Communication

Leveraging Canine Disease Models in Pharmaceutical Sciences: A One Health Path to Parallel Drug Development

Jonathan P. Mochel *

Posted Date: 28 January 2026

doi: 10.20944/preprints202504.0325.v2

Keywords: one health; comparative medicine; canine models; in silico in vitro modeling

Communication

Leveraging Canine Disease Models in Pharmaceutical Sciences: A One Health Path to Parallel Drug Development

Jonathan P. Mochel

Precision One Health Initiative, Department of Pathology, University of Georgia College of Veterinary Medicine, 30602 Athens, GA, USA; jpmochel@uga.edu

Abstract

Despite recent advances in biomedical research, translating preclinical findings into effective therapies remains a critical challenge, particularly for complex diseases such as cancer and neurodegenerative disorders. Spontaneous diseases in companion animals, especially dogs, provide a powerful, yet underutilized, bridge to human medicine. Naturally occurring cancers, neurodegenerative disorders, and cardiovascular, renal, and ocular diseases in dogs recapitulate many of the key biological and clinical features observed in humans, including shared pathophysiologic mechanisms, heterogeneous disease trajectories, and clinically relevant patterns of response and resistance to therapy. These models allow for the evaluation of novel therapies, including immunotherapies and gene-based treatments, in immunologically competent systems. The integration of patient-derived organoids with physiologically based pharmacokinetic (PBPK) modeling provides a powerful framework for linking cellular-level drug responses to whole-organism exposure profiles, thereby enhancing mechanistic understanding of therapeutic action and improving the accuracy of translational predictions across species. To fully realize this potential, sustained investment in enabling infrastructure, standardized biobanking, and interdisciplinary training is essential to support scalable model generation, rigorous characterization, and broad dissemination across the translational research community.

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 models, while foundational to basic biomedical research, often fail to capture the biological complexity and heterogeneity of human disease 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

 doi:10.20944/preprints202504.0325.v2

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 studies and human clinical trials.

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 heterogenetity of human diseases. Unlike induced rodent models, where diseases are often artificially 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 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 of HF pathophysiology 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 its therapeutic modulation remains a cornerstone 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 that inform therapeutic management in both species. Likewise, comparative studies on the ocular surface have shown that dogs closely resemble the anatomy and physiology of the human eye (Sebbag and Mochel, 2020). Numerous studies have established the dog as a valuable model for advancing human ophthalmic research, particularly in understanding tear film dynamics. 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.

 doi:10.20944/preprints202504.0325.v2

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 are miniaturized, self-organizing tissue models derived from stem cells that retain key functional and structural features of their organ of origin. 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, 2025) 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 (Martinez et al., 2025). A relatively recent advance in organoid technology is the development of organoid-on-a-chip platforms, which further enhance the physiological relevance of conventional static organoid cultures. These systems integrate controlled microfluidic flow to deliver nutrients and oxygen, remove metabolic waste, and impose physiologically relevant shear stress, thereby improving tissue viability, functional maturation, and experimental control relative to static conditions. Animal-derived organoids are increasingly being coupled to microfluidic organoid-on-chip prototypes (e.g., OrganoidChip) to support controlled handling and immobilization and to enable higher-throughput functional imaging under standardized conditions (Moshksayan et al., 2023, 2025).

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)

 doi:10.20944/preprints202504.0325.v2

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. Spontaneously occurring disease in dogs represents more than a surrogate for human pathology; it is a distinct and powerful translational resource that captures biological complexity, disease heterogeneity, and clinically relevant therapeutic responses under real-world conditions. The

 doi:10.20944/preprints202504.0325.v2

scientific and clinical impact of this resource will ultimately be determined by the robustness of the experimental, computational, and organizational systems developed to support its rigorous characterization and integration into translational research pipelines.

