

PERSPECTIVE

Model-Based Reverse Translation Between Veterinary and Human Medicine: The One Health Initiative

Benjamin Schneider¹, Violeta Balbas-Martinez², Albert E. Jergens³, Inaki F. Troconiz², Karin Allenspach³ and Jonathan P. Moche^{1*}

There is growing concern about the limitations of rodent models with regard to recapitulation of human disease pathogenesis. Computational modeling of data from humans and animals sharing similar diseases provides an opportunity for parallel drug development in human and veterinary medicine. This “reverse translational” approach needs to be supported by continuing efforts to refine the *in silico* tools that allow extrapolation of results between species.

CPT Pharmacometrics Syst. Pharmacol. (2017) 00, 00; doi:10.1002/psp4.12262; published online on 0 Month 2017.

IMPROVING THE PREDICTABILITY OF ANIMAL MODELS USED IN PRECLINICAL RESEARCH

Translational research remains the consensual model to develop candidate drugs into clinical therapeutics. In the translational framework, drug pharmacokinetics (PKs) and pharmacodynamics (PDs) are first characterized in animal models, and the results of those preclinical studies are then extrapolated to humans. Currently, out of the few candidates that move forward to the development stage, 35% attrition in phase II studies are caused by failure to demonstrate clinical efficacy.¹ These high failure rates, combined with few relevant translational animal models in preclinical research, highlight the need for alternative approaches at the early stage of the research and development (R&D) lifecycle. One such approach is the reverse translational model.

A well-known application of the reverse translational paradigm consists in the prediction of drug side effects and/or efficacy for individual patients using specific single nucleotide polymorphism information. The scope of reverse translation is actually broader, as we see it as an opportunity to synergize the information available from humans and animals sharing analogous diseases to develop improved predictions and therapies for both human and veterinary patients (Figure 1).

The innovative nature of this approach, underpinned by the “One Health” initiative, is based on the underlying hypothesis that the use of animal models that spontaneously develop similar diseases to humans will improve the predictability of preclinical models used for biomedical research purposes. In return, quantitative PK/PD information gathered from human clinical studies present an opportunity to stimulate veterinary drug development, thus optimizing the utilization of existing resources and the application of available knowledge (i.e., from humans to animals and *vice versa*). This contrasts starkly with the common translational practice of developing genetically engineered animal models of disease in preclinical research.

In reverse translational pharmacology, computational modeling of drug PK/PD assists in the selection of promising therapeutic candidates and the prediction of their optimal dosing schedules (i.e., dose and frequency) in humans and animals. This is achieved through extrapolation of disposition kinetics, efficacy, and safety data from/to spontaneous animal models of the human disease pathophysiology to/from the clinic.

One Health and comparative medicine to support drug R&D

One Health is a cross-disciplinary effort aiming to improve the assessment, treatment, and prevention of disease in people and animals.² An important subfield of One Health is comparative medicine, which offers the possibility to use spontaneous animal models with naturally occurring diseases for drug R&D. These animal models have unique experimental advantages, especially over the mouse, which may provide insight into previously intractable diseases. In particular, many human disorders, including cancer, diabetes mellitus, chronic enteropathies (e.g., inflammatory bowel diseases (IBD)), hypertension, and congestive heart failure have well-studied clinical analogs in dogs (Supplementary Table S1). Domesticated animals also share several environmental risk factors with humans, simplifying experimental controls. In addition, biological relevance of genomic data can be supported by identifying human-animal genetic homologs, as is the case in IBD, in which the importance of genetic susceptibility in disease development has been established in both species. Below, we highlight three examples of diseases in which reverse translational modeling have been used to support pharmaceutical research.

