Review

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Review

Are We Going to the Dogs? Human Disease Phenotypes in Canines

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Abstract

Companion dogs are increasingly recognized as translational models for studying human physiology and disease. Unlike conventional or genetically engineered laboratory models, dogs are outbred, immunocompetent animals that spontaneously develop complex diseases whose pathogenesis and environmental exposures commonly overlap with those of humans. These distinctive features create opportunities to study mechanisms of disease, progression, and therapeutic responses under conditions that more closely resemble clinical reality. This review highlights evidence for the translational relevance of canine models across multiple therapeutic areas. We further discuss how advances in genomics, transcriptomics, spatial biology, *in vitro*, and *in silico* model systems are expanding the translational utility of canine models for applications in human medicine. Although important species differences must be carefully weighed, dogs represent a uniquely valuable comparative model for elucidating disease mechanisms, informing drug development, and accelerating the translation of scientific discoveries to human medicine.

Keywords: comparative physiology; translational medicine; canine; spontaneous disease; one health; drug development

Introduction

Murine models have played, and continue to play, a critical role in our understanding of biological pathways, enabling genetic manipulation on a large scale and under highly controlled experimental conditions [1]. However, they often fail to recapitulate the ecological, immunological, and physiological contexts in which chronic diseases develop in humans [2–4]. As the scientific community moves toward more predictive, biologically relevant models, companion animals offer a unique opportunity to study disease pathogenesis, progression, and therapeutic response in biological cohorts that share the same environment as humans. Unlike conventional laboratory models, dogs are outbred, immunocompetent animals that spontaneously develop complex, heterogeneous diseases [5,6]. They are exposed to the same environmental pollutants and allergens as humans [7], share overlapping microbial communities within households [8], and maintain circadian rhythms that closely mimic, and are entrained by, human activity [9–13]. Importantly, dogs' shorter lifespan relative to humans enables the study of disease progression and therapeutic response on an accelerated timescale. Collectively, these features provide a compelling biological rationale for studying how real-world exposomic, behavioral, and socioecological factors shape health and disease trajectories. In this context, dogs have become central to the comparative oncology paradigm, as they develop spontaneous tumors within genetically structured breeds and intact tumor microenvironments. Canine cancers, such as osteosarcoma, lymphoma, glioma, and urothelial

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carcinoma, among others, share remarkable histopathological, molecular, genetic, and environmental similarities with their human counterparts, as well as comparable treatment responses [6,14,15]. The translational utility of the companion animal model is further supported by the availability of advanced information technology and large data collection programs such as the National Cancer Institute's Comparative Oncology Trials Consortium (COTC] and the Integrated Canine Data Commons, that enable the collection, annotation and archiving of large cancer datasets [16,17]. These resources facilitate the construction of cross-species molecular atlases and enable federated learning across veterinary and human datasets.

This review examines the evidence supporting the dog as a translational model across multiple therapeutic areas, from the genomic and phenotypic foundations of cross-species disease comparability to emerging technologies and quantitative systems pharmacology that are expanding the translational utility of canine models for human medicine.

Genetics to Phenotypes in Canine Patients: What Makes a Disease "Comparable"?

Humans and dogs share extensive genetic predispositions to disease [18]. With approximately 400 dog breeds worldwide, there is a large gene pool that can be leveraged to identify various genotypic-phenotypic relationships [18]. Selective breeding provides interbred genetic models, while the diversity of dog breeds allows for genetic variation in the population as a whole. This breed-specific genetic variation, combined with a shared human environment, underlies an estimated 500 heritable disorders common to both species [19], positioning the dog as a powerful genetic model for human disease. Beyond their shared lifestyle and role as spontaneous disease models, dogs develop tumors driven by age-related somatic mutations that recapitulate the histological features, biological behavior, and molecular underpinnings of human cancers [20]. Moreover, selective breeding for traits such as body size, morphology, behavior, and coat color, has fixed alleles that predispose specific breeds to defined disease phenotypes (**Fig.1**) [18].

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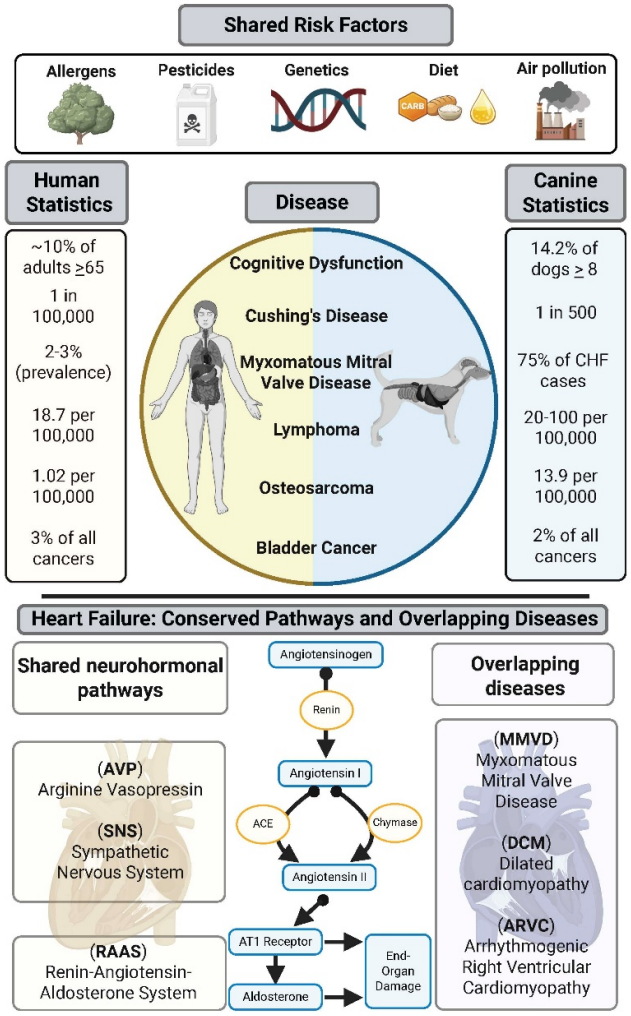

Figure 1. Shared risk factors and comparative disease statistics in humans and dogs. (Top) Environmental and genetic risk factors shared between species, including allergens, pesticides, and genetics, as well as secondary exposures such as diet and smoke. (Center) Select diseases occurring spontaneously in both species, with key statistics for humans (left) and dogs (right). (Bottom) Conserved mechanisms in cardiovascular disease, including shared neurohormonal pathways (left), the RAAS cascade (center, adapted from Mochel and Danhof, 2015), and overlapping cardiac diseases (right). One image (diet) was generated using ChatGPT-5.2 (OpenAI, 2026). The figure was otherwise adapted from images created with BioRender.com.

