Moving past animal experiments to understand human neurological disease

openaccessgovernment.org/article/moving-past-animal-experiments-to-understand-human-neurological-disease/173839/

Richard J. Miller, PhD, Professor Emeritus of Pharmacology at Northwestern University Feinberg School of Medicine, says that the belief monkeys and other animals are essential for performing translationally useful research for human neurological disease is outdated and incompatible with 21st-century science

The science is now clear: It's time to challenge the prevailing use of animals for studying the brain and human neurological diseases.

Animals fail to model human neurological disease

Using animals to model human neurological disease is severely limited. This is particularly true when it comes to diseases of the nervous system. Numerous fundamental differences exist between the brains of monkeys and humans. [1,2] These include the relative proportions of neuronal types, their laminar distribution, gene expression profiles, and morphology. These disparities are critical when trying to answer questions about the causes of diseases that are exclusively human.

Consider that, as opposed to humans, monkeys don't suffer from Alzheimer's, Parkinson's, Huntington's diseases, or most other uniquely human neurological disorders. This means scientists must attempt to artificially induce these disorders in animals to "model" them for research purposes.

Because the pathophysiology of these diseases is often poorly understood, generating such models in animals is basically impossible and inevitably produces few translatable results. [3] This applies especially to diseases like schizophrenia and depression, for which there is no clear neuropathology to model. Animal models for these disorders are basically scientific malapropisms.

As a result, while drug development using animal models has a 90% failure rate, it's even worse for neurological diseases. For example, the current failure rate for Alzheimer's drugs is 99.6%.[4]

Poor translation leads to ineffective treatments

The degree of translation for neurological disorders is so poor that the National Academies of Sciences, Engineering, and Medicine [5] concluded that: "Advances in genetics and other new technologies are beginning to bring forth new molecular targets

and identify new biomarkers", and that these are "opportunities to accelerate early stages of drug development for nervous system disorders in the absence of animal models that reflect disease and predict efficacy."

This statement is bolstered by the proliferation of many human-based alternatives to the use of monkeys and other animals, resulting in more effective and ethical science.

Innovative human-based technologies must replace animals

Human stem cell-based technologies [6,7], in particular, human brain organoids [8, 9,10], now allow scientists to investigate brain functions in the context of personalized medicine, opening the door to understanding neurological diseases that reflect the entire diversity of the human race, rather than in monkeys or mice.

Together with other human-based paradigms, including live brain imaging, [11,12] human transcriptomics [13, 14], and detailed analyses of post-mortem brain tissue, [15] these methodologies are far more likely to elucidate the causes of human neurological diseases than studying monkeys.

In a powerful confirmation of these new technologies, the U.S. National Institutes of Health issued a statement on February 1, 2024 [16] that it will now prioritize developing and using novel alternative methods (NAMS) rather than animal experiments. This follows the passage of the FDA Modernization Act 2.0 [17], allowing the U.S. Food and Drug Administration to accept human cell-based data for new drug approval in lieu of previously required experimental results from animals.

Non-human primate or rodent experimentation no longer represents the cutting-edge of 21st-century human neurological disease research. Human-relevant models of the brain, and not animals, are key for learning about neuropsychiatric diseases and potential treatments.

References

1. https://www.nature.com/articles/d41586-019-00198-7
2. https://www.nature.com/articles/s41467-021-22741-9
3. https://pubmed.ncbi.nlm.nih.gov/21052075/
4. http://www.medicalnewstoday.com/articles/314442. php; 11/30/16
5. https://pubmed.ncbi.nlm.nih.gov/28287687/3/10/17
6. https://www.rochester.edu/newscenter/tissue-on-chip-drug-development-tool-trace-bmps-589512/#:~:text=Rochester%20is%20one%20of%20four,the%20need%20for%20animal%20trials
7. https://pathsocjournals.onlinelibrary.wiley.com/doi/10.1002/path.6244
8. https://www.nature.com/articles/s41467-023-43141-1
9. https://www.nature.com/articles/s41592-023-02080-x
10. http://dx.doi.org/10.1016/j.stem.2023.11.013
11. https://doi.org/10.1038/s41380-023-02352-0

12. http://dx.doi.org/10.1016/j.bpsc.2023.08.008
13. http://dx.doi.org/10.1016/j.biopsych.2023.08.017
14. http://dx.doi.org/10.1073/pnas.2302534120
15. http://dx.doi.org/10.1016/j.neuroimage.2021.118559
16. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-catalyzing-development-novel-alternatives-methods
17. https://pubmed.ncbi.nlm.nih.gov/36762462/

Please Note: This is a Commercial Profile