Cancer research

About 6 million dogs are diagnosed with cancer each year, and >50% of dogs of 10 years or more will develop cancers, such as lymphoma, osteosarcoma, and melanoma.³ Although murine models have been extremely useful for studying the biology of cancer development, mice usually

¹Department of Biomedical Sciences, Iowa State University College of Veterinary Medicine, Ames, Iowa, USA; ²Department of Pharmacy and Pharmaceutical Technology, Pharmacometrics and Systems Pharmacology, University of Navarra, Pamplona, Spain; ³Department of Veterinary Clinical Sciences, Iowa State University College of Veterinary Medicine, Ames, Iowa, USA. *Correspondence: J P Moche (jmoche@iastate.edu)
Received 28 September 2017; accepted 23 October 2017; published online on 0 Month 2017. doi:10.1002/psp4.12262

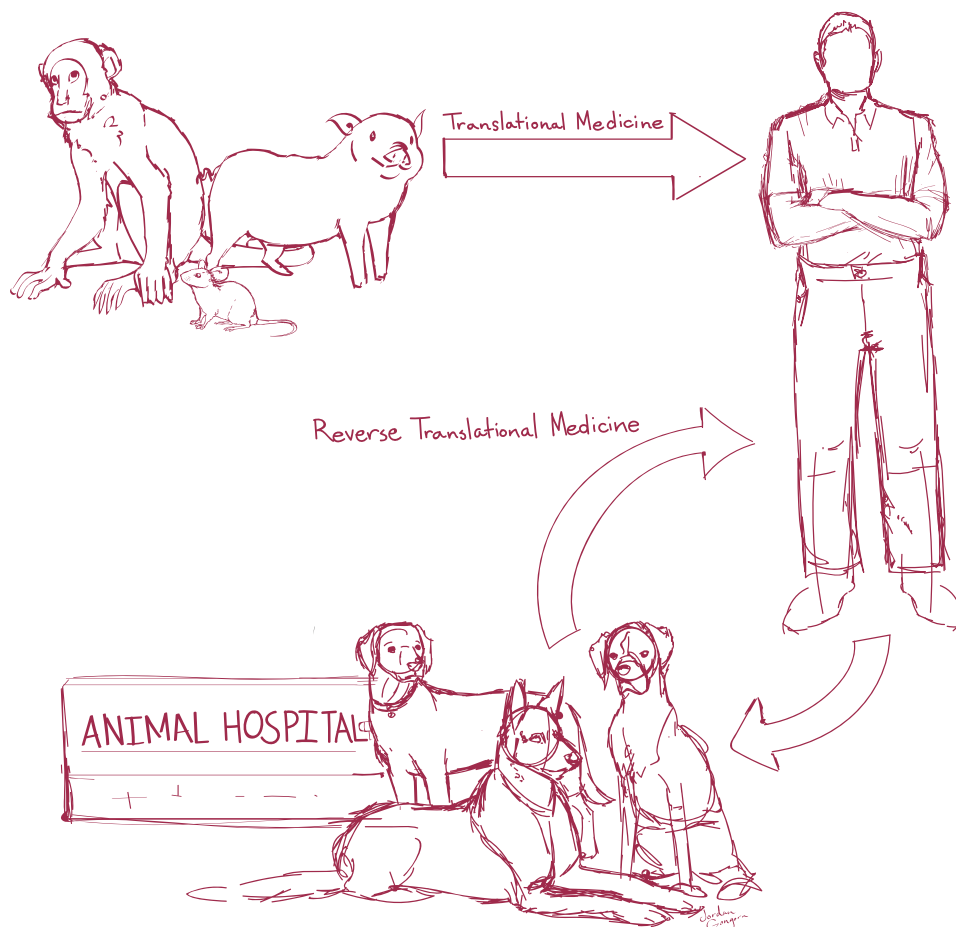


Figure 1 Translational vs. reverse translational sciences. Reverse translational sciences is a bidirectional approach in which clinical findings from patients are used to design early studies in relevant animal models of (spontaneous) disease. The information generated in animal studies will later be used to predict the efficacy and safety of future therapeutics in human clinical trials.