Importantly, both humans and canines have highly complete and well-annotated genomes that enable robust cross-species comparisons, with recent canine reference genomes utilizing long-read sequencing [21]. Despite substantially lower sequence coverage, previous survey sequencing of the canine genome captured slightly more human transcripts (29,673 vs 29,529) and genes (18,473 vs 18,311) than mouse alignments, although a smaller fraction of protein-coding sequence was covered (61% vs 77%) [22]. More recently, '(…) *comparative epigenomic studies involving human and mouse further draw the idea that the human genome has greater similarities with the dog genome than the mouse genome*' [23]. When integrated with spontaneous disease phenotypes and shared household environment, these genomic parallels establish the dog as a powerful translational model.

To fully harness the extensive genetic diversity across breeds, the Dog10K consortium was established in 2019, culminating in the publication of 2,000 canid genomes [21]. More recently, the consortium launched the Dog10K database to democratize access to these resources, which encompass DNA variant and de-novo mutation data, bulk RNA-sequencing, single nuclei and single

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cell RNA-sequencing (sn- and scRNA-seq) [24]. Additional genomic resources, including the Dog Aging Project, Dog Biomedical Variant Database Consortium, Dog Genome SNP Database—iDOG, Golden Retriever Lifetime Study (Morris Animal Foundation), and The NHGRI Dog Genome Project, collectively expand the infrastructure available for comparative and translational research [18].

Despite substantial molecular conservation between species, exemplified by shared mutations in ESR1 and BRCA2 in human breast cancer and canine mammary tumors [15], important differences warrant careful consideration. For example, the BRAF(V600E) mutation is rare in human bladder cancer, whereas the homologous BRAF V595E mutation is present in ~85% of canine muscle-invasive urothelial carcinomas [25]. Paradoxically, this high prevalence positions the dog as a spontaneous model not for human bladder cancer per se, but for studying BRAF-driven tumorigenesis and evaluating targeted therapies applicable to other BRAF-mutant human cancers, such as melanoma [26].

Additionally, a persistent methodological challenge is the limited availability of canine-reactive antibodies. Cross-reactive human antibodies with high sequence homology to canine targets are routinely tested as surrogates; however, achieving target specificity without off-target effects remains difficult, underscoring the need to validate reagent cross-reactivity, including primers and druggable targets, on a case-by-case basis [27].

While human medicine benefits from extensive genomic resources and highly annotated clinical data that inform diagnostics and research, veterinary medicine generates large volumes of data [20] that remain largely underutilized [28]. Coordinated efforts to improve data accessibility, standardization, and archiving are needed to unlock the full potential of this spontaneous disease model for large-scale reverse translational research.

Cross-Domain Evidence Supporting the Dog as a Translational Model

Oncology: Where Dogs Move the Needle

Shared physiology and common etiologic factors underpin the histologic, genetic, and molecular similarities between canine and human cancers, as well as their comparable tumor biology and therapeutic responses [6]. Naturally occurring cancers in pet dogs capture clinically relevant aspects of human disease that are incompletely modeled in mice, including tumor heterogeneity, metastatic progression, and treatment resistance [14]. Many of the biochemical pathways that drive human cancers are conserved in canine tumors, supporting the use of dogs in both translational research and preclinical evaluation of novel therapeutics [5]. The following subsections highlight a few cancer types with strong cross-species parallels.

Osteosarcoma

Osteosarcoma is a highly metastatic primary bone tumor that occurs in both humans and dogs, sharing many key clinical, histological, and molecular features across species. In humans, osteosarcoma has an incidence of 1.02 per 100,000 and is the third most common cancer in adolescents [29]. In dogs, incidence is substantially higher (13.9 per 100,000) and the disease is generally more aggressive. In both species, osteosarcoma is characterized by early micrometastatic dissemination and the subsequent emergence of chemotherapy resistance [30]. Although human osteosarcoma is most strongly associated with the adolescent growth spurt, the predilection for large and giant dog breeds and the involvement of IGF-1 signaling implicate bone growth as a contributing factor in both species [31]. Canine and human osteosarcoma share molecular alterations in pathways involving TP53 [32], as well as biomarkers of cell cycle regulation, immune infiltration, and epigenetic remodeling [33].

Lymphoma

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Lymphoma is one of the most common hematopoietic malignancies in both species, with non-Hodgkin lymphoma (NHL) and, in particular, diffuse large B-cell lymphoma (DLBCL) representing the predominant subtype [34–36]. In the United States alone, NHL is projected to account for approximately 19,000 deaths in 2025 [37]. In dogs, standard chemotherapy induces complete remission in approximately 90% of patients; however, most ultimately relapse, with a median survival of approximately 12 months [34]. Given that the most meaningful progress in DLBCL treatment has come from immunotherapy, canine lymphoma offers a unique opportunity to study tumor-immune interactions within an intact tumor microenvironment. Recent immune-profiling of canine B-cell lymphoma (BCL) has revealed cross-species conservation of prognostic markers, with variation in immune composition associated with differential chemotherapy response; findings that parallel observations in human DLBCL (Didehvar et al., 2025).

Bladder Cancer

Bladder cancer (BC) is the most common malignancy of the urinary tract in humans, with approximately 500,000 new cases diagnosed annually worldwide, accounting for about 3% of all cancers [39]. In dogs, more than 95% of bladder cancers are muscle-invasive urothelial carcinomas (iUCs) that closely mirror human muscle-invasive bladder cancer (MIBC) in morphology, biological behavior, metastatic progression, and response to therapy, including shared luminal and basal molecular subtypes [40,41]. The marked breed predisposition in Scottish Terriers, which carry an approximately 20-fold increased risk of developing BC, further offers a unique genetic context for studying disease susceptibility, early detection, and prevention strategies [42].

Glioma

Malignant glioma (MG) occurs spontaneously in humans and dogs at broadly comparable frequencies and carries a dismal prognosis in both species. Canine gliomas show strong similarity to human pediatric gliomas, including comparable aneuploidy, mutational burden, DNA methylation patterns, and shared abnormalities affecting receptor tyrosine kinase signaling, TP53, IDH1, and cell-cycle pathways [43]. Because canine gliomas arise in large, immunocompetent animals, they provide an informative platform for evaluating neurosurgical and radiotherapeutic strategies, as well as emerging immunotherapies, such as anti-glioma vaccines, immune checkpoint inhibitors, and adoptive T-cell therapy [44].

Clinical Translation: from Bench to Trial

Because the number of potential molecular targets and candidate drugs far exceeds the capacity for clinical testing, robust preclinical models are essential for supporting go/no-go decisions. Comparative oncology trials in dogs with naturally occurring tumors have repeatedly addressed this need, generating critical translational data on antitumor activity, tolerability, pharmacokinetic/pharmacodynamic (PK/PD) relationships, and candidate biomarkers of response across multiple therapeutic modalities [45].

