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The Role of Experimental Animal Models in Advancing Veterinary and Biomedical Research

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Abstract

The use of experimental animal models as the basic tool in the development of veterinary medicine as well as biomedical research has been in use over a century. The models play important roles in comprehending the pathogenesis of diseases, testing the therapeutic interventions, determining the safety of drugs and interpreting the results of basic scientific findings into clinical practices. It is based on the considerations of anatomical similarity, physiological relevance, genetic tractability, and ethical appropriateness that the selection of the appropriate animal models is considered. Conventional models such as mice, rats, rabbits and non-human primates have been replaced by new models such as zebrafish, pigs and genetically modified organisms that have their own distinct merits with regard to particular research questions. The latest technological changes in genome editing, in this case, CRISPR-Cas9 systems have transformed the production of disease models in a way never before seen before. Moreover, the translation value of animal research has been increased by the advancement of advanced imaging modalities, omics, and computational methods. Although animal models are indispensable, there comes with them ethical obligations that require observation of the principle of replacement, reduction and refinement. In the present state of research, the topics of enhancing the translatability of animal models to human patients, understanding differences in the manifestations of diseases by species, and incorporating alternative approaches where scientifically justified are of concern. This review paper discusses the history of animal models, the ways they have been used in different fields of research, the technological advances that have increased their use, the ethical considerations that regulate their use and future prospects such as the incorporation of human-relevant in vitro systems and computational models to supplement animal research.

Keywords: Experimental animal models, Biomedical research, Veterinary medicine, Translational research.

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1. Introduction

Use of animals in research studies can be traced back to thousands of years ago, when physicians of ancient Greece did anatomical research on animals to learn the physiology of humans [1]. Nonetheless, systematic use of animal models in contemporary biomedical and veterinary studies occurred in the late 19th century and early 20th century as a result of the emergence of germ theory and experimental pathology [2]. These baseline research works confirmed that controlled experiments in animal models could help in offering reproducible data on disease pathogenesis and therapeutic reactions that could not be attained by observational research on their own.

Animal models are characterized as non-human living organisms that have been utilized to study biological processes, disease pathogenesis, or therapeutic interventions with the aim of obtaining information that could be used in other species, especially the humans and domestic animals [3]. The main assumption in animal model research is that preserved biological processes across species allow generalization of model organism results on target species which has been upheld by evolutionary biology and comparative physiology [4].

Various factors such as phylogenetic relationship with the target species, compatibility of anatomical structures and physiological systems, recapability of disease phenotypes, pragmatic aspects such as breeding behavior and housing needs and ethical suitability of the animal models used in research are used to select the right animal models [5]. There is no ideal animal model that fully models all the features of human or veterinary diseases and results should be cautiously interpreted and verified in a variety of different model systems when possible [6].

Technological advancements in genetic modification, molecular imaging, genomic analysis and computational modeling have revolutionized contemporary animal research and enlarged the capabilities and the translational relevance of animal models [7]. At the same time, increased ethical consciousness and regulations have enhanced more humane and scientifically strict methodologies of animal testing, which manifests itself through the principles of replacement, reduction, and refinement [8].

2. Historic Development of Animal Model.

The use of animals in medical research dates back to the time of the ancient civilizations where Aristotle did comparative anatomy research and Galen did vivisection on pigs and primates to study human anatomy and physiology [9]. Nevertheless, these initial studies were largely observational and did not have a controlled experimental structure that is typical of present studies. In the 17th century, the scientific revolution brought experimental rigor to the study of animals, such as the case of William

Harvey, who demonstrated the circulation of blood by performing experiments on a variety of animal species [10].

The revolution in bacteriological studies at the end of the 19th century reshaped the animal model studies. Vaccination experiments in chickens, sheep, and cattle against the cholera and anthrax by Louis Pasteur, showed the possibility of animal models to be used to understand disease processes as well as to design and test preventive interventions [11]. Formulated based on animal experiments, Robert Koch was able to determine the causal relationship between certain microorganisms and diseases [12].

At the beginning of the 20th century, researchers like Clarence Cook Little developed the first laboratory mouse colonies, which formed the basis of standardized genetic strains, which rose experimental reproducibility and aided the rise of mammalian genetics [13]. These mouse strains were inbred and they formed the basis of immunological studies, cancer biology and toxicology studies.