Conclusion: One Health in Action

As the biomedical field increasingly adopts enabling technologies such as patient-derived organoid platforms and physiologically based pharmacokinetic (PBPK) modeling, the translational value of spontaneous canine disease models is further amplified by the ability to couple mechanistic, tissue-level interrogation with quantitative, whole-organism exposure–response prediction. These tools support mechanistic understanding of disease pathophysiology, 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 treating comparative research as peripheral and instead recognize it as a core pillar of modern translational science. Achieving this shift will require dedicated infrastructure, standardized biobanking and data-sharing ecosystems, interdisciplinary training, and sustained policy and funding support. Integrating spontaneous disease models in dogs is therefore not merely an incremental opportunity; it is a strategic necessity for advancing more predictive and mechanistically grounded therapeutic development, reducing reliance on less informative experimental systems, and strengthening the One Health continuum for both animal and human health.

Declaration of Assistive AI in Scientific Writing

ChatGPT-5.2 (OpenAI, 2025) was used to assist in drafting and improving the grammar of this manuscript. Its use was limited to enhancing readability and supporting the writing process, 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 by the authors, who take full responsibility for the final content of the publication.

References

1. **Ambrosini** YM, Park Y, Jergens AE, Shin W, Min S, Atherly T, Borcherding DC, Jang J, Allenspach K, Mochel JP, Kim HJ. Recapitulation of the accessible interface of biopsy-derived canine intestinal organoids to study epithelial-luminal interactions. PLoS One. 2020 Apr 17;15(4):e0231423. doi: 10.1371/journal.pone.0231423. PMID: 32302323; PMCID: PMC7164685.
2. **American Veterinary Medical Association**. (2008). *One Health: A new professional imperative* (One Health Initiative Task Force report). https://www.avma.org/sites/default/files/resources/onehealth_final.pdf.
3. **Atkins** CE, Keene BW, Brown WA, Coats JR, Crawford MA, DeFrancesco TC, Edwards NJ, Fox PR, Lehmkuhl LB, Luethy MW, Meurs KM, Petrie JP, Pipers FS, Rosenthal SL, Sidley JA, Straus JH. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. J Am Vet Med Assoc. 2007 Oct 1;231(7):1061-9. doi: 10.2460/javma.231.7.1061. PMID: 17916031.

[1] Committee on Publication Ethics. *COPE Core Practices*. COPE; 2017. Updated regularly. Available from: https://publicationethics.org

[2] International Committee of Medical Journal Editors. *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*. ICMJE; updated 2024. Available from: https://www.icmje.org

