Translational Biomedical Research: Challenges and Solutions of Using Animal Models

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ABSTRACT

In translational research, utilisation of laboratory animal models contributes significantly to the understanding of human diseases, diagnostics, and therapeutics. Due to their genetic, anatomical, and physiological similarities to humans, their use allows for *in vivo* studies to assess the safety, efficacy, and side effects of potential treatments before human trials. However, the relevance is often challenged by significant physiological and genetic differences between species. Additionally, ethical concerns regarding the use of animals' research and variability and reproducibility issues also arise due to differences in strains, breeding practices, and housing conditions, complicating the consistency and reliability of experimental outcomes. To address these challenges, researchers are exploring alternative approaches such as *in vitro* models, organoids, and computational simulations, which offer promising and ethical substitutes for animal models. Despite these developments, animal models remain indispensable for certain investigations due to their ability to replicate complex biological processes and disease mechanisms. Collaborative efforts to standardise protocols and promote data sharing are essential to improve the reproducibility and translational value of animal research.

Key Words: *Animal models, Translational research, Challenges in translational research, Alternative to animal models.*

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Laboratory animal-based research has played a major role in the growth of information about human diseases, diagnosis, and treatment throughout the past century.[1] Thus far, mice have been the most frequently used model in mammalian biology. Mice are a great animal model due to advantages, including ease of breeding, short generation times, and comparatively large offspring numbers.[2] There is a great genetic similarity, around 90%, between humans and animals such as mice. *In vivo* studies are conducted to evaluate the ethical concerns associated with the discovery of a medicine or component, equipment, toxicological tests, dosage, and side effects before a therapeutic agent is eventually used in humans. Animal models thus provide a controlled avenue for the investigation of intricate biological pathways, including normal and abnormal genetic functions in healthy and diseased states. In understanding the mechanisms and suggesting therapeutic solutions in complex multiorgan system diseases such as diabetes, cancer, cardiovascular conditions, and neurodegenerative (ND) diseases, animal models are used due to their similarity with human biology and creating human-like responses.[3]

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For understanding genetic diseases and making therapeutic methods, transgenic and knockout mice are essential research animals for research in a controlled environment.[4] Such a controlled research environment is difficult to have in human investigation due to practical and ethical issues.[5] However, this use of animal models is faced with various experimental and ethical challenges. Unlike before, greater than expected differences have surfaced recently between animals such as rodents and humans.[2] These known and unknown other differences may affect the applicability of translational research and create cause for concern. The variability between human and animal biology may affect the expected translational research results in humans.

Animal models have the drawbacks of reproducibility and variability. Research has demonstrated that genetic backgrounds, environmental factors, and experimental techniques can all have a substantial impact on the outcomes of animal trials.[6] Significant genetic variations exist between laboratory animals such as mice, rats, and humans which can affect the validity and applicability of scientific studies. While animals have a large amount of DNA in common, this closeness, however, does not ensure that genetic connections and functions are the same. The research based on animal models is not always reliable, especially when exploring genetic diseases. This is because animals and humans have some variations in gene expression, regulation, and mutation. These variations influence the normal biological processes, pathophysiology of diseases, and possible therapies. For instance, gene expression is influenced by factors such as regulatory elements and

transcription factors which can vary in humans and animals. This is true for genes which are generally considered as conserved. Hence, resemblance in regulatory systems in animals may not be functionally equivalent to humans and results in distinct gene expression patterns. The onset and progression of diseases such as cancer are affected by such variations in genetic regulation. This phenomenon is further complicated by intraspecies variation in the rates and types of mutations. Due to genetic variations, the other alternate strategies such as *in vitro* models and humanoid animal models become significant in translational research. Many animal models failed to exhibit mutations that are commonly found in human diseases.[7] This is one of the limitations in research exploring the mutation-driven pathophysiology of diseases. Moreover, humans show relatively higher levels of genetic variability than animals. This entails that animal models may not truly reflect the human genetic diversity.[8]

The generalisability and applicability of animal models are impacted by physiological differences in organ form and function between humans and research animals. These differences provide substantial hurdles for biomedical research. Although mice and rats—two popular laboratory animals—share many basic characteristics with humans, there are major distinctions in the structure and performance of the organs that can impact how experimental data are interpreted.[8] For instance, the cardiovascular system can vary in heart rate, blood pressure, and response to different stimuli, even though it is similar in all mammalian species. These variations could yield different results when researching cardiovascular conditions or testing medications associated with them. The immune system is another area where physiological differences are evident and stand out the most. Hence, the outcomes of immunopathological research on animal models may not translate in similar human outcomes. This is due to the fact that animals and humans react differently to pathogens and therapeutic agents used against those pathogens.[9] This underscores the danger of the application of exclusive animal model studies. As a result, therapies that show promising results in animal models may not produce the same outcomes in human clinical trials. The differences in metabolic pathways between humans and animals pose another challenge in translational research. Animals such as mice and rats have different biological processes to metabolise medicine and other chemicals that affect medicine therapeutic studies.[10]