The second part of the 20th century was marked by the encroachment of the methodology of molecular biology into the research of animal models. In 1980s, transgenic technology was developed, which allowed the insertion of foreign genes into the genome of animals, allowing the investigation of gene functionality and the development of disease models [14]. This enabled gene targeting in embryonic stem cells using homologous recombination and creating knockout mice with controlled and accurate modification of endogenous genes [15]. Most recently, CRISPR-Cas9 genome editing has made genetic modification democratic, allowing very fast and accurate I can generate animal models in a variety of species [16].

3. Common Animal Models and Some of the Uses.

3.1 Rodent Models

About 95% of all laboratory animals in the study all over the world are mice and rats [17, 46-47]. Their extensive use expresses many practical and scientific benefits such as limited size, brief generation period, elevated fertility, comparatively cheap maintenance, comparatively known genetics, and broad accessibility of research tools and reagents [18].

Mice have a unique genetic tractability with thousands of inbred strains, genetically modified lines and mutant collections present in repositories like the Jackson Laboratory [19]. There are strain types that are used in various research applications such as immunodeficient mice to study immunografts, spontaneous disease models such as NOD mice used to study diabetes, as well as humanized mice with normal human immune system used to study infectious disease and immunotherapy [20].

One of the areas that rats are beneficial is in regard to their bigger size, which eases the surgical process, blood sampling, and monitoring physiological conditions [21]. Rat models have found specific use in neuroscience studies, cardiovascular physiology, toxicology and behavioural research.

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3.2 Large Animal Models

Large animal models, such as the pigs, sheep, dogs, and non-human primates have the advantage of being anatomically and physiologically similar to humans that are not possible with smaller animal species [22]. The models are especially useful in the development of surgical techniques, the testing of medical devices, and in the field of translational research in organ transplantation, cardiovascular surgery, and orthopedic surgery.

Perhaps the most useful translational model is the pig which shares its organ size with humans, exhibits similar cardiovascular and gastrointestinal physiology, and has the same skin structure [23]. The use of porcine models has contributed to the creation of techniques in interventional cardiology, research on wound healing and xenotransplantation [24].

Canine models have been very useful in orthopedic research, hereditary disease research and cancer research, and spontaneously occurring canines in dogs have been used as spontaneous models in comparative oncology research [25]. Through the domestic dog, there are more than 350 known hereditary diseases, many of which have homologous diseases in humans, and which make the dog a useful source of disease genes and therapeutic approaches [26].

The best-known phylogetically closely related models of humans are non-human primates (especially rhesus Macaques and cynomolgus Macaques) [27]. The translational benefits of studying neuroscience, infectious diseases and the development of vaccines are the genetic, anatomical, physiological and behavioral parallels with humans [28]. Nevertheless, their application is fraught with a lot of ethical issues, expensive nature and practical difficulties which require close justification [29].

3.3 Aquatic and Avian Models

Zebrafish has now taken an important place as a model of vertebrates because of their low size, high fecundity, transparent embryos that allow real time observation of embryonic development, quick development and genetic manipulability [30]. The zebrafish models have been especially useful in developmental biology, tox screening, cardiovascular studies and high throughput drug discovery [31].

The classical developmental biology models have been chicken embryos, whose access, low cost and external development have enabled experimental manipulations [32]. Avian models are still used in embryonic development research and in vaccine preparation research.

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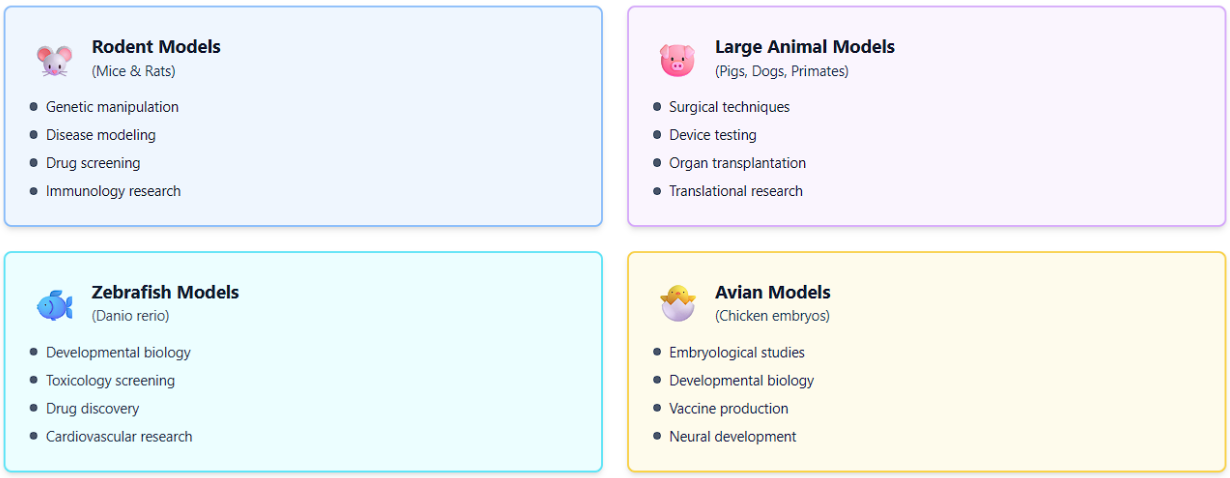

