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One Medicine and the importance of maintaining large animal disease models in biomedical research

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INTRODUCTION

This invited Perspective is addressed to the scientific, medical and veterinary medical communities and their associated patients and caregivers to emphasize the importance of maintaining large (non-rodent) and companion animal models for biomedical research in general and rare and genetic disease research, in particular. The author is a comparative medicine specialist who has spent his entire career caring for animals in research laboratories and supporting animal models of rare and genetic disorders. Comparative medicine focuses on the similarities and differences between veterinary and human medicine[1] and is, thus, critical to this *Rare Disease and Orphan Drugs Journal* (*RDODJ*) Special Topic, " Notably, the scientific community's ability to utilize these important models is under great stress at the present time due to unbalanced discussions in the public and political spheres concerning the value of animal-based research. The aims of this Perspective are threefold: first to provide background on animal models in the context of the One Medicine concept; second, to summarize challenges currently facing animal-based research in the United States; and third, to offer suggestions for animal research moving forward.

ONE MEDICINE

Despite many key differences between species, the concept of One Medicine exemplifies the historical and continuing importance of animal models in studying human pathophysiology, particularly for rare and genetic diseases. This is emphasized by the numerous examples that populate the manuscripts in this Special Topic of *RDODJ*.

One Medicine is a concept first coined by C. W. Schwabe and refers to the complementarity between human and veterinary medicine[2]. It fundamentally pertains to the commonality of these two disciplines as they confront similar diseases with analogous treatments. The comparative ties between human and veterinary medicine are often said to trace back to the nineteenth-century German physician Rudolf Virchow, known as the "Father of Modern Pathology", who wrote: "Between

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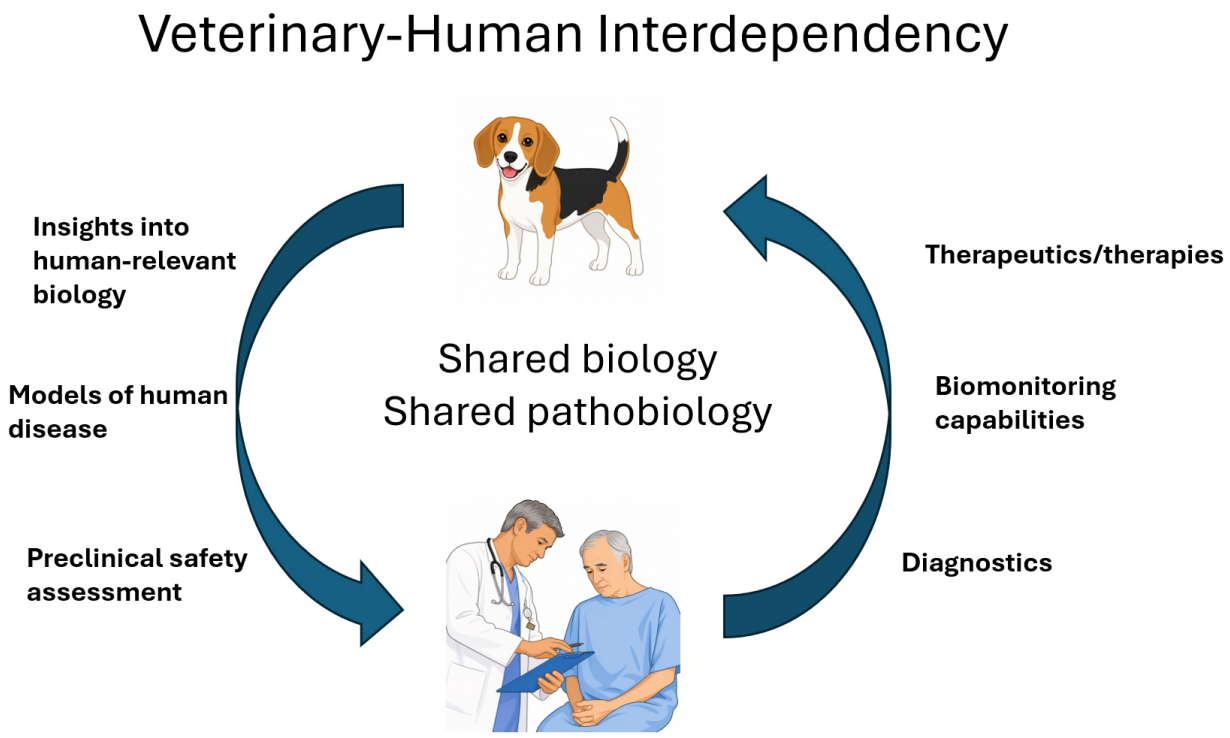


Figure 1. Schematic showing the veterinary-human interdependency that epitomizes One Medicine. As illustrated, shared biology and pathobiology between animals and humans leads to mutual benefits.

animal and human medicine, there is no dividing line-nor should there be. The object is different, but the experience obtained constitutes the basis of all medicine"[3].