Conventional and targeted therapies. In osteosarcoma, canine studies supported the development of limb-sparing surgery, regional chemotherapy delivery, and whole-body hyperthermia, helping shape subsequent strategies in human disease management [46,47]. Dogs with osteosarcoma also informed the evaluation of mTOR pathway inhibition in a phase I rapamycin trial, supporting the translational development of mTOR inhibitors in human sarcoma [48,49]. In NHL, the canine model dates to the 1970s, when bone marrow transplantation studies contributed to techniques subsequently adopted in human hematologic practice [50], and has since supported the evaluation of agents including pegylated liposomal doxorubicin and the PMEG prodrug GS-9219 [51,52]. Dogs have also contributed to the development of several kinase inhibitors. The RTK inhibitor toceranib (SU11654), developed in parallel with sunitinib in humans, exemplifies the comparative oncology paradigm [53,54]. Canine lymphoma models have similarly supported the evaluation of Bruton's

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tyrosine kinase inhibitors, with both ibrutinib and acalabrutinib showing acceptable tolerability and antitumor activity in dogs with BCL [55,56]. Canine trials have also generated translational data for the XPO1 inhibitor verdinexor [57], the HSP90 inhibitor prodrug STA-1474 [58], the VCP inhibitor CB-5339 [59], and the procaspase activator PAC-1, whose canine data directly informed subsequent human phase I trials in high-grade glioma and uveal melanoma [45,60,61].

Immunotherapy. Spontaneous canine tumors are particularly valuable for immunotherapy research because they arise in immunocompetent hosts with an intact tumor microenvironment. Cross-species conservation of leukocyte composition, regulatory T-cell expansion during tumor progression, and immune-regulatory molecule expression further supports their use for evaluating immunotherapeutic strategies [62]. Among the most compelling examples is liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) in osteosarcoma [31]. Early studies in dogs with spontaneous appendicular osteosarcoma helped establish the rationale for subsequent human trials; in children with osteosarcoma, the addition of L-MTP-PE to standard postoperative chemotherapy improved overall survival, with a trend toward improved event-free survival [63,64]. Dogs with spontaneous pulmonary metastases have also served as a preclinical model for cytokine-based immunotherapy: inhaled liposomal interleukin-2 (IL-2) was shown to be safe and biologically active in metastatic disease, further illustrating the value of canine models for testing immunotherapies in advanced cancer settings [65]. Canine studies have also been used to evaluate several vaccine-based immunotherapies across tumor types. These include HER2-targeted vaccination in osteosarcoma [66], telomerase-targeted vaccination in BCL [67], and disialoganglioside GD3-targeted vaccination in melanoma [68]. In canine brain tumors, vaccine approaches have likewise shown feasibility and immunological activity, although the study by Andersen and colleagues evaluated an autologous tumor lysate vaccine with toll-like receptor ligands rather than a GD3-targeted strategy [69]. Early-stage development of canine immune checkpoint inhibitors is already underway, with therapeutic antibodies targeting PD-1 [70] and CTLA-4 [71] having been generated and evaluated in preclinical or early translational settings. Such studies may be particularly informative for aggressive metastatic solid tumors, including osteosarcoma and angiosarcoma, where durable responses remain difficult to achieve. Collectively, these studies demonstrate that dogs with spontaneous metastatic disease can yield actionable data on safety, immunogenicity, and biological activity of candidate immunotherapies.

Adoptive cell therapies and tumor microenvironment modulation. Dogs are also emerging as a translational platform for adoptive cell therapies, enabling evaluation of feasibility and activity in spontaneous cancers before advancement to human trials. Recent work includes CD20-directed CAR T cells in canine BCL [72], adoptive NK-cell therapy in combination with radiotherapy in sarcoma [73], and a USDA-CVB-regulated pilot study using human-derived xenogeneic CAR T cells, which were well tolerated, induced remission, and could be tracked *in vivo* by PET imaging [74]. Naturally occurring canine tumors provide a valuable system for studying therapeutic modulation of the tumor microenvironment, including macrophage depletion with liposomal clodronate [75], blockade of CCR2-dependent monocyte recruitment [76] and CCR4-targeted depletion of regulatory T cells in invasive bladder cancer [77]. This is especially relevant in brain tumors, where the canine model allows investigation of slowly evolving and highly complex microenvironmental interactions that are difficult to capture in conventional experimental systems [78]. Recent immune-profiling studies in canine BCL have further demonstrated cross-species conservation of prognostic features within the tumor microenvironment [38].

Valvular Disease and Cardiomyopathy

In humans, the main drivers of heart failure (HF) are ischemic heart disease, followed by hypertension and valvular heart diseases [79]. In dogs, HF is driven predominantly by myxomatous mitral valve disease (MMVD), accounting for about 75% of clinical cases, followed by dilated cardiomyopathy (DCM), which occurs most commonly in large and giant breeds [80]. Canine HF

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often manifests as congestive heart failure (CHF), a presentation in which elevated cardiac filling pressure leads to fluid accumulation, especially in the lungs.

The rationale supporting the dog as a model for heart diseases has been comprehensively reviewed by Pyle [81]. In brief, canine cardiovascular anatomy closely parallels that of humans, including a four-chambered heart with structurally and functionally comparable valves [82]. The electrical conducting system also shares basic anatomical and physiological features, although canine cardiomyocytes exhibit significantly higher inward rectifier potassium currents than their human counterparts [83,84]. Distinct morphological features of the canine heart include an ovoid shape with a more ventrally oriented apex, as well as a more extensive coronary venous network and robust collateral circulation, which, together with differences in lipid biology [85], contribute to the relative resistance of dogs to coronary artery disease [86].

Conserved Neurohormonal Mechanisms

In humans, progression from compensated cardiac dysfunction to symptomatic HF is marked by robust neurohormonal activation, driven primarily by stimulation of the sympathetic and renin-angiotensin-aldosterone systems (RAAS), promoting vascular constriction, sodium retention and maladaptive remodeling [87]. Although data on treatment-naïve RAAS activation in dogs with CHF remain limited, multiple clinical trials have established the benefit of RAAS modulation in this population [88,89]. Recent work from our consortium further suggests that higher doses of angiotensin converting enzyme inhibitors (ACEI) are associated with improved survival in dogs at the initial onset of CHF [90].

Aldosterone breakthrough has been described in experimental models of HF, as well as in clinical cases of HF in dogs [91,92]. Moreover, circulating RAAS activity exhibits diurnal variations in both species; in dogs, feeding time is a key determinant of RAAS chronobiology, blood pressure, and renal electrolyte handling [9,12,13]. These natural oscillations have prompted efforts to time ACEI dosing to circadian rhythms, though the clinical benefit of chronotherapy in hypertension remains debated [93]. Overall, the cross-species conservation of RAAS physiology and its role in HF pathophysiology provide a strong rationale for studying the PK and PD of RAAS-modulating therapies in canine experimental models and naturally occurring CHF [13,94–97].

Another conserved mechanism in canine and human HF is the non-osmotic activation of arginine vasopressin (AVP, also known as antidiuretic hormone (ADH), which is primarily driven by arterial underfilling secondary to reductions in stroke volume and cardiac index. In dogs, this has been shown in preclinical and clinical stages of HF [98,99]. The inverse association between ADH and serum chloride concentrations in canines further supports non-osmotic neurohormonal activation, consistent with earlier observations in human patients with HF [100,101].