Figure 1. Comparative Overview of Major Animal Model Systems

Each model system offers distinct advantages: rodents for genetic manipulation and disease modeling, large animals for surgical and device testing, zebrafish for developmental and toxicology studies, and avian models for embryological research.

4. Disease Modeling: Applications.

4.1 Infectious Disease Models

For the study of the pathogenesis of infectious diseases, the assessment of antimicrobial activity, and the creation of vaccines, animal models have played a significant role. The appropriate models mimic such features of human or veterinary infections as the routes of transmission, tissue tropism, immune response, and disease progression [33].

Mice have widely been used in bacterial, viral, fungal and parasitic infections, but species differences require close interpretation [34]. The emerging infectious diseases such as Ebola, Zika virus, and SARS-CoV-2 have required the use of non-human primate models as the key systems to test vaccines and develop therapeutics [35].

4.2 Cancer Models

Animal models of cancer have developed on the earlier transplantable tumor cell lines to include more advanced genetically engineered models that replicate tumor initiation, tumor progression, tumor metastasis, and tumor response to therapy [36]. Other models such as xenograft models which involve the implantation of human tumor cells into mice with no immune system continue to be used in preclinical screening of drugs [37].

Mice with oncogenes successfully transferred into the genome or tumor suppressor inactivation in genetically engineered mouse models give more physiologically relevant systems that form tumors in the native tissue environment with normal immune systems [38]. The spontaneous cancer models in the

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companion animals, especially dogs, have become an acknowledged useful comparative oncology model that fill the gap between rodent models and human clinical trials [39].

4.3 Disease Models of Cardiovascular and Metabolic Diseases.

Use of animal models has played a significant role in explaining the mechanisms of cardiovascular diseases and the therapeutic interventions. The atherosclerosis models in mouse, rabbit and pig have offered information on lipoprotein metabolism, dysfunction of endothelial and plaque formation [40]. Animals have been pivotal to the concept of designing and testing cardiovascular devices and interventional surgery [41].

Models of animal diabetes mellitus, obesity and metabolic syndrome have been well developed and characterized. Spontaneously diabetic NOD mouse is a model of type 1 diabetes whereas genetically obese mice is a model of type 2 diabetes [42].