do not adequately represent many of the features constitutive of human cancers, including genomic instability and tumor heterogeneity.⁴ In dogs, cancers develop naturally within a syngeneic host and tumor microenvironment, and in the context of an intact immunity. Dogs and human cancers share similar features, such as background genetics, histological appearance, therapeutic response, and acquired resistance.⁴ One good example of the use of canine models to support cancer therapy pertains to the development of the inflammatory cytokine interleukin (IL)-12 as a potential treatment for malignant melanoma. The use of cytokines to enhance antitumor immunity has been recognized as an important immunomodulatory approach in cancer management. Yet, historically, the high risk for systemic toxicity presented by IL-12 dosing has prevented development of this cytokine into a therapeutic. A strong genetic similarity exists between canine and human IL-12 (i.e., 84% homology for the ligand and 68% homology for the receptor), whereas dogs develop spontaneous malignant melanoma with similar biology to human tumors. These analogies provided impetus for the characterization of IL-12 PK/PD, efficacy, and toxicity in canine clinical trials.⁵ Results from the dog study showed that high levels of IL-12 could be safely administered subcutaneously to patients with malignant

melanoma, while maintaining both systemic immunological and clinical activity. This was demonstrated by measuring serum IL-12 and other representative biomarkers (e.g., IL-10) over time, and establishing PK/PD models of IL-12. These findings in dogs were key to guide the sponsor's decision to move forward with a phase I clinical trial in humans. In turn, preliminary studies focusing on IL-12 gene electrotransfer in dog patients with melanoma have shown promising results for the treatment of spontaneous canine tumors.⁶

Inflammatory bowel disease

IBD is a highly prevalent disorder in both humans and dogs. Importantly, dogs with IBD exhibit similar clinical symptoms, show involvement of the same cells, inflammatory genes and molecular pathways, and have a time course of disease progression similar to humans. In fact, a copious amount of literature has established that human and canine IBD have common clinical and molecular features, such that clinical trials in dogs with IBD are particularly relevant to study the efficacy and safety of candidate drugs intended for use in humans.⁷ In a recent collaboration between the Iowa State University and the University of Navarra, IBD was modeled using a network systems approach based on Boolean

equations.⁸ The model was used to simulate the effect of a noncompetitive antagonist of the purinergic receptor P2X7 and guide dose selection for an upcoming clinical study in IBD in dogs. The model used inflammatory biomarkers IL-1 β and IL-18 as well as the tissue damage biomarkers matrix metalloproteinases as surrogate end points of efficacy. Assuming that matrix metalloproteinases levels are associated with clinical disease activity, results from the simulations showed that the selected dose of the drug candidate should antagonize at least 75% of the target receptor. These findings will now inform the design of a proof-of-concept study in IBD dogs prior to clinical development in humans.

Congestive heart failure

Another therapeutic indication in which modeling efforts have been made to better characterize the effects of drugs in naturally occurring animal models of human disease is congestive heart failure (CHF). In humans and dogs, CHF is often synergistic with renin angiotensin aldosterone system (RAAS) overactivation. This is due to the excessive release of renin from the juxtaglomerular apparatus, a well-described compensatory mechanism to the reduced cardiac output observed in symptomatic stages of CHF. Although there is no mathematical description of the PK/PD of angiotensin-converting enzyme (ACE) inhibitors in spontaneous cases of canine CHF, the kinetics and effects of benazeprilat have been characterized in a low-salt diet model of RAAS activation.⁹ Similar to humans, ACE inhibitors are commonly dosed in the morning in dogs. However, using a nonlinear mixed-effect model to describe the dynamics of RAAS biomarkers in dogs, Mochel *et al.*⁹ have shown that the timing of food intake exerts a synchronizing effect on the RAAS, such that dosing with ACE inhibitors should be adjusted according to the time of food intake. Using a mechanism-based PK/PD model, the authors further established that ACE activity alone was not a predictive marker of RAAS activity in dogs because, as reported in humans, benazeprilat exerts a moderate effect on angiotensin II and aldosterone, despite a complete and long-lasting inhibition of ACE.