MMVD in Humans and Dogs

Degenerative MMVD, often presenting as mitral prolapse, is the leading indication for mitral valve repair or replacement in humans, affecting 2-3% of the general population with prevalence increasing steeply with age [102]. In dogs, MMVD is the most prevalent acquired heart disease, accounting for 75% of canine CHF [80]. Canine MMVD follows a similar age dependency but also exhibits marked breed predispositions: in small-to-medium breeds, prevalence in older dogs is commonly reported at 30-70%, reaching up to 90% in Cavalier King Charles Spaniels by approximately 10 years of age [103]. These naturally occurring cases represent a large resource to study disease pathomechanisms, natural history, and therapeutic response.

Comparative anatomic studies have identified multiple structural parallels between the canine and the human mitral valve, including annulus architecture, aorto-mitral continuity, and chordal network [104]. At the tissue level, MMVD is characterized by leaflet thickening, disruption of the extracellular matrix, and myofibroblast activation, ultimately leading to mitral regurgitation in both species [105]. An important distinguishing feature, however, is that canine MMVD is generally regarded as a relatively homogeneous disease, whereas two main clinicopathological phenotypes

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exist in humans; among these, Barlow's disease most closely resembles canine MMVD [81]. Beyond this epidemiological and histopathological overlap, canine and human MMVD share conserved molecular pathways driving valve remodeling, including serotonergic signaling through the 5-HT_2B receptor [106], which intersects with core profibrotic programs such as TGF-β [105].

Genetic Cardiomyopathies in Humans and Dogs

Dilated cardiomyopathy is a prevalent cause of HF in humans, with over 60 associated genes and a significant familial component [107,108]. Clinical symptoms may only appear after a prolonged subclinical (asymptomatic) phase [109]. Canine DCM has comparable heritability, with breed-associated clustering and autosomal inheritance reported in several breeds (e.g., Great Danes, Doberman Pinschers) [110]. In Doberman Pinschers, DCM follows a two-stage course in which the asymptomatic phase closely resembles the subclinical stage of human DCM [81]. A key translational parallel with human DCM is the high arrhythmic risk: approximately one-third of Doberman Pinschers are reported to die suddenly during the occult phase of the disease. Beyond sudden cardiac arrest, both human and canine DCM typically present with syncope, exercise intolerance, arrhythmias, and pulmonary congestion [111]. Common biological pathways governing sarcomeric structure and regulation (e.g., titin), as well as RNA-splicing control (e.g., RBM20) have been implicated in dogs and humans. RNA-binding motif protein 20 (RBM20) is a cardiac splicing factor involved in arrhythmogenic DCM in humans and in a naturally occurring, early-onset DCM phenotype in Standard and Giant Schnauzers carrying a 22-bp frameshift deletion [112,113]. RBM20 regulates alternative splicing of titin (TTN) and a broader network of cardiac transcripts. Accordingly, RBM20 cardiomyopathy is characterized by mis-splicing programs with downstream effects that include calcium-handling pathways, consistent with heightened arrhythmic susceptibility observed in RBM20-associated disease. Comparative genetic studies in predisposed breeds have isolated additional candidate loci (including *RNF207* and *PRKAA2*) of potential relevance to human DCM [114].

Arrhythmogenic right ventricular cardiomyopathy (ARVC) typically presents in adulthood and may be exacerbated by training or exercise [115]. It is primarily a disease of the cardiac desmosome, the intercellular junction complex that provides mechanical coupling between cardiomyocytes [116]. Multiple genetic mutations have been identified in desmosome-related genes, with incomplete penetrance indicating contributions from both genetic and environmental factors. In well-phenotyped cohorts, a causal variant is typically identified in approximately 50-60% of patients [117]. The clinical presentation, natural history, and histopathology of canine ARVC closely overlap with those of the human disease, including ventricular tachyarrhythmias of right ventricular origin, syncope, progression to CHF in a subset of patients, and sudden cardiac death [118]. In dogs, there is a clear breed predisposition to ARVC, with prevalence reaching 25% in Boxers [119]. Notably, most of the canonical human ARVC genes have not been identified as primary drivers in this breed; instead, the main canine-associated variant is an 8-bp deletion in striatin (*STRN*] associated with reduced STRN expression [120,121]. Despite these differences, both species share strong pathophysiological features, characterized by desmosomal disruption and impaired cell-cell adhesion, which promote cardiomyocyte loss and culminate in the defining lesion of fibro-fatty myocardial replacement.

From Isolated Cardiac Diseases to the Cardiorenal Metabolic Axis

Cardiovascular disease, chronic kidney disease, type 2 diabetes, and obesity are now understood to share interconnected pathophysiological mechanisms: a concept now formalized by the American Heart Association through the Cardiovascular-Kidney-Metabolic health paradigm [122]. This framework creates an opportunity for preclinical research in dogs, enabling longitudinal, within-subject profiling of multiple biological variables, such as blood pressure, serum chemistry, lipoprotein analysis, glucose/insulin levels, RAAS peptides, oxidative stress markers, and serum/urine/fecal metabolomics. Despite unique features in lipid metabolism, dogs have been

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extensively used to study metabolic obesity, diabetes, dyslipidemia, and their response to therapeutic interventions. In a comprehensive analysis published in the *Journal of Lipid Research*, dogs were identified as the second most translatable model (after non-human primates) among 24 animal species for studying dyslipidemia and related pharmacological agents in humans [123]. More recently, our consortium demonstrated that feeding healthy beagles an isocaloric Western diet induced features of metabolic syndrome, including elevated blood pressure, increased fasting glucose, a shift from HDL- to LDL-cholesterol, and changes consistent with renal-metabolic coupling [124].

Expanding the Translational Landscape

The translational relevance of the canine model extends well beyond oncology and cardiology, encompassing safety pharmacology, gastrointestinal, ophthalmic, neurologic, and endocrine disorders that share conserved pathophysiological features with their human counterparts. A defining strength of the dog as a translational model lies in its ability to capture the complex, systems-level nature of human diseases; an area where rodent models typically fall short.

Dogs also exhibit organ-specific physiological features that closely parallel human biology. The canine heart recapitulates the electrophysiology of the human heart, including ventricular repolarization, ion channel composition (e.g., human ether-a-go-go related gene (hERG) potassium (K+) channel activity), and QT interval dynamics [125]. These similarities justify the long-standing (and continued) use of dogs in safety pharmacology, where murine models often fail to predict human-relevant proarrhythmic liabilities, such as QT-interval prolongation [126].

