogs share similar environmental exposures, lifestyle factors, and, in some cases, genetic susceptibilities with humans. These shared characteristics enhance their relevance as translational models for biomedical research. Moreover, their shorter lifespans facilitate the study of disease progression and therapeutic outcomes over compressed timelines. When paired with emerging technologies—such as patient-derived organoid systems and in silico modeling, spontaneous canine models provide an ethically sound and scientifically robust bridge between preclinical experimentation and human clinical application.

The Comparative Value of Spontaneous Canine Models

What makes spontaneous canine models unique compared to conventional animal systems is their ability to closely mimic the complexity and variability of human diseases. Unlike induced rodent models, where diseases are often introduced through genetic modification or chemical exposure, diseases in dogs occur naturally and are influenced by genetics, environment, and aging. This provides canine models with a level of biological realism that is often lacking in a laboratory setting.

For instance, canine cognitive dysfunction (CCD) shares noticeable behavioral and pathological features with early-stage Alzheimer's disease (Schütt et al., 2016, 2018; Ambrosini et al., 2020; de Sousa et al., 2023). Aged beagles have shown to accumulate amyloid-beta (Aβ) plaques and exhibit cognitive deficits, closely mirroring the progression of human dementia (Schütt et al., 2016). Additional studies have identified tau pathology and neuroinflammatory changes in aging dogs, further reinforcing their value in neurodegeneration research (Head, 2013). As with most natural animal models of Alzheimer's disease—excluding goats, sheep, and chimpanzees—dogs exhibit Aβ pathology and some indications of tau abnormalities, but do not develop fully formed neurofibrillary tangles (Head, 2013). In oncology, the parallels are also compelling (Khanna et al., 2006). Canine urothelial carcinoma exhibits similar histological characteristics, genetic drivers (e.g., BRAF mutations), and therapeutic responses as human bladder cancer (Knapp et al., 2000; Knapp et al., 2020). Unlike many murine models which do not have a functional immune system or rely on artificial tumor induction, dogs develop cancer in an intact immune and physiological environment. This makes them especially valuable for studies investigating immunotherapy, cell and gene therapies (Mochel et al., 2019; Dow, 2020). In cardiovascular research, dogs with myxomatous mitral valve disease (MMVD) exhibit diastolic dysfunction similar to human heart failure with preserved ejection fraction (HFpEF), while canine dilated cardiomyopathy (DCM) shares characteristics with systolic heart failure (HFrEF). Importantly, canine and human myocardium are similarly enriched in β-myosin heavy chain isoforms, supporting translational comparisons in myocardial excitation-contraction coupling (Fuller et al., 2007). A critical component in both species is the overactivation of the renin-angiotensin-aldosterone system (RAAS), which drives vascular inflammation, myocardial remodeling, and fibrosis. As shown in experimental and clinical studies (BENCH, 1999; Pitt et al., 1999; Atkins et al., 2007; Mochel et al., 2013, 2015; Hammond et al., 2023), RAAS dysregulation is central to disease progression in canine and human CHF, and therapeutic modulation of this system remains a cornerstone of treatment in both veterinary and human medicine. Comparative trials evaluating agents such as ACE inhibitors (BENCH, 1999; Atkins et al., 2007), mineralocorticoid receptor antagonists (Pitt et al., 1999; Coffman et al., 2021), and novel neprilysin inhibitors (e.g., sacubitril/valsartan) (Mochel et al., 2019) in dogs have yielded insights into therapeutic strategies that inform both species. At last, numerous studies have established the dog as a valuable model for advancing human ophthalmic research, particularly in understanding tear film dynamics and improving diagnostic techniques. Sebbag et al. (2019) investigated how tear film volume influences fluorescein dye kinetics in Beagle dogs, demonstrating parallels to human ocular pharmacokinetics and the critical impact of tear volume on drug bioavailability. Complementing this, Sebbag et al. (2018a, 2018b) evaluated methods for tear fluid collection, comparing Schirmer strips and ophthalmic sponges, and highlighting best practices to preserve biomarker integrity. Altogether, these findings support the use of canine models to advance human eye health research.

Organoids and PK/PD Modeling: Enhancing Mechanistic Insight

Recent advances in three-dimensional (3D) cell culture have opened new avenues for translational research using veterinary species. Organoids—miniaturized, self-organizing tissue models derived from stem cells—retain key functional and structural features of the original organ. These systems offer a physiologically relevant and scalable platform for drug testing, toxicology studies, and disease modeling (Sato et al., 2009; Clevers, 2016; Fatehullah et al., 2016).

Building on previous work by Chandra et al. (2019) in animal health, Zdyrski et al. (2024) recently reported the cultivation, maintenance, and molecular profiling of two novel adult stem cell–derived canine organoid lines—endometrium and pancreas—complementing previously established models of bladder, lung, and liver derived from two genetically related dogs. Organoids from five distinct tissues were generated for each donor and analyzed using bulk RNA sequencing, enabling a unique comparison between individuals across multiple organs and the identification of specific cell populations, including glandular epithelial cells within the endometrial organoids. Organoid systems provide a scalable, ethically sound complement to in vivo studies. Importantly, organoids can be derived from individual patients, both canine and human, preserving their genetic and epigenetic heterogeneity. This allows for personalized modeling of disease progression and varying drug responses. This is particularly relevant for precision medicine approaches, where understanding variability in treatment outcomes is critical.