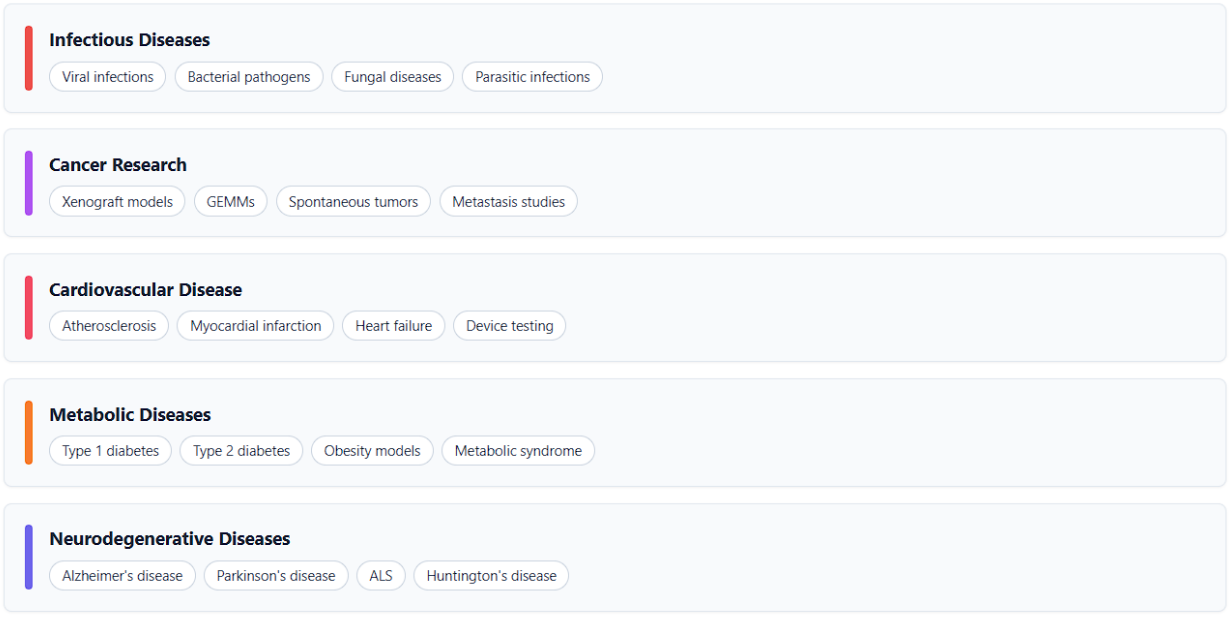

Figure 2. Applications across Major Disease Categories

Disease modeling spans infectious diseases, cancer research, cardiovascular conditions, metabolic diseases, and neurodegenerative disorders. Each category requires model selection based on disease-specific requirements and translational goals.

5. Improvements in Technology in Animal Model Research.

With the introduction of programmable nucleases, and specifically the CRISPR-Cas9 systems, animal model generation has been revolutionized through the ability to make rapid and precise modifications to the genome at low cost [43]. CRISPR technology has made it possible to knock out and knock-in, knock out point mutations and chromosomal rearrangements in a variety of species that have previously been difficult or impossible to genetically modify [44].

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Non-invasive imaging modalities have revolutionized studies of animals by allowing longitudinal studies in single animals and decreasing the number of animals needed and allowing visualization of biological processes dynamically. Fluorescence and bioluminescence imaging can be used to monitor gene expression, tumor proliferation and cellular migration in living animals. Sophisticated imaging systems such as micro-computed tomography, magnetic resonance imaging and positron emission tomography modified to fit the needs of small animal research have anatomical and functional data resolutions close to those of clinical systems.

Omics technologies such as genomics, transcriptomics, proteomics and metabolomics have been incorporated in the research of animal models that offer a holistic molecular description of the biological states. Single-cell RNA sequencing is the profiling method that allows the study of cellular heterogeneity in tissues and uncovers the responses of cells of a particular type that are not detectable by analyzing bulk tissues.