When microbial gene catalogs from the mouse, pig, and dog were mapped onto a human gut gene catalog, only about 20% of mouse genes and 33% of pig genes overlapped, compared with approximately 63% of dog genes [8]. The degree of microbiomic overlap suggests that pet dogs may serve as a more physiologically relevant model than rodents for studying diseases involving the gut-brain axis (such as Alzheimer's) [127,128]. Similarly, the canine digestive system bears a closer resemblance to that of humans in terms of luminal pH and intestinal transit time [129]. These similarities have direct implications for predicting oral absorption and bioavailability of therapeutic drugs. Recent PK studies have extended these observations across the full ADME (Absorption, Distribution, Metabolism, Excretion) continuum, underscoring the relevance of canines for modeling gastric emptying, tissue blood flows, or the expression and activity of key metabolic enzymes and transporter proteins that govern drug metabolism and excretion [130,131]. However, important species differences have also been identified [131,132], including specific conjugation pathways, bile acid pools, and renal organic anion transport. This knowledge helps delineate the circumstances under which interspecies extrapolation is justified and when *in silico*-based adjustments are warranted. Overall, the dog is a well-characterized preclinical species for physiologically-based PK modeling, enabling more accurate predictions of human systemic exposure than rodent models alone [133].

In ophthalmology, the dog is an established large-animal model for inherited retinal degeneration because many canine retinal diseases occur spontaneously, are genetically defined, and closely parallel human retinal disorders. Studies in dogs have helped define inheritance patterns and causal mutations and establish natural-history metrics for disease staging. This work has also enabled the evaluation of therapeutic strategies ranging from neuroprotection to gene augmentation and mutation-specific knockdown or replacement approaches [134]. Comparative studies on the ocular surface have similarly demonstrated that dogs closely recapitulate the anatomy and physiology of the human eye. Cross-species parallels include ocular dimensions, lacrimal gland architecture and drainage, blink rate, and tear volume and composition [135]. Dogs also naturally develop ocular surface diseases that overlap with human clinical phenotypes [136]. Combined with the ability to safely and repeatedly sample tears for PK and biomarker analyses, these features support the use of the dog for translational and pharmacological research on the ocular surface [137–140].

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Neurologic disorders provide another important area in which the dog has translational value. Canine epilepsy encompasses a broad etiologic spectrum, including genetic forms and symptomatic epilepsies secondary to trauma, infection, or neoplasia, thereby recapitulating the major categories of human epilepsy. Accordingly, canine epilepsy has been used to study disease mechanisms, clinical heterogeneity, and responses to antiepileptic drugs [141]. Canine cognitive dysfunction serves as a spontaneous model of age-related cognitive decline and early Alzheimer-like neurodegeneration. Affected dogs develop behavioral impairment accompanied by neuropathologic changes, particularly Aβ-related pathology, that parallel early-stage human disease [127]. Dementia and cognitive dysfunction are estimated to affect approximately 10% of adults aged ≥65 years in humans [142] and 14.2% of dogs aged ≥8 years [143]. The aging process in dogs is marked by a gradual decline in multiple organ systems. "Inflammaging", a chronic, low-grade inflammatory state linked to frailty, multiple illnesses, and death, occurs spontaneously in dogs and closely resembles the aging process in humans [144]. This framework is exemplified by the Dog Aging Project, a large longitudinal cohort established to define how genetic, environmental, and lifestyle factors shape aging trajectories in companion dogs [145].

Cushing's disease is a severe endocrine disorder caused by a pituitary neuroendocrine tumor secreting excessive ACTH, which leads to overstimulation of the adrenal glands and elevated cortisol production [146]. Prolonged exposure to excess cortisol has major adverse effects on health and is associated with increased risk of stroke, diabetes, obesity, depression, anxiety, and a markedly higher likelihood of death due to cardiovascular disease and cancer [147,148]. In dogs, Cushing's disease occurs far more frequently than in humans, with an incidence of approximately 1 in 500 compared with about 10 in 1 million in people [149]. More than 80% of canine cases that are caused by ACTH-secreting pituitary neuroendocrine tumors develop clinical manifestations similar to those seen in human patients, including hypertension, obesity, diabetes mellitus, myopathy, and dermatologic changes [150,151]. Because of these similarities, canine Cushing's disease represents an excellent naturally occurring model for investigating targeted therapies that may benefit both veterinary patients and humans affected by this rare disorder.

Enabling Technologies for Cross-Species Translation

Transcriptomics Revolution

The advent of next generation sequencing (NGS) and the concurrent decline in sequencing costs have driven an exponential increase in genomic and transcriptomic data generation. Cutting-edge platforms including scRNA-seq have contributed to the creation of human atlases which combine hundreds of thousands of cells to identify tissue specific genes and analyze cell states and lineage histories [152]. Because scRNA-seq is species-agnostic, non-human atlases have been generated across a range of tissues and non-model organisms, including tigers, bats, dogs, and cats [153]. This technology has allowed canine scRNA-seq and the creation of atlases spanning healthy and diseased states across multiple tissue types and immune cell populations [154–156]. Advancing immunotherapeutic development across species requires such cross-species molecular insights. Comparative scRNA-seq of human and canine NK cells revealed conserved cell proportions and interactions, while also identifying key species-specific differences, notably the absence of a reliable cell surface marker such as CD56 in canine NK cells [155]. Although nearly every human tissue and cancer type has been profiled by scRNA-seq, the resolution of complex cell-cell interactions remains incomplete; a gap that is critical to disease understanding.

More recently, spatial biology platforms enabling spatially resolved transcriptomics and proteomics have begun to complement single-cell approaches, preserving tissue context that is lost in dissociation-based methods. Most novel platforms are initially developed and validated for human and rodent applications, with species-adapted panels and reagents becoming available for other species only after a considerable lag. However, recent advancements now enable the use of reduced animal probe sets (GeoMx) or species-agnostic sequencing-based platforms (Visium and Stereo-seq).

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These platforms have only recently been applied in veterinary medicine, with probe-based platforms such as GeoMx used in canine oral squamous cell carcinoma [157] and osteosarcoma [158]. Species-agnostic sequencing platforms have also been used in dogs including Stereo-seq in a cognitive dysfunction study [159], Visium for vein grafts [160] and osteosarcoma [161]. Within osteosarcoma, scRNA-seq and Visium spatial transcriptomics between human, patient-derived xenograft, mouse, and canine samples revealed that canine tumors showed strong concordance across anatomical sites [161]. Despite the expanding availability of these platforms, key challenges remain, including the complexity of large-scale data analysis, limited bioinformatic capacity, and barriers to data sharing and dissemination.

New Approach Methodologies - Organoids

Advances in transcriptomics and spatial biology have transformed tissue characterization and deepened our understanding of disease mechanisms. Complementing these molecular insights, predictive *in vitro* models are essential for assessing drug efficacy and safety and supporting personalized medicine applications. Conventional *in vitro* systems, including 2D cultures, have driven significant progress in biomedical research; however, their limited predictive capacity, combined with growing ethical imperatives to reduce animal use, has motivated the development of New Approach Methodologies (NAMs), which encompass both *in vitro* and *in silico* platforms [162]. Among these, 3D spheroid cultures represent an incremental advance, introducing architectural complexity to otherwise clonal 2D systems [163].