William Osler, a Canadian physician considered to be the "Father of Modern Medicine", studied briefly under Rudolf Virchow in Europe and later served on the Johns Hopkins medical faculty[4]. His work was instrumental in fostering ties between human and veterinary medicine in North America. Osler forged an educational bridge between these two fields at McGill University where he taught pathology to both medical and veterinary students using a comparative pathology approach[5]. The shared biology between humans and animals contributes in numerous ways to therapeutic advancement [Figure 1] and allows each discipline to leverage knowledge.

Dogs and cats, particularly, develop naturally occurring genetically homologous inherited diseases that bridge the gap between rodent studies in the laboratory and human clinical trials[6-8]. Their breed structure and reduced genetic heterogeneity offer significant translational value to enable gene discovery and demonstrate efficacy beyond randomized ethically constrained human clinical trials drawn from small populations[9,10]. As a result, canine and feline models have contributed substantially to research and drug development in a range of genetic diseases[7,11].

My own research collaborations as a veterinary pathologist working in a medical center offer additional examples of the One Medicine concept. I worked with colleagues on preclinical studies using colony-raised dogs with a naturally occurring glycogen storage disease type Ia (GSD Ia) due to mutations in the glucose-6-phosphatase (*G6PC*) gene. This gene has been knocked out in mice, but the murine phenotype is not as close to humans. Our work included characterization of affected dogs that underwent gene therapy using an adeno-associated virus (AAV)-*G6PC* construct[12,13]. This preclinical research demonstrated adequate safety and efficacy to justify clinical trials, leading to Food and Drug Administration (FDA) approval of AAV

vector-mediated gene therapy for GSD Ia. The ability to follow a dog over its lifespan of 10-15 years following treatment, e.g., for an inherited disorder of metabolism, provides richer clinical data relevant to treatment of children with these disorders, compared to the short 2-3-year lifespan of a rodent. From a safety perspective, GSD Ia-related hepatic tumors occurred up to 8 years after AAV vector treatment, providing insight on potential similar adverse effects in humans. These findings point to the bidirectional nature of One Medicine and an ideal scenario in which companion animals can ultimately benefit from earlier experimental studies.

In addition to their value for rare and genetic diseases, large animal models have played a crucial role in the development of therapeutic approaches for which rodent models are impractical. My collaborations have included novel bioengineering techniques for chemical ablation of neoplasms[14]. These methods were first developed using cadaveric and in silico modeling approaches[15] and rodent models[16], and then eventually scaled up into large animal studies, prior to bringing them to the clinic in people. Using the One Medicine concept, these interventional approaches have also been used in veterinary clinical trials in companion animals, such as treatment of inoperable head and neck cancers in feline patients[17].

STRESSES ON THE ANIMAL RESEARCH COMMUNITY

Policies regulating animal research

People in the United States and globally have a deep and long-held bond with companion animals, particularly dogs and cats. This bond underlies misgivings about the use of animals in research and has guided animal welfare legislation. This is best illustrated by circumstances in 1966 that led the United States Congress to pass a law that later became the Animal Welfare Act (AWA) (P.L. 89-544)[18]. Congressional deliberations and passage of the original law were prompted by publication of a Life magazine article concerning abduction of a family dog later found to have been euthanized in a medical research facility[19]. Remarkably, the public outcry to this story surpassed that of any other articles that year in Life, including those on the ongoing Vietnam war and enactment of the Civil Rights Act two years prior[20]. The original AWA, together with amendments and further legislation, has dramatically transformed research animal care and oversight.

Importantly, animal research in the United States is performed under layers of governmental (U.S. Department of Agriculture) and individual corporate/university (Institutional Animal Care and Use Committee) protections. Due to this oversight and the sensitivity of involved scientists, veterinarians and staff, animal care and welfare is currently conducted at a high level of quality and oversight in most U.S. institutions. Furthermore, reflecting on the Life magazine article mentioned earlier, research is now done on purpose-bred animals[21].