Liver is one of the main organs metabolising medicines in animals and humans. However, there are structural and functional differences of liver between animals and humans. The variation in liver enzymatic activity and expression leads to differences in the medicine metabolism and toxicity. Such as the liver, bone structure, and function also show differences between animals and humans. The bone structure and healing process in rodents is different from humans.[11] Absence and presence of distinctive osteon in bone and pathophysiology of bone remodelling demonstrate such differences. Hence, the outcomes of musculoskeletal research such as the development of orthopaedic devices and bone grafting procedures carried out on animal models may mislead the researchers regarding their application in humans. Lastly, the neuroanatomical and neurophysiological variations observed in animals and humans pose a challenge to neurological and psychiatric illness research.[12] The neurodegenerative (ND) diseases such as Alzheimer's and Parkinson's diseases studied in animal models may not accurately reflect the disease patterns in humans. The anatomical and pathophysiological discrepancies mentioned above between animals and humans highlight the cautious consideration of animal research outcomes while applying them to human health and disease states. Studies on animal models should not be considered the only reliable source of translational research.

Besides biological differences between animals and humans that affect translational research, there are additional issues with the use of animals which result in inconsistent research outcomes. These include variations in animal strains, breeding and housing conditions, and unstandardised research protocols. Different animals have various genetic and phenotypical strains that yield different research results in the same experimental settings.[6] Research outcomes are affected by genetic drifting or accumulation of peculiar genetic features that result from the use of various breeding methods across laboratories. Similarly, housing conditions have a significant influence on research outcomes for example group *versus* individual housing, temperature, illumination, and size of the cage affect the animal's biological processes and behavioural response. Each of such housing conditions creates stress levels that impact the physiology of animals. Any such stress is an important confounder in experiments related to cancer, obesity, and autoimmune diseases.[13]

The variability and reproducibility issues put the advancement of valid and reliable preclinical investigations at a greater disadvantage. This hinders the advancement and innovation of new scientific knowledge across various fields, and the rate of failure is higher in studies which use animal models.[14] The flawed conclusions increase the risk of developing incorrect treatment approaches which eventually halt such research projects. This failure of translational research might increase the burden of disease in society by not addressing them appropriately with strong preclinical research data. The scientific community, especially in the South East Asia including Pakistan, where research needs to develop its standard further, must collectively develop strategies to mitigate such experimental design issues and explore alternate approaches in translational research using animal models which ensure public trust in translational research outcomes alongside the advancement of scientific knowledge.

The struggle and challenges associated with the moral and practical constraints of using animal models for scientific research, for example, the replacement of animals has led scientists to explore various other methods as viable alterna-

tives, and to the creation of new research models.[1] Organoids, *in vitro* models, and computational simulations are some examples which have been proposed as potential substitutes for animal models used in biomedical translational research. Organoids or mini-organs, are tiny 3-dimensional tissue structures developed in vitro that resemble the complexity and functionality of human organs.[15-17] These can be developed from various sources such as embryonic stem cells (ESC), induced pluripotent stem cells (iPSCs), or neonatal or adult stem cells (ASC).[15] They provide researchers with a more physiologically appropriate platform to examine medication responses and disease causes. The use of organoids in translational research is promising in preclinical research including medicine testing and in therapeutics such as personalised and regenerative medicine, genetic repair, and transplantation.[18] The bioprinting technology using various mechanisms has been developed over the past decade for making organoids.[19] Besides the use of organoids, the use of *vitro* models such as tissue slices and cell cultures as an alternative to animal models in preclinical research also minimise the ethical dilemmas and unpredictability that come with using animal models to study biological processes. Computational simulations allow researchers to replicate biological processes and forecast results by use of mathematical models and algorithms.[20] These approaches provide practical and moral substitutes for animal testing. Additionally, these substitute models also provide better translational relevance and predictive capacity, which may eventually advance biological research and medicine development. Although these alternative models are growing and getting more relative accuracy, however, the animal models will continue to have a place in research exploring complex, normal, and abnormal processes and testing medicines.

CONCLUSION

In understanding human diseases, diagnosis, and developing new therapeutic approaches translational research is essential. Though the use of animal models has advantages, the capacity of commonly used animal models in biomedical translational research is limited in mimicking the human structures and functions of various organ systems. This can lead to a large gap in translational research. The use of alternatives of animal models addresses such issues and are promising future research methods. These alternatives provide strict similarity and applicability. Southeast Asian countries such as Pakistan still heavily rely on animal models in research. Countries such as Pakistan could improve its biomedical translational research profile by adopting newer alternatives of laboratory animals.

COMPETING INTEREST:

The author declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SAA: Conceptualisation, literature search, and writing of the manuscript for publication.

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