Stem cell cultures encompass embryonic, adult induced pluripotent stem cells (iPSC), and adult stem cells. iPSC cultures were first described in 2006 [164], followed shortly by adult stem cell-derived organoids grown in a 3D matrix, together ushering in a new era of *in vitro* technologies [165]. Since then, human organoids have been generated for a variety of tissue types, diseases, and tumors [166,167], while veterinary organoid models are rapidly being established [168–170]. For example, canine organoid models have been established for mammary tumors that retain key driver mutations in *PIK3CA* and *TP53*, providing a comparative model for human breast cancer [171], while canine urothelial carcinoma-derived organoids exploit the high prevalence of canine MIBC to model the muscle-invasive form of the human disease [172]. Veterinary iPSC lines have trailed in development because of '*low reprogramming efficiency, lack of standardization, unique epigenetic barriers, and ambiguous pluripotency states*' [173]. However, canine iPSCs have successfully been generated using various viruses and starting cell types including fibroblasts, peripheral blood mononuclear cells (PBMCs), urine, and adipose tissue [173].

Although adult stem cell and tissue-derived organoids have revolutionized stem cell biology in the context of personalized medicine, they typically recapitulate only the epithelial component of the tissue while lacking other critical cell types including immune cells, fibroblasts, and vasculature (**Fig.2**] [166]. Co-culture protocols that combine organoids with additional cell types are emerging, though significant methodological challenges remain. Reports in human medicine exist, for example in gastric cancer using dendritic cells (DCs), CD8+ T cells, and myeloid-derived suppressor cells (MDSCs) [174], as well as with pancreatic ductal adenocarcinoma [175]. Successfully incorporating multiple cell types requires additional controls, complex media, and specialized readouts to account for the increased heterogeneity in the culture.

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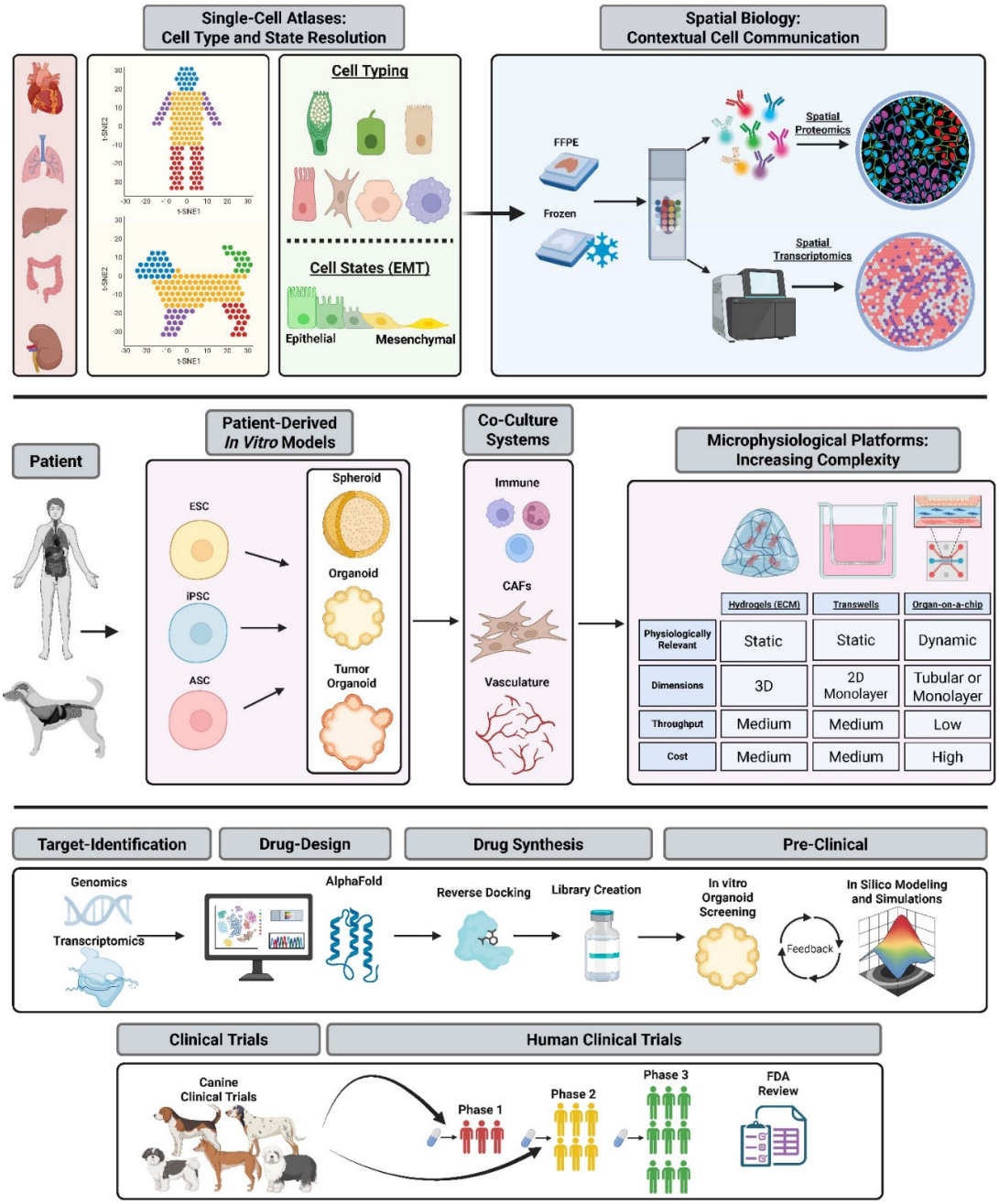

Figure 2. Integrated multi-omic tissue characterization, personalized in vitro modeling, and comparative human-canine translational pipeline for drug discovery. (Top) Single-cell RNA-seq atlases define cell types and cell states, including epithelial-to-mesenchymal transition, in human and canine tissues. Spatial profiling of formalin-fixed paraffin-embedded and frozen tissue sections complements dissociation-based approaches by preserving spatial context through spatial transcriptomics and proteomics. (Middle) Patient-derived stem cells: embryonic, induced pluripotent, and adult stem cells give rise to spheroids, organoids, and tumor organoids. Multicellular complexity is increased through co-culture with immune cells, cancer-associated fibroblasts, and vasculature, and through culture in platforms of increasing physiological relevance, including hydrogel-based 3D matrices, Transwell inserts, and dynamic organ-on-a chip/microphysiological systems. (Bottom) A translational drug development pipeline integrating computational target identification (genomics, transcriptomics, AlphaFold-based structure prediction, reverse docking), chemical library creation, in vitro organoid screening, and in silico perturbation modeling. Canine clinical trials in dogs with spontaneous disease

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serve as a translational bridge, informing dose selection, biomarker strategies, and go/no-go decisions for human Phase 1-3 trials and regulatory review. Abbreviations: ASC, adult stem cell; CAF, cancer associated fibroblast; EMT, epithelial-to-mesenchymal transition; ESC, embryonic stem cell; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; iPSC, induced pluripotent stem cell; scRNA-seq, single-cell RNA sequencing. Figure adapted from images created with BioRender.com.

