



**COMMENTARY**

# Cortical evolution 2018: Advantages of animal model species

Verónica Martínez-Cerdeño<sup>1,2</sup>  | Stephen C. Noctor<sup>2,3</sup> <sup>1</sup>UC Davis School of Medicine; Institute for Pediatric Regenerative Medicine and Shriners Hospitals for Children of Northern California, Sacramento, California<sup>2</sup>UC Davis School of Medicine, MIND Institute, Sacramento, California<sup>3</sup>UC Davis School of Medicine, Department of Psychiatry and Behavioral Sciences, Sacramento, California**Correspondence**

Verónica Martínez-Cerdeño, Shriners Hospital, 2425 Stockton Boulevard, Sacramento, California, 95817.

Email: vmartinezcerdeno@ucdavis.edu

and

Stephen C. Noctor, UC Davis School of Medicine, UC Davis MIND Institute, 2805 50th Street, Sacramento, CA 95817

Email: scnector@ucdavis.edu

**Funding information**

National Institute of Mental Health, Grant/Award Number: R01MH094681 (VMC), R01MH101188 (SCN); Shriners Hospitals for Children; UC Davis School of Medicine, Department of Psychiatry.

## 1 | COMMENTARY

When choosing an animal species for research, the researcher must consider the phenomenon to be studied. The problem to be addressed may be driven simply by curiosity, by questions on evolution, or by biomedical problems. About 90% of published research studies involve mice and rats raising the obvious question of what advantages murids hold over other species for research. Herein, we discuss the appropriateness and advantages of animal models for biological and biomedical research. Consideration of the advantages of each species and broadening the scope of studies to include more species for further advance scientific knowledge. This report is based on an open table discussion that took place among attendees of the Cortical Evolution Conference in Las Palmas, Spain in June 2018.

The use of animals as models to study human anatomy and physiology began in ancient Greece. Research on animal models is founded on the concept that other species share fundamentally important characteristics with human (for review see: Ericsson, Crim, & Franklin, 2013). Today, the use of animal models in biomedical research has expanded to the point that of 108 Nobel Prizes awarded for Physiology or Medicine, 96 were directly dependent on animal research (Nobel Price website). What are the criteria to choose an adequate animal model for a specific research project? For researchers interested about how particular functions operate in a given species, that species is the best animal model: for example, the best model for studying brain function is *Kinyongia msuyae* (a chameleon). However, basic studies driven purely by curiosity can translate into valuable biomedical findings. For example, the knowledge acquired from the woodpecker brain can be translated into studies of traumatic brain injury in human (comment by Zoltan Molnar). Evolutionary studies are

those that search for the processes that produced the diversity of life, that govern the complexity of shared organ systems, and when and how a given species appeared on Earth. Animal models used for evolutionary studies are called reference species, that species can be used to inform our understanding of other species. Evolutionary studies involve the use of many species, not a single species as is common with most biomedical research. A special challenge that evolutionary biology faces is the lack of sufficient reference species (comment by Chet Sherwood). More reference species should be developed to advance the field of comparative neurobiology.

The goal of biomedical research is to expand the knowledge of medicine, and encompasses basic, preclinical, and clinical research. Animal models for biomedical research vary from one-celled organisms to complex species such as human. Invertebrates (*Drosophila melanogaster* and *Caenorhabditis elegans*) and fish (zebrafish) are often used in genetic studies and drug development, while a majority of biomedical studies are carried out in rodents. To measure the comparative use of different model species, we searched on PubMed (January 1, 2017/August 12, 2018) for publications in which the word "mouse" or "mice" appeared in the text and yielded 114,582 publications. Searching for the word "rat" yielded 31,414 publications. *Drosophila*: 5,869, zebrafish: 5080, chicken: 4,333, guinea pig: 683, rhesus macaque: 359, and ferret: 207. This literature search included publications investigating both biomedical and basic research questions into any organ systems or animal behavior. To estimate how often a given species is used to study a specific organ system we searched for publications in which the term "cerebral cortex" appeared in the text together with the term for a specific species such as "mice/mouse", "rat", or "chicken". Note that this literature search is neither comprehensive, nor does it guarantee that the published