Opening the “Black Box” of complex biological networks

The reductionist approach to biomedical research has been successful in identifying key mechanisms contributing to disease modulation. However, it has become increasingly apparent that a more integrated approach is required to characterize the pathophysiology of complex biological systems. This was nicely illustrated with the IBD example above for which a systems pharmacology model comprised of 43 nodes and 298 interactions was developed by combining human and animal data on a large number of cytokines, immune cells, and proteins to predict the therapeutic efficacy of prospective candidate drugs. As high-throughput sequencing and metabolomics techniques continue to improve, this mechanistic model could be expanded further to decipher the mechanisms by which diet and genetic backgrounds impact disease susceptibility.¹⁰

CONCLUSION

Reverse translational pharmacology is an expanding field of research with the promise to improve existing preclinical models for better characterizing the efficacy and safety of candidate drugs and, ultimately, selecting the most promising therapeutics intended for use in humans. In return, from the perspective of developing veterinary pharmaceuticals for spontaneous diseases in animals, reverse translational pharmacology also presents an opportunity to leverage information from PK and PD studies in humans for the benefit of veterinary medicine. The success of the reverse translational paradigm relies on more systematic interdisciplinary research and cross talks among physicians, veterinarians, and quantitative scientists. To achieve this, the Comparative Oncology Program of the National Cancer Institute has established a multicenter collaborative network of 22 veterinary academic partners known as the Comparative Oncology Trials Consortium. The mission of the Comparative Oncology Trials Consortium is to answer biological questions geared to inform the development path of chemotherapeutics for future use in human patients with cancer. Additional initiatives from the National Institute of Health include several multimillion-dollar funding opportunities to foster collaborative programs for multidisciplinary teams (e.g., PAR-17–340 and RFA-CA-17-002). Active participation of industrial partners is also key to the success of reverse translational research. This was exemplified by the 5-year Cooperative Research and Development Agreement between the US Food and Drug Administration Center of Veterinary Medicine and Certara (www.certara.com) aiming to deliver physiologically based PK dog models and assesses the impact of polymorphic variations on interspecies extrapolation. Regulatory incentives to develop parallel (veterinary and human) drug development programs could present an opportunity to encourage such collaborations in the future.

Acknowledgment. The authors would like to thank Jordan Gongora (Biomedical Sciences, Iowa State University) for her graphic design support.

Author Contributions. All co-authors participated in the writing and technical editing of the manuscript.

Conflict of Interest. The authors declared no conflict of interest.

1. Waring, M.J. *et al.* An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat. Rev. Drug Discov.* **14**, 475–486 (2015).
2. National Center for Emerging and Zoonotic Infectious Diseases (17 May 2012). Centers for Disease Control and Prevention. <<https://www.cdc.gov/ncezid/index.html>> (2012).
3. Jacob, J.A. Researchers turn to canine clinical trials to advance cancer therapies. *JAMA* **315**, 1550–1552 (2016).
4. 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.* **6**, e1000161 (2009).
5. Paoloni, M. *et al.* Defining the pharmacodynamic profile and therapeutic index of NHS-IL12 immunocytokine in dogs with malignant melanoma. *PLoS One* **10**, e0129954 (2015).
6. Lamprecht, U. *et al.* Gene electrotransfer of canine interleukin 12 into canine melanoma cell lines. *J. Membr. Biol.* **248**, 909–917 (2015).

7. Jergens, A.E. *et al.* Intestinal cytokine mRNA expression in canine inflammatory bowel disease: a meta-analysis with critical appraisal. *Comp. Med.* **59**, 153–162 (2009).
8. Balbas Martinez, V., Allenspach, K., Kingsbury, D., Jergens, A.E., Troconiz, I. & Mochel, J.P. One Health: translational and reverse translational modeling of inflammatory bowel disease using an advanced Boolean network. Population Approach Group in Europe Meeting, Budapest, Hungary. <<https://www.page-meeting.org/default.asp?keuze=abstracts&id=41&t=programItem&m=Posters%20:%20Wednesday%20morning>> (2017).
9. Mochel, J.P., Fink, M., Peyrou, M., Soubret, A., Giraudel, J.M. & Danhof, M. Pharmacokinetic/pharmacodynamic modeling of renin-angiotensin aldosterone biomarkers following angiotensin-converting enzyme (ACE) inhibition therapy with benazepril in dogs. *Pharm. Res.* **32**, 1931–1946 (2015).
10. Swanson, K.S. & Schook, L.B. Canine nutritional model: influence of age, diet, and genetics on health and well-being. *Curr. Nutr. Food Sci.* **2**, 115–126 (2006).

© 2017 The Authors CPT: Pharmacometrics & Systems Pharmacology published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (<http://psp-journal.com>)