Organoids can be cultured in a variety of platforms ranging from 3D extracellular matrices, whether animal-derived (Matrigel), plant-derived, or plastic, to bioreactors that agitate the media and can increase culture volume and cell yield for industrial applications. In their native 3D format, organoids expand rapidly; however, access to both the luminal and basal compartments of the epithelium is precluded. Their complex three-dimensional architecture also complicates imaging and quantitative analysis [176]. Organoids can also be converted into 2D monolayers on Transwell inserts which enable permeability assays, drug screening, and monitoring of tight junctions. This technique has successfully been used for both human [177] and canine [178] organoids. Although static systems offer higher throughput and lower cost, there is growing interest in dynamic organ-on-a-chip platforms, some of which integrate microfluidic flow to better recapitulate tissue-level physiology (e.g., Emulate, Mimetas, and Alveolix) [179]. These platforms aim to create more physiologically relevant *in vitro* systems, such as models of renal epithelial cells cultured in parallel with endothelial cells and monocytes [180]. Despite broad interest across academia, industry, and regulatory agencies, adopting these platforms remains challenging owing to high costs, technical complexity, the need for specialized expertise, and reduced throughput relative to conventional systems. Bioprinting represents another emerging platform for fabricating physiologically relevant, multi-cellular constructs, though it has not yet been applied to veterinary organoid systems [181].

The predictive potential and use of NAMs in personalized medicine remains significant. While genetic engineering has been used extensively in human organoids, canine mammary tumor organoids are, to our knowledge, the only ones to have been genetically engineered using CRISPR/Cas9 [171]. Despite the growing breadth of NAMs, only a limited number of organoid-informed clinical trials have been initiated to date [166]. This paradigm has not yet been implemented in veterinary medicine, likely owing to cost constraints and limited infrastructure. Nevertheless, the mechanistic insights afforded by veterinary organoids, combined with the large population of naturally diseased patients, represent a compelling and largely untapped opportunity to accelerate therapeutic development in both human and veterinary medicine (**Fig.3**).

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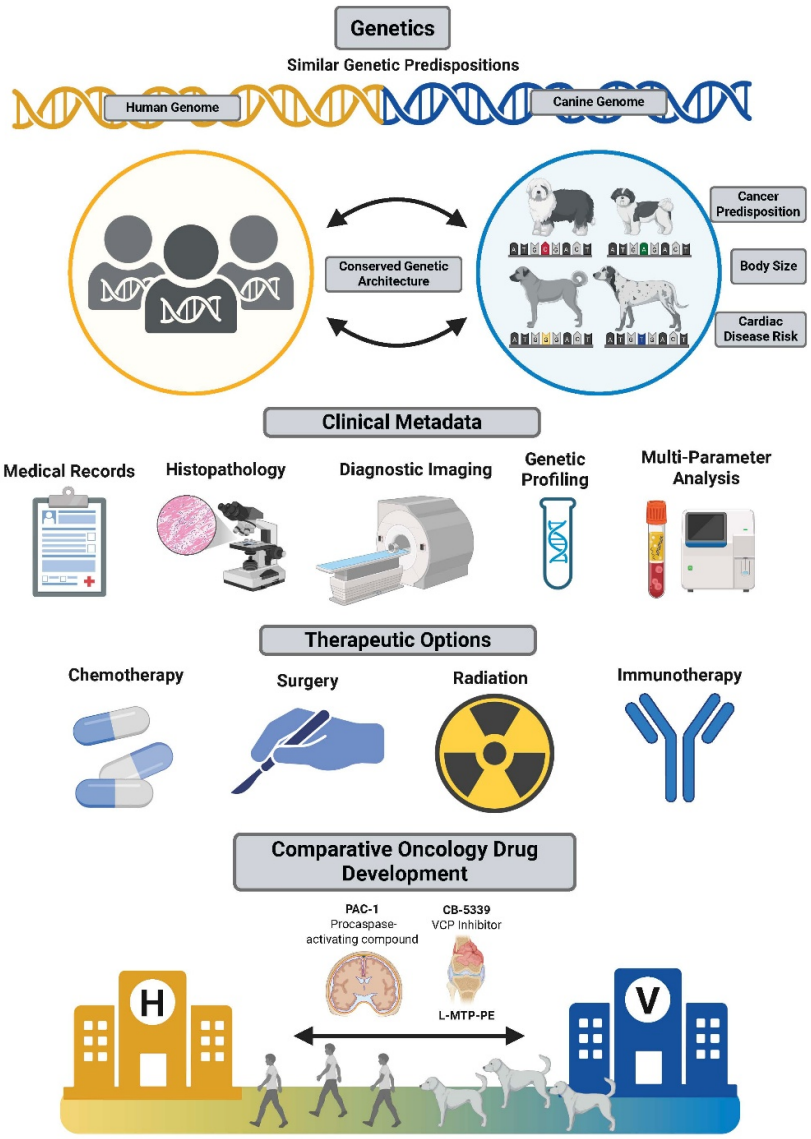

Figure 3. Comparative genetics, clinical metadata integration, and translational drug development from spontaneous canine cancer models to human therapeutics. (Top) Humans and dogs share similar genetic predispositions. Selective breeding has produced extensive breed-specific diversity, with naturally occurring genetic variation that can be harnessed for comparative disease studies. (Middle) Clinical metadata collected in parallel across species, including medical records, histopathology, diagnostic imaging, genetic profiling, and multiplex biomarker analysis, supports shared therapeutic modalities such as chemotherapy, surgery, radiation, and immunotherapy. (Bottom) Translational drug development: data generated in veterinary patients (V) with spontaneous cancer can directly inform human (H) drug development and vice versa, as exemplified by agents such as PAC-1, CB-5339, and L-MTP-PE. Abbreviations: CB-5339, valosin-containing protein inhibitor; H, human medicine; L-MTP-PE, liposomal muramyl tripeptide phosphatidylethanolamine; PAC-1, procaspase-activating compound 1; V, veterinary medicine. Figure adapted from images created with BioRender.com.

Quantitative Tools for Translation: PK/PD, QSP, and Model-Informed Decisions

Quantitative pharmacology provides a generalizable framework for translating preclinical findings from animal models and cell-based assays to support model-informed predictions of human drug exposure, efficacy, and safety. It achieves this by explicitly linking drug exposure, mode of action, and biological responses [182]. At its core, PK/PD modeling uses drug concentration time-

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courses as the driving force of the pharmacological effect(s) [183]. This exposure-response relationship can be modeled *empirically* or, when supported by sufficient biological knowledge and data, *mechanistically*, providing a stronger foundation for cross-species extrapolation. In this paradigm, prediction of human response is no longer defined by simple "dose equivalence" (e.g., derived from empirical scaling between species). Instead, it is established by modeling systemic and, where feasible, target-site exposure profiles, and demonstrating concordant drug exposure-response relationships between preclinical species and humans.