 doi:10.20944/preprints202504.0325.v2

4. **BENCH** (BENazepril in Canine Heart disease) Study Group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. J Vet Cardiol. 1999 May;1(1):7-18. doi: 10.1016/S1760-2734(06)70025-X. PMID: 19081317.
5. **Chandra** L, Borcherding DC, Kingsbury D, Atherly T, Ambrosini YM, Bourgois-Mochel A, Yuan W, Kimber M, Qi Y, Wang Q, Wannemuehler M, Ellinwood NM, Snella E, Martin M, Skala M, Meyerholz D, Estes M, Fernandez-Zapico ME, Jergens AE, Mochel JP, Allenspach K. Derivation of adult canine intestinal organoids for translational research in gastroenterology. BMC Biol. 2019 Apr 11;17(1):33. doi: 10.1186/s12915-019-0652-6. PMID: 30975131; PMCID: PMC6460554.
6. **Clevers** H. Modeling Development and Disease with Organoids. Cell. 2016 Jun 16;165(7):1586-1597. doi: 10.1016/j.cell.2016.05.082. PMID: 27315476.
7. **Coffman** M, Guillot E, Blondel T, Garelli-Paar C, Feng S, Heartsill S, Atkins CE. Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: The BEnazepril Spironolactone STudy (BESST). J Vet Intern Med. 2021 Jul;35(4):1673-1687. doi: 10.1111/jvim.16155. Epub 2021 May 24. PMID: 34028078; PMCID: PMC8295662.
8. **de Sousa** AA, Rigby Dames BA, Graff EC, Mohamedelhassan R, Vassilopoulos T, Charvet CJ. Going beyond established model systems of Alzheimer's disease: companion animals provide novel insights into the neurobiology of aging. Commun Biol. 2023 Jun 21;6(1):655. doi: 10.1038/s42003-023-05034-3. PMID: 37344566; PMCID: PMC10284893.
9. **Dow** S. A Role for Dogs in Advancing Cancer Immunotherapy Research. Front Immunol. 2020 Jan 17;10:2935. doi: 10.3389/fimmu.2019.02935. PMID: 32010120; PMCID: PMC6979257.
10. **European Medicines Agency**. (2020). EMA Regulatory Science to 2025. Strategic Reflection. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.
11. **Fatehullah** A, Tan SH, Barker N. Organoids as an in vitro model of human development and disease. Nat Cell Biol. 2016 Mar;18(3):246-54. doi: 10.1038/ncb3312. PMID: 26911908.
12. **Fuller** GA, Bicer S, Hamlin RL, Yamaguchi M, Reiser PJ. Increased myosin heavy chain-beta with atrial expression of ventricular light chain-2 in canine cardiomyopathy. J Card Fail. 2007 Oct;13(8):680-6. doi: 10.1016/j.cardfail.2007.05.006. PMID: 17923362.
13. **Gabriel** V, Zdyrski C, Sahoo DK, Dao K, Bourgois-Mochel A, Kopper J, Zeng XL, Estes MK, Mochel JP, Allenspach K. Standardization and Maintenance of 3D Canine Hepatic and Intestinal Organoid Cultures for Use in Biomedical Research. J Vis Exp. 2022 Jan 31;(179). doi: 10.3791/63515. PMID: 35156656.
14. **Garden** OA, Volk SW, Mason NJ, Perry JA. Companion animals in comparative oncology: One Medicine in action. Vet J. 2018 Oct;240:6-13. doi: 10.1016/j.tvjl.2018.08.008. Epub 2018 Aug 27. PMID: 30268334.
15. **Gordon** I, Paoloni M, Mazcko C, Khanna C. The Comparative Oncology Trials Consortium: using spontaneously occurring cancers in dogs to inform the cancer drug development pathway. PLoS Med. 2009 Oct;6(10):e1000161. doi: 10.1371/journal.pmed.1000161. Epub 2009 Oct 13. PMID: 19823573; PMCID: PMC2753665.
16. **Hammond** HH, Ames MK, Domenig O, Scansen BA, Yang NT, Wilson MD, Sunshine E, Brunk K, Masters A. The classical and alternative circulating renin-angiotensin system in normal dogs and dogs with stage B1 and B2 myxomatous mitral valve disease. J Vet Intern Med. 2023 May-Jun;37(3):875-886. doi: 10.1111/jvim.16687. Epub 2023 Mar 23. PMID: 36951394; PMCID: PMC10229370.
17. **Head** E. A canine model of human aging and Alzheimer's disease. Biochim Biophys Acta. 2013 Sep;1832(9):1384-9. doi: 10.1016/j.bbadis.2013.03.016. Epub 2013 Mar 23. PMID: 23528711; PMCID: PMC3937962.
18. **Hu** H, Gehart H, Artegiani B, LÖpez-Iglesias C, Dekkers F, Basak O, van Es J, Chuva de Sousa Lopes SM, Begthel H, Korving J, van den Born M, Zou C, Quirk C, Chiriboga L, Rice CM, Ma S, Rios A, Peters PJ, de Jong YP, Clevers H. Long-Term Expansion of Functional Mouse and Human Hepatocytes as 3D Organoids. Cell. 2018 Nov 29;175(6):1591-1606.e19. doi: 10.1016/j.cell.2018.11.013. PMID: 30500538.
19. **Jamei** M, Bajot F, Neuhoff S, Barter Z, Yang J, Rostami-Hodjegan A, Rowland-Yeo K. A mechanistic framework for in vitro-in vivo extrapolation of liver membrane transporters: prediction of drug-drug

 doi:10.20944/preprints202504.0325.v2

interaction between rosuvastatin and cyclosporine. Clin Pharmacokinet. 2014 Jan;53(1):73-87. doi: 10.1007/s40262-013-0097-y. PMID: 23881596; PMCID: PMC3889821.