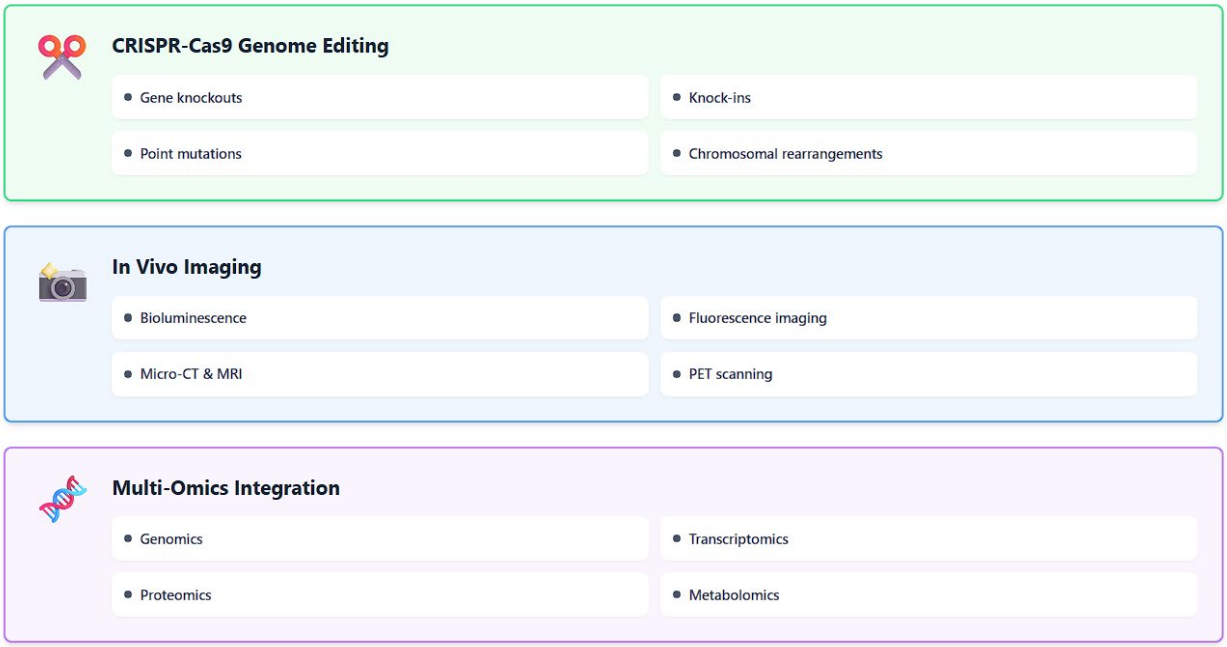

Figure 3. Technological Innovations in Animal Model Research

CRISPR-Cas9 genome editing, in vivo imaging modalities, and multi-omics integration have dramatically expanded the precision, efficiency, and translational potential of animal model research.

6. Ethical Rationale and Legal Standards.

Animal research is governed by the ethics principle of replacement, reduction, and refinement, which were initially formulated by Russell and Burch in 1959 [45]. Replacement is a technique that does not involve the use of animals or it substitutes. Reduction entails schemes that reduce the number of animals but statistical validity is achieved. Refinement involves processes which reduce pain, suffering and distress and optimize the welfare of animals during the research.

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The use of the Three R's has already been integrated into regulatory measures and institutional animal care and use committees in considering proposed research protocols in regard to these principles throughout the world. Various jurisdictions have very large regulatory requirements on animal research, but broadly research protocols must be prospectively reviewed and approved by institutional ethics committees.

Ethical research practices and scientific validity also require the objective evaluation of animal welfare in research. Welfare assessment is used in conjunction with physiological indicators, behavioral, and clinical scoring systems to identify and reduce adversity welfare levels. Strategies to be refined can be environmental enrichment, analgesic and anesthetic use, training and voluntary participation in the procedures by the animals and humane endpoints to reduce suffering, but still achieve the scientific goals.

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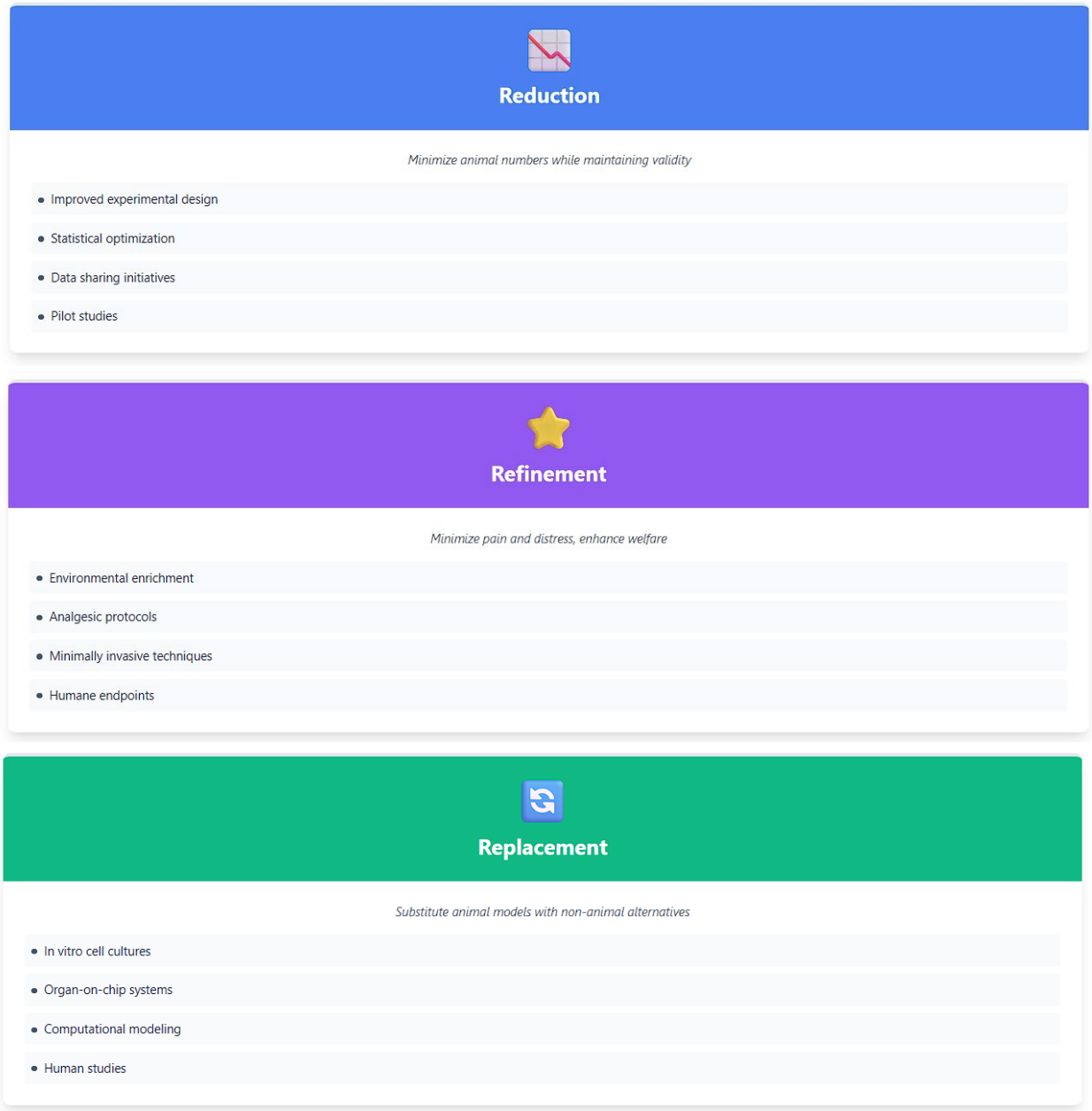