Quantitative systems pharmacology (QSP) builds on this foundation by incorporating mechanistic representations of disease pathophysiology and drug effects within the context of the underlying biological systems being modeled [184]. It was formally defined by the QSP Workshop Group of the NIH (2011) as *'(…) an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs'.*

Practically, QSP models integrate multiscale data, ranging from molecular interactions (e.g., target engagement) and cellular signaling to tissue remodeling and organ function, to evaluate how therapeutic responses can propagate through complex biological systems.

Collectively, PK/PD and QSP modeling approaches facilitate a translational paradigm shift away from traditional heuristic interspecies comparisons, such as simple allometric dose scaling, toward mechanism-based, exposure-driven quantitative approaches that enable reproducible predictions, rigorous hypothesis testing, and scalable extrapolation of efficacy and safety across species. These tools are being increasingly used for the rational selection of drug doses, dosing schedules, and drug combinations, thereby informing and optimizing the design of first-in-human (FIH) clinical trials [185]. As such, they are now integral to modern model-informed drug development, providing an essential foundation for translating preclinical data into actionable clinical strategies [186].

Limitations of the Canine Model

Despite the broad translational potential of spontaneous canine disease models, their use in translational research is constrained by both biological and methodological limitations. Biological constraints, discussed in preceding sections, include interspecies differences in xenobiotic disposition, gastrointestinal, and renal physiology [131], and immune-cell activation and cytokine responses, among others [187]. Moreover, because individual breeds carry distinct mutational profiles, any single breed's ability to model the genetic diversity of human populations is inherently limited [18]. Beyond these biological constraints, methodological considerations are equally important. Compared with rodent studies, canine trials are generally more costly and logistically demanding, owing in part to longer study durations and greater drug requirements [6].

An additional challenge in canine translational research is the marked heterogeneity of the patient population. Companion dogs vary substantially in breed, body size, sex, age, environment, and disease risk, and although stringent eligibility criteria can reduce this variability, such restrictions may further complicate recruitment and reduce cohort size [145]. Combined with the difficulty of recruiting sufficient numbers of eligible client-owned patients, these factors contribute to studies that often suffer from low statistical power, inconsistent endpoint definitions, incomplete reporting, and, in some settings, owner-dependent outcome assessments [188]. Data quality in canine translational research is poised to improve through strengthened trial oversight and reporting standards, expanded access to clinically annotated biobanked canine samples, and broader adoption of molecular profiling approaches. In particular, the increasing use of NGS and other genomic, transcriptomic, and proteomic methods is narrowing the technical gap between canine and human studies, although important limitations remain, including the incomplete availability of validated canine-specific reagents [4]. The development of coordinated infrastructures such as the COTC has further strengthened the field by providing the framework needed to integrate naturally occurring canine diseases into the development of human drugs, devices, and imaging techniques [16].

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Ethical considerations are also paramount in studies involving client-owned dogs, as participation depends on informed owner consent. Owners must be clearly informed about how knowledge gained through trial enrollment may benefit companion animals and humans broadly, even when the trial is not designed to provide a direct therapeutic benefit to their individual pet [189].

Future Directions: Toward "One Medicine"

Conventional preclinical models too often fail to predict human outcomes, resulting in high clinical trial attrition and increasing development timelines and costs. An integrated comparative canine clinical trials platform, one that couples mechanistic biomarker discovery with therapeutic evaluation, directly addresses this gap by enabling rapid proof-of-concept studies in immunocompetent hosts with spontaneous disease. While human and murine atlases have expanded rapidly, enabling high-resolution, cell-resolved mapping of cellular states, lineage trajectories, and microenvironmental niches across tissues and disease contexts [190,191], comparable resources in companion animals remain sparse [154,192]. The expanding accessibility of NGS technologies creates an opportunity to generate comprehensive genetic and molecular datasets from dogs, enabling the construction of multi-modal, cross-species atlases. In particular, single-cell RNA-seq, combined with proteomics and now spatial transcriptomics, provide an opportunity to resolve the architecture of canine tissues and tumors *in situ*, link molecular programs to histologic context, and establish reference frameworks that align organoids with matched primary tissues and clinically annotated specimens across species [193]. Critically, as we build these resources, there is a need to define harmonized protocols for tissue procurement, processing, and annotation, enabling rigorous comparisons across species.

As NGS and spatial biology tools become increasingly accessible, these approaches enable data-driven identification of disease-relevant targets directly from patient tissues, capturing context-dependent cell states, pathway activation, and microenvironmental influence. These targets can then be mapped to protein-coding sequences and corresponding three-dimensional structures predicted at scale using AI-enabled structure-prediction platforms such as AlphaFold [194]. Structure-based docking and virtual screening can subsequently accelerate the identification of candidate ligands using "lock-and-key" principles, substantially narrowing the search space for subsequent medicinal chemistry and experimental validation.

In a revisited drug development paradigm, PK, efficacy, and safety data generated in canine patients with naturally occurring disease can be leveraged to streamline pharmaceutical research and development, support early go/no-go decisions, and de-risk translation by informing dose selection, exposure targets, and biomarker strategies for first-in-human studies [3]. Patient-derived canine organoids can provide a unique intermediate validation layer, enabling functional assessment of target engagement and PD surrogate endpoints of efficacy in model systems that retain key features of disease-relevant architecture, cellular diversity, and inter-patient heterogeneity. Within this framework, candidate ligands derived from structure-based docking and virtual screening can be triaged *in vitro* using canine organoids to identify the most promising compounds, thereby reducing and refining the set of candidates advancing to *in vivo* evaluation. When integrated with quantitative modeling frameworks that scale exposure-response relationships across species, these data have the potential to improve the probability of success in human clinical trials by strengthening translational dose selection and reducing late-stage attrition, particularly in Phase II. Grounded in One Health principles, this integrated approach has the potential to deliver safe and effective therapeutic innovations that benefit both humans and their companion animals.

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Declaration of Assistive AI in Scientific Writing

ChatGPT-5.2 (OpenAI, 2026), Grok 4.2 Beta (xAI, 2026), and Claude Opus 4.6 (Anthropic, 2026) were used to support the writing process. Their use was exclusively limited to improving grammar and enhancing readability, without generating new data, analyses or conclusions. Use of AI assistance is disclosed in line with prevailing authorship and publication-ethics guidance from the *Committee on Publication Ethics* (COPE[1]) and the *International Committee of Medical Journal Editors* (ICMJE[2]). All AI-generated text was reviewed and edited thoroughly by the authors, who take full responsibility for the final content of the publication.

Author Contributions: All authors contributed equally to the development, drafting, editing, and critical revision of the manuscript, and all authors have read and approved the final version.

Conflict of Interest: Jonathan Mochel is a co-founder of 3D Health Solutions Inc., a small biotechnology company specializing in the development of animal-derived organoids for drug testing. Christopher Zdyrski is the Director of Research and Product Development at 3D Health Solutions.

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