20. **Khanna** C, Lindblad-Toh K, Vail D, London C, Bergman P, Barber L, Breen M, Kitchell B, McNeil E, Modiano JF, Niemi S, Comstock KE, Ostrander E, Westmoreland S, Withrow S. The dog as a cancer model. Nat Biotechnol. 2006 Sep;24(9):1065-6. doi: 10.1038/nbt0906-1065b. PMID: 16964204.
21. **Klinedinst** BS, Le ST, Larsen B, Pappas C, Hoth NJ, Pollpeter A, Wang Q, Wang Y, Yu S, Wang L, Allenspach K, Mochel JP, Bennett DA, Willette AA. Genetic Factors of Alzheimer's Disease Modulate How Diet is Associated with Long-Term Cognitive Trajectories: A UK Biobank Study. J Alzheimers Dis. 2020;78(3):1245-1257. doi: 10.3233/JAD-201058. PMID: 33252089; PMCID: PMC7895545.
22. **Knapp** DW, Glickman NW, Denicola DB, Bonney PL, Lin TL, Glickman LT. Naturally-occurring canine transitional cell carcinoma of the urinary bladder A relevant model of human invasive bladder cancer. Urol Oncol. 2000 Mar-Apr;5(2):47-59. doi: 10.1016/s1078-1439(99)00006-x. PMID: 21227289.
23. **Knapp** DW, Dhawan D, Ramos-Vara JA, Ratliff TL, Cresswell GM, Utturkar S, Sommer BC, Fulkerson CM, Hahn NM. Naturally-Occurring Invasive Urothelial Carcinoma in Dogs, a Unique Model to Drive Advances in Managing Muscle Invasive Bladder Cancer in Humans. Front Oncol. 2020 Jan 21;9:1493. doi: 10.3389/fonc.2019.01493. PMID: 32039002; PMCID: PMC6985458.
24. **LaLonde-Paul** D, Mouttham L; Dog Aging Project Consortium; Promislow DEL, Castelhano MG. Banking on a new understanding: translational opportunities from veterinary biobanks. Geroscience. 2023 Jun;45(3):1439-1450. doi: 10.1007/s11357-023-00763-z. Epub 2023 Mar 8. PMID: 36890420; PMCID: PMC10400517.
25. **LeBlanc** AK, Mazcko CN. Improving human cancer therapy through the evaluation of pet dogs. Nat Rev Cancer. 2020 Dec;20(12):727-742. doi: 10.1038/s41568-020-0297-3. Epub 2020 Sep 15. PMID: 32934365.
26. **Lin** Z, Gehring R, Mochel JP, Lavé T, Riviere JE. Mathematical modeling and simulation in animal health - Part II: principles, methods, applications, and value of physiologically based pharmacokinetic modeling in veterinary medicine and food safety assessment. J Vet Pharmacol Ther. 2016 Oct;39(5):421-38. doi: 10.1111/jvp.12311. Epub 2016 Apr 17. PMID: 27086878.
27. **Lombardo** T, Dotti S, Villa R, Cinotti S, Ferrari M. Veterinary biobank facility: development and management for diagnostic and research purposes. Methods Mol Biol. 2015;1247:43-60. doi: 10.1007/978-1-4939-2004-4_4. PMID: 25399087.
28. **Martinez** MN, Mochel JP, Toutain PL. Evolving value and validity of animal models in veterinary therapeutic research: Impact of scientific progress. Eur J Pharm Sci. 2025 Jul 1;210:107111. doi: 10.1016/j.ejps.2025.107111. Epub 2025 Apr 24. PMID: 40286991.
29. **Mochel** JP, Peyrou M, Fink M, Strehlau G, Mohamed R, Giraudel JM, Ploeger B, Danhof M. Capturing the dynamics of systemic Renin-Angiotensin-Aldosterone System (RAAS) peptides heightens the understanding of the effect of benazepril in dogs. J Vet Pharmacol Ther. 2013 Apr;36(2):174-80. doi: 10.1111/j.1365-2885.2012.01406.x. Epub 2012 May 8. PMID: 22568394.
30. **Mochel** JP, Danhof M. Chronobiology and Pharmacologic Modulation of the Renin-Angiotensin-Aldosterone System in Dogs: What Have We Learned? Rev Physiol Biochem Pharmacol. 2015;169:43-69. doi: 10.1007/112_2015_27. PMID: 26428686.
31. **Mochel** JP, Fink M, Peyrou M, Soubret A, Giraudel JM, Danhof M. Pharmacokinetic/Pharmacodynamic Modeling of Renin-Angiotensin Aldosterone Biomarkers Following Angiotensin-Converting Enzyme (ACE) Inhibition Therapy with Benazepril in Dogs. Pharm Res. 2015 Jun;32(6):1931-46. doi: 10.1007/s11095-014-1587-9. Epub 2014 Dec 2. PMID: 25446774.
32. **Mochel** JP, Teng CH, Peyrou M, Giraudel J, Danhof M, Rigel DF. Sacubitril/valsartan (LCZ696) significantly reduces aldosterone and increases cGMP circulating levels in a canine model of RAAS activation. Eur J Pharm Sci. 2019 Feb 1;128:103-111. doi: 10.1016/j.ejps.2018.11.037. Epub 2018 Nov 30. PMID: 30508581.
33. **Mochel** JP, Ekker SC, Johannes CM, Jergens AE, Allenspach K, Bourgois-Mochel A, Knouse M, Benzekry S, Wierson W, LeBlanc AK, Kenderian SS. CAR T Cell Immunotherapy in Human and Veterinary Oncology: Changing the Odds Against Hematological Malignancies. AAPS J. 2019 Apr 8;21(3):50. doi: 10.1208/s12248-019-0322-1. PMID: 30963322.