Public distrust of science, political polarization, and animal rights activism

Despite this regulation, oversight, and high level of animal care, a constellation of interrelated factors has created what can be seen as a "perfect storm" facing the animal research community in the United States. At the core of this problem are ongoing ethical questions regarding the use of animals in biomedical research and testing[22]. While the vast majority of animal research in U.S. institutions is conducted with high standards of care and welfare, troubling adverse incidents have been reported[23]. This situation has been greatly compounded by a growing distrust of science in the post-COVID era driven by political polarization, misinformation, and the perception of a lack of integrity by scientists[24,25].

For context, the widespread global threat to the scientific community was documented in a 2011 survey done by the journal Nature showing that nearly one-quarter of biologists had been affected by animal activists[26]. While the debate on the use of animals in biomedical research has generally been measured and peaceful,

extremists within the animal activist community have unfortunately at times employed violent acts and rhetoric as well as intimidation tactics to push their agenda[27,28].

Parallels have been drawn between the approaches used by animal rights and anti-vaccine activists to generate distrust in science[29,30]. This alliance has developed in part because animal experimentation is required to produce effective vaccines. Thus, from a purist vantage point, those against animal research should also be opposed to vaccination. With that said, animal rights organizations generally supported vaccination during the recent COVID-19 pandemic[31,32]. Ironically for the One Medicine concept, this distrust has led pet owners to question the role of animal vaccination[33].

Now, for the first time, there is alignment of the animal rights activist agenda with political and scientific leadership at the highest levels of the United States government. The alliance has mostly worked to achieve their collective goal of reducing or eliminating the use of animals in research through policy initiatives such as the FDA Modernization Act 2.0[34]. This law, in particular, will substantially impact National Institutes of Health (NIH) funding of biomedical research using animals (see discussion of alternatives to animal research below)[35]. Similar policies to reduce animal use have been enacted by FDA[36], Environmental Protection Agency[37], and Department of Defense[38]. Over and above these initiatives, there have been instances of seemingly ill-conceived political directives. For instance, an order from low-level political leadership at Health and Human Services to end use of nonhuman primates (NHPs) at the Centers for Disease Control and Prevention prompted considerable scientific backlash[39].

An even more consequential example of the potentially deleterious effects of the alliance between animal activism and the current United States government administration concerns the Oregon National Primate Research Center (ONPRC), the oldest and largest of the seven national primate centers. Initial discussions between the ONPRC Board and NIH would have eliminated its research function and converted the facility to a sanctuary, thus removing 25% of all NHPs from the national inventory[40]. Disturbingly, the effort to halt the ONPRC's research followed a lengthy animal rights activist campaign and after a former high-level employee from one of these groups began working as an advisor to the NIH. This plan was ultimately abandoned, with ONPRC leadership instead choosing to retain their research function while gradually shifting focus to research alternatives (see further below)[41]. While this compromise clearly was preferred by the research community compared to the original sanctuary idea, the reduction in NHPs produced by the ONPRC will further exacerbate an existing national shortage.

It will be useful to examine a few examples of what ONPRC research has contributed to the study of rare and genetic diseases, as this will provide some indication of the loss to the national NHP infrastructure. Researchers at ONPRC discovered a naturally occurring mutation in the gene leading to Bardet-Biedl Syndrome retinal degeneration and neuropathy leading to the first NHP model of this syndrome[42]. Importantly, work was conducted to advance cell therapy and retinal treatment development[43]. ONPRC researchers identified a naturally occurring mutation of neuronal ceroid lipofuscinosis (Batten Disease) in Japanese macaques[44], and a rhesus macaque model of hypomyelinating leukodystrophy due to a mutation in PLP1[45]. ONPRC rare-disease models are naturally occurring genetic variants and are invaluable as translational models for gene therapy development. The ONPRC provides multi-generational pedigreed primate colonies of rhesus and other macaques with deep phenotyping and longitudinal life history data[46]. ONPRC is the home of the macaque Genotype and Phenotype Resource that provides searchable, annotated macaque variant data derived from whole genome sequence[47]. Moreover, NHPs are vital models in rare and genetic disease work for bridging the rodent to human gap in a manner analogous to that described earlier for companion animals. These models help in the study of vector spread in large organs, immune responses to gene-edited cells, durability of gene expression and various methods of cell and gene delivery.