studies used those species. Nevertheless, it provides a comparative measure of the relative use of different animal models. This literature search produced 1,060 publications that included the terms “cerebral cortex” and “mice”; 524 publications with “cerebral cortex” and “rat”, 15 studies on dog, 12 on ferret, 11 on zebrafish, 10 on *Drosophila*, 9 on rhesus macaque, and 3 on chicken. Among these species, over 64% of publications included mice, 31% rats, and less than 1% mentioned other species such as dog, ferret, drosophila, rhesus monkey, rabbit, guinea pig, chimpanzee, bat, elephant, turtle, chick, lizard, or zebrafish. These ratios could be expected to change for publications researching different organ systems and biomedical problems.

Animal models for biomedical research are used to interrogate mechanisms underlying normal and disease states at the genetic, molecular, proteomic, cellular, organ, system, and behavioral level. The reasons that the majority of biomedical and biological work is conducted in mouse include the affordable cost to house, breed, and maintain, a relatively short gestation, relative ease to handle, and wide availability of genetic manipulations. Some potential disadvantages include inbreeding, differences between strains, idiosyncrasies of murids, unique anatomical considerations, phylogenetic distance from human, and more. Mouse colonies are inbred to the point that a laboratory mouse responds differently both behaviorally and physiologically to specific tasks than a wild mouse. So, we can question whether the laboratory mouse is a good model for the wild mouse (comment by Pasko Rakic). Data supporting this idea have been reported in studies of neurogenesis where wild mice did not exhibit neurogenesis after performing similar tasks as laboratory mice (Klaus et al., 2012). Another important consideration is that murids (rats and mice) are unusual rodents in several respects. For example, they do not possess cortical cholinergic interneurons and their locus coeruleus is different than in other mammalian species (Comment by Paul Manger) (Bhagwandin, Fuxe, & Manger, 2006). Furthermore, mice are phylogenetically further from humans than other species such as carnivores (Cannarozzi, Schneider, & Gonnet, 2007). Anatomically speaking the rodent cerebral cortex exhibits core similarities with that of human including inside out generation of cortical neurons and the overall pattern of cortical layering and connectivity. However there are important differences, for instance in the subplate zone (Montiel et al., 2011). The adult brain of a carnivore more closely resembles that of the human because of its gyrencephalic cerebral cortex, and the similar positioning of the hippocampus, as is the case of ferret (comment by Sharon Juliano). These data make us wonder, can data obtained in mouse be extrapolated to human? The response depends on the question asked and the parameters to be measured. In this context, the mouse is a good model to answer genetic questions if the gene under study and its product are conserved in human (comment by Zoltan Molnar). For example, as several transcriptome modules correlate with Alzheimer's disease progression are strongly conserved among mouse and human (Miller, Horvath, & Geschwind, 2010), it would be appropriate to extrapolate related data obtained in mouse to human. Nonhuman primates provide the closest model to human for several reasons including their close phylogenetic relation. Some conditions may be studied best in primates, like infectious diseases such as AIDS, hepatitis, malaria, or respiratory syncytial virus. For example, infection of

simian immunodeficiency virus (SIV) in macaques and other nonhuman primates produced a model that resembled HIV infection and AIDS in humans and has advanced prevention and treatment of HIV in human (Veazey & Lackner, 2017).