 doi:10.20944/preprints202504.0325.v2

34. **Moshksayan** K, Harihara A, Mondal S, Hegarty E, Atherly T, Sahoo DK, Jergens AE, Mochel JP, Allenspach K, Zoldan J, Ben-Yakar A. OrganoidChip facilitates hydrogel-free immobilization for fast and blur-free imaging of organoids. Sci Rep. 2023 Jul 12;13(1):11268. doi: 10.1038/s41598-023-38212-8. PMID: 37438409; PMCID: PMC10338466.
35. **Moshksayan** K, Khanna R, Camli B, Yakay ZN, Harihara A, Zdyrski C, Mondal S, Hegarty E, Mochel JP, Allenspach K, Ben-Yakar A. A microfluidic platform for culturing and high-content imaging of adult stem cell-derived organoids. Sci Rep. 2025 Nov 17;15(1):40162. doi: 10.1038/s41598-025-23883-2. PMID: 41249220; PMCID: PMC12623891.
36. **Paoloni** MC, Mazcko C, Fox E, Fan T, Lana S, Kisseberth W, Vail DM, Nuckolls K, Osborne T, Yalkowsy S, Gustafson D, Yu Y, Cao L, Khanna C. Rapamycin pharmacokinetic and pharmacodynamic relationships in osteosarcoma: a comparative oncology study in dogs. PLoS One. 2010 Jun 8;5(6):e11013. doi: 10.1371/journal.pone.0011013. PMID: 20543980; PMCID: PMC2882366.
37. **Pitt** B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709-17. doi: 10.1056/NEJM199909023411001. PMID: 10471456.
38. **Rabinowitz** PM, Natterson-Horowitz BJ, Kahn LH, Kock R, Pappaioanou M. Incorporating one health into medical education. BMC Med Educ. 2017 Feb 23;17(1):45. doi: 10.1186/s12909-017-0883-6. PMID: 28228144; PMCID: PMC5322638.
39. **Schneider** B, Balbas-Martinez V, Jergens AE, Troconiz IF, Allenspach K, Mochel JP. Model-Based Reverse Translation Between Veterinary and Human Medicine: The One Health Initiative. CPT Pharmacometrics Syst Pharmacol. 2018 Feb;7(2):65-68. doi: 10.1002/psp4.12262. Epub 2017 Nov 27. PMID: 29178333; PMCID: PMC5824107.
40. **Schütt** T, Helboe L, Pedersen LØ, Waldemar G, Berendt M, Pedersen JT. Dogs with Cognitive Dysfunction as a Spontaneous Model for Early Alzheimer's Disease: A Translational Study of Neuropathological and Inflammatory Markers. J Alzheimers Dis. 2016 Mar 15;52(2):433-49. doi: 10.3233/JAD-151085. PMID: 27003213.
41. **Schütt** T, Pedersen JT, Berendt M. Chapter 15 - The Domestic Dog as a Model for Human Brain Aging and Alzheimer's Disease, Jeffrey L. Ram, P. Michael Conn, Conn's Handbook of Models for Human Aging (Second Edition). Academic Press, 2018, Pages 177-194.