New approach methodologies (NAMs) and animal activism

Recently, the animal rights activist community has spent significant narrative attacking the translational relevance of animal models. As highlighted by the discussion of repurposing the ONPRC above, this narrative has been underpinned by useful advances in NAMs that allow leveraging of human-based cell and tissue systems[48]. In turn, these activist groups have shifted their strategy from the traditional animal welfare focus. The main prior strategy was to find real or perceived lapses in the care and/or welfare of animals in the research setting and to then use this information in campaigns to cause the public to question the quality and oversight of animal care[49]. Increasingly, animal rights activist communities are concentrating on scientific issues of animal research, including the development of NAMs. This shift to scientific issues includes the reproducibility of animal studies[50,51], the translational relevance of animal models[52,53], and concerns about the low productivity and high cost of drug discovery and development, blaming this on the present heavy reliance on suboptimal animal models[54]. Collectively these concerns have resulted in a narrative that animal models are old irrelevant methods that can be replaced by newer models (NAMs).

NAMs are changing and portend to change further the patterns of animal use in research[55,56]. It should be noted that the use of NAMs is in keeping with the 3Rs (replace, reduce, refine) method of working with research animals, a system first proposed in 1959 by Russell and Burch and in place since the advent of Institutional Animal Care and Use Committees in 1985[57].

Historically, advances in biomedicine have depended heavily on animal models despite known limitations and high ethical and fiscal cost[58]. This historical paradigm is being altered and modified by recent events, including NAMs, and a loosening of regulatory frameworks such as the passage of the FDA Modernization Act 2.0 that allows development of new therapies without the explicit requirement of testing in animals[34]. These changes bode to diminish reliance on large animal models in pharmaceutical and chemical testing paradigms[59], but to date do little to change the overall need for these models in other important uses such as in rare and genetic disease research. Animal activist groups through their affiliated scientific units, have become involved in the advancement of NAMs using their own scientists and working in conjunction with academic and government groups. This has occurred especially in certain areas of chemical toxicology, such as using NAMs in skin and ocular irritation testing[60,61]. Because many activists have the underlying objective of abolishing the use of animals in biomedical research, they have publicly framed the issues as NAMs versus animal models. This gives the impression that the time is currently ripe to replace all animals used in biomedical research and testing. However, although NAMs are proving useful as models, no existing NAM can model how a gene functions in a whole human or other animal organism, how an organ works, or how a disease progresses, all important factors for rare and genetic disease research[62].

Lost in the NAMs narrative is the fact that there is never a single best model or platform to address every scientific question. Instead, the correct model is one that is exquisitely tailored to the scientific or regulatory question being addressed. Animal activist organizations come to the table with a strong inherent ideological bias because their central underpinning tenet is to abolish animal use rather than issues of translation from model to human, or even from model to other animals. Considering all points above, the scientific consensus is that animal models are still needed despite the advances of NAMs[63,64].

MOVING FORWARD WITH ANIMAL RESEARCH

There are a variety of ways through which the scientific community can positively influence the evolving "perfect storm" confronting animal research. First, scientists who use animal models must ensure that they optimize their work utilizing best practices in both animal care and welfare, and experimental usage, considering experimental design, statistical support, issues of translational outcome, and study reproducibility. Importantly scientists must embrace working in a true 3Rs (replace, reduce, refine) model,

adopting NAMs whenever and wherever possible.

Secondly, the research community must focus on public outreach to explain why and how animals are used in experiments. Scientists who use animals must agree to present their work in public discourse. Too many scientists and medical professionals are reluctant to interact with the lay public on animal use issues. Institutions must recognize legitimate public concerns and work to make their facilities and programs as transparent as possible so that trust is rebuilt. Studies have shown that people are more accepting of animal research when it is justified and explained transparently[65,66].

Third, advocacy and patient support groups must speak up and help defend keeping these models available to the scientific community. Patients and caregivers should participate in the public discussion. Disease support groups should acknowledge the role of animal models in the discovery and development of new therapies by featuring them prominently on websites, brochures, and patient literature. When they fund researchers that use animal models, this should be actively acknowledged.

Finally, veterinarians, who are the most trusted professionals concerning the topic of research use of animals[65], must use their platform to educate their client bases on One Medicine and the role of animals in research for humans and companion animals. They can do this when they provide treatments for their patients, emphasizing the role of research and testing. In the view of the author, the One Medicine narrative is a powerful antidote to the misperception that animal models are not human relevant. Expanding the One Medicine narrative, showing the linkage of animal and human biology and medicine, will help combat a misleading activist narrative that dismisses the human relevancy of animal model studies. A promising way for the veterinary profession to engage will be the expansion of veterinary clinical trials, where privately owned pets benefit directly from animal research[67].

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Authors' contributions

The author contributed solely to the article.

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Not applicable.

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During the preparation of this manuscript, the beagle image in Figure 1 was generated by ChatGPT. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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