In addition to their use as standalone test systems, organoids can complement in vivo studies by providing mechanistic insights into pharmacological responses at the cellular level. For instance, organoids can be utilized to evaluate drug-induced hepatotoxicity or altered barrier function in the gut before conducting animal or clinical studies (Hu et al., 2018; Gabriel et al. 2022; Shin et al., 2025). This iterative bench-to-bedside approach reduces reliance on high-volume animal testing while refining hypotheses for downstream validation, in agreement with the 3Rs ("Reduce, Refine, Replace") paradigm. Importantly, integrating organoid-derived in vitro data, such as hepatic metabolism rates or intestinal permeability, into physiologically-based pharmacokinetic (PBPK) frameworks enhances the predictive power of these models. PBPK models simulate the absorption, distribution, metabolism, and excretion (ADME) of compounds across species by integrating anatomical, physiological, and biochemical parameters. This enables the estimation of first-in-animal and first-in-human dose ranges with greater precision, supporting regulatory submissions and de-risking early-stage drug development (Jamei et al., 2014; Lin et al., 2016). When applied in a One Health context, these technologies converge to create a more efficient, mechanistically informed, and ethically sound drug development pipeline.

Therapeutic Development and Regulatory Perspectives

The evolving regulatory landscape is increasingly recognizing the value of comparative and spontaneous disease models in accelerating therapeutic development. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have acknowledged the translational relevance of veterinary data (EMA, 2020). In several cases, data generated from canine clinical trials have contributed to Investigational New Drug (IND) applications and have directly influenced the design and execution of human clinical studies (Khanna et al., 2006; LeBlanc et al., 2020).

One notable example is the FDA's Comparative Oncology Program (COP), established by the National Cancer Institute, which facilitates the integration of canine cancer trials into the broader drug development pipeline (Gordon et al., 2009). This program enables the evaluation of novel agents in pet dogs with spontaneous tumors, often in parallel with early-phase human studies. The resulting data, spanning pharmacokinetics, pharmacodynamics, and tumor response, have been instrumental in prioritizing candidates for advancement and in identifying early biomarkers of efficacy or toxicity (Paolini et al., 2010; LeBlanc et al., 2020). Canine clinical trials offer multiple advantages that enhance their utility in translational research. They are conducted in veterinary referral centers or academic hospitals, generating data under real-world clinical conditions. The patient population reflects naturally occurring disease in a genetically diverse cohort, improving the external validity of findings. Another key strength of these studies is the ability to collect rich longitudinal datasets. Advanced imaging, serial blood sampling, and repeated biopsies are routinely feasible in canine patients, allowing for the monitoring of pharmacodynamic markers, disease progression, and long-term safety. These data can support the refinement of dosing regimens, identification of resistance mechanisms, and validation of surrogate endpoints; all within a condensed clinical timeline. Their

integration into regulatory science not only improves predictive accuracy but also enhances the efficiency and ethical grounding of modern drug development.

Building Infrastructure for Comparative and Translational Integration

To fully leverage the potential of spontaneous canine models in translational research, targeted investments in infrastructure, policy, and workforce development are necessary. A major barrier to broader adoption is the lack of standardized protocols for clinical trials, sample collection, and data reporting across veterinary institutions. Without harmonization, cross-study comparisons become challenging, and the reproducibility of findings may be compromised. Developing consensus guidelines for trial design, outcome measures, and adverse event reporting would facilitate regulatory engagement and promote broader scientific adoption. Centralized biobanking initiatives are also critical. Veterinary biorepositories that house annotated tissue samples, organoids, and biological fluids enable large-scale studies of disease mechanisms and therapeutic responses (Lombardo et al., 2015; LaLonde-Paul et al., 2023). Coupled with detailed clinical metadata, these resources support biomarker discovery, omics-driven stratification, and retrospective validation studies. Expanding access to these high-quality biospecimens can accelerate progress across multiple disease domains. Equally important is the cultivation of a workforce fluent in both veterinary and human biomedical science. Interdisciplinary training programs are needed to break down institutional and epistemological silos.

Dual-degree programs, cross-training fellowships, and shared research appointments can foster a new generation of investigators who operate seamlessly across species boundaries (Rabinowitz et al., 2017). Co-mentorship models, shared core facilities, and collaborative grant mechanisms can further cement these cross-sector relationships. Sustained funding is the key to success. Despite the crucial groundwork laid by programs like the NIH's Comparative Oncology Program, broader investment is necessary to incorporate veterinary models into mainstream translational pipelines. Public-private partnerships and international consortia offer promising opportunities for scale, particularly in areas that are underfunded, such as chronic liver disease or neurodegeneration in veterinary patients. Mechanisms that encourage industry involvement, such as regulatory fast tracks or data-sharing agreements, could help attract resources and attention to comparative models. Ultimately, a comprehensive infrastructure that supports high-quality comparative research will not only advance veterinary care but also transform the predictive power of preclinical science. Spontaneous disease in dogs is not just an analog to human pathology; it is a translational asset in its own right. The systems we build now will determine how fully we capitalize on its potential.

Conclusion: One Health in Action

As the biomedical field embraces new technologies—such as organoid platforms and PBPK modeling—the value of spontaneous canine models only deepens. These tools enhance mechanistic understanding, support dose optimization, and enable cross-species extrapolation in ways that reduce risk and improve efficiency across the drug development pipeline. Importantly, these advances do not merely serve veterinary science or human medicine in isolation—they represent a unified effort to solve shared health challenges through collaboration and integration.

To fully realize the promise of these models, the scientific community must move beyond viewing comparative research as peripheral. It must be recognized as a cornerstone of modern translational strategy—one that requires dedicated infrastructure, interdisciplinary training, and sustained policy and funding support. The integration of spontaneous disease models in dogs is not just an opportunity for progress—it is a necessity for building a more predictive, humane, and equitable future for both animal and human health.

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