42. **Sebbag** L, McDowell EM, Hepner PM, Mochel JP. Effect of tear collection on lacrimal total protein content in dogs and cats: a comparison between Schirmer strips and ophthalmic sponges. BMC Vet Res. 2018 Mar 1;14(1):61. doi: 10.1186/s12917-018-1390-7. PMID: 29490661; PMCID: PMC5831202.
43. **Sebbag** L, Harrington DM, Mochel JP. Tear fluid collection in dogs and cats using ophthalmic sponges. Vet Ophthalmol. 2018 May;21(3):249-254. doi: 10.1111/vop.12502. Epub 2017 Aug 27. PMID: 28845579.
44. **Sebbag** L, Kirner NS, Allbaugh RA, Reis A, Mochel JP. Kinetics of Fluorescein in Tear Film After Eye Drop Instillation in Beagle Dogs: Does Size Really Matter? Front Vet Sci. 2019 Dec 19;6:457. doi: 10.3389/fvets.2019.00457. PMID: 31921915; PMCID: PMC6930880.
45. **Sebbag** L, Mochel JP. An eye on the dog as the scientist's best friend for translational research in ophthalmology: Focus on the ocular surface. Med Res Rev. 2020 Nov;40(6):2566-2604. doi: 10.1002/med.21716. Epub 2020 Jul 31. PMID: 32735080.
46. **Shin** DS, Yang JY, Jeong HN, Mun SJ, Kim H, Son MJ, Bae MA. Hepatotoxicity evaluation method through multiple-factor analysis using human pluripotent stem cell derived hepatic organoids. Sci Rep. 2025 Mar 28;15(1):10804. doi: 10.1038/s41598-025-95071-1. PMID: 40155664; PMCID: PMC11953279.
47. **Waring** MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, Pairaudeau G, Pennie WD, Pickett SD, Wang J, Wallace O, Weir A. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov. 2015 Jul;14(7):475-86. doi: 10.1038/nrd4609. Epub 2015 Jun 19. PMID: 26091267.
48. **Zdyrski** C, Gabriel V, Ospina O. et al. (2024). A Multi-Tissue Comparison and Molecular Characterization of Canine Organoids. bioRxiv 2022.07.15.500059; doi: https://doi.org/10.1101/2022.07.15.500059.

 doi:10.20944/preprints202504.0325.v2

49. **Zdyrski** C, Gabriel V, Ospina O, Nicholson HF, Catucci M, Melvin BJ, Wickham H, Sahoo DK, Dao K, Aguilar Meza LS, Ralston A, Bedos L, Bastian W, Honold S, Piñeyro P, Pawlak A, Corbett MP, Douglass EF, Allenspach K, Mochel JP. Establishment and transcriptomic characterization of canine organoids from multiple tissues. Front Cell Dev Biol. 2025 Nov 24;13:1680376. doi: 10.3389/fcell.2025.1680376. PMID: 41378311; PMCID: PMC12686805.