Other experimental models include in vitro culture of animal or human cells, organotypic cultures, and the novel method of animal derived-organoids. In vitro models are widely used for cellular and molecular biology studies and are extremely useful for rapid through put drug testing. Organoids are grown from stem cells that proliferate and can be differentiated into small and simplified 3D versions of an organ. These organ systems comprise multiple cell types that upon exposure to controlled factors can exhibit preferential organization and fate, such as cortical brain tissue. Cortical organoids are able to reproduce aspects of the proliferative regions of the developing cortex and are organized in a laminar pattern that resembles cortical development in vivo. This highlights a potential strength for organoids as useful models for early developmental events. A challenge faced with very promising in vitro systems, such as cortical organoids, is overcoming disadvantages that include low reproducibility and unwanted differentiation into other tissue types.

What are the criteria to choose a good animal model of human disease? In the 1980s, Leader and Padgett listed nine criteria to choose an appropriate animal model (Leader & Padgett, 1980): It should: (a) accurately reproduce disease/lesion; (b) available to multiple investigators; (c) exportable; (d) if genetic, polytocous; (e) large enough for multiple biopsies/samples; (f) fit into most animal facilities; (g) easily handled; (h) available in multiple species; and (i) sufficient lifespan for longitudinal observation. Forty years later these considerations remain valid. However, additional considerations can be added: (j) conserved molecular pathways that modulate disease in human; (k) highly reproducible; (l) responsive to known disease treatments; and (m) not reproducible in nonanimal models.

The wealth of data obtained from animal research has immeasurably improved our understanding of fundamental mechanisms guiding development and function of the central nervous system within and across species, and improved our understanding of human health. Careful consideration of the advantages of each species and broadening the scope of studies to include more species when possible, will further advance research in all fields of study.

## ORCID

Verónica Martínez-Cerdeño  <https://orcid.org/0000-0002-9613-3603>

Stephen C. Noctor  <https://orcid.org/0000-0001-5236-4525>

## REFERENCES

- Bhagwandin, A., Fuxe, K., & Manger, P. R. (2006). Choline acetyltransferase immunoreactive cortical interneurons do not occur in all rodents: A study of the phylogenetic occurrence of this neural characteristic. *Journal of Chemical Neuroanatomy*, 32(2–4), 208–216. <https://doi.org/10.1016/j.jchemneu.2006.09.004>
- Cannarozzi, G., Schneider, A., & Gonnet, G. (2007). A phylogenomic study of human, dog, and mouse. *PLoS Computational Biology*, 3(1), e2. <https://doi.org/10.1371/journal.pcbi.0030002>
- Ericsson, A. C., Crim, M. J., & Franklin, C. L. (2013). A brief history of animal modeling. *Missouri Medicine*, 110(3), 201–205.

- Klaus, F., Hauser, T., Lindholm, A. K., Cameron, H. A., Slomianka, L., Lipp, H. P., & Amrein, I. (2012). Different regulation of adult hippocampal neurogenesis in Western house mice (*Mus musculus domesticus*) and C57BL/6 mice. *Behavioural Brain Research*, 227(2), 340–347. <https://doi.org/10.1016/j.bbr.2011.07.026>
- Leader, R. W., & Padgett, G. A. (1980). The genesis and validation of animal models. *The American Journal of Pathology*, 101(3 Suppl), S11–S16.
- Miller, J. A., Horvath, S., & Geschwind, D. H. (2010). Divergence of human and mouse brain transcriptome highlights Alzheimer disease pathways. *Proceedings of the National Academy of Sciences of the United States of America*, 107(28), 12698–12703. <https://doi.org/10.1073/pnas.0914257107>
- Montiel, J. F., Wang, W. Z., Oeschger, F. M., Hoerder-Suabedissen, A., Tung, W. L., Garcia-Moreno, F., ... Molnar, Z. (2011). Hypothesis on the dual origin of the mammalian subplate. *Frontiers in Neuroanatomy*, 5, 25. <https://doi.org/10.3389/fnana.2011.00025>
- Veazey, R. S., & Lackner, A. A. (2017). Nonhuman primate models and understanding the pathogenesis of HIV infection and AIDS. *ILAR Journal*, 58(2), 160–171. <https://doi.org/10.1093/ilar/ilx032>