Figure 4. The Three R's Framework for Ethical Animal Research

Replacement, Reduction, and Refinement represent fundamental ethical obligations in animal research, balancing scientific objectives with animal welfare considerations.

7. Challenges and Limitations

Although animal models have played an important role in biomedical wisdom, translational failures are still a great problem, and despite numerous interventions being effective in the animal models, they do not always translate their efficacy in human clinical trials. Differences in species anatomy, physiology, genes, lifespan, and environmental exposures are some of the causes of translational gaps. Ineffective

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experimental design such as insufficient sample size, absence of randomization and blinding and selective reporting have been cited to decrease reproducibility and translational success.

Immense interspecies variations are found in immune systems, metabolic pathways and drug metabolic processes that influence disease vulnerability and reaction to therapy. The pharmacodynamics and pharmacokinetics of the different species require the attention of specific dose selection and delivery route in cases where animal studies are to be applied to human use.

Although genetic uniformity of inbred laboratory strains has improved the experimental reproducibility, this may not be the genetic variation found in human populations. Strain-specific phenotype may influence the susceptibility and response to therapy with one strain being responsive to a particular intervention and not responsive to another.

8. Other and Complementary therapies.

Science Cell culture systems offer an animal research substitute study to particular research enquiries, such as screening studies and cellular mechanistic studies. Three-dimensional culture models such as organoids have a high capacity to recap tissue architecture as opposed to conventional two-dimensional cultures. Organ-on-a-chip technologies combine microfluidics with human cells to form micro-physiological systems that can model the functions of an organ. Although these systems have the benefits of human-relevant biology, they are not capable of yet living up to the complexity of intact organisms.

Physiologically-based pharmacokinetic modeling and artificial intelligence-based predictions are computational methods that are used to supplement experimental research more and more. Computational models are models that combine current data and are used to predict future outcomes, designs of experiments and to minimize the number of animals needed. Nevertheless, computational models have to be experimentally validated and suffer due to the quality of underlying data.

The modern practice focuses on the combination of various methodologies of tiered testing plans which include in vitro, in silico, and in vivo tests used in a complementary manner. Reducing the use of animals through integrated approaches can be done without jeopardizing scientific quality because animal studies are narrowed down to the most promising interventions and the most relevant questions.

9. Conclusion

Experimental animal models have been and still remain invaluable to veterinary medicine and biomedical research. Their work covers knowledge on the basics of biological mechanisms, the mechanisms of disease, development of treatment regimens, and evaluation of safety and efficacy. The variety in the models of animals offers a continuum of experimental systems that aligns research questions to the right models.

Genome editing, imaging, omics profiling, and computational analysis technological advances have significantly provided animal models with new capabilities and translation potential. At the same time,

ethical standards and governance have also developed to provide human care and encourage application of the principles of replacement, reduction and refinement.

There are still problems with enhancing the success of translation, overcoming species-related variations, and increasing reproducibility. The future of animal model study is in combination with other complementary methods such as human-relevant in vitro models, computational modeling, and precision medicine approaches. This type of integrated strategy, that combines the advantages of multiple methodologies, has the potential to provide more efficient, human-centered, and translational research that is still able to contribute to the development of scientific knowledge and improve human and animal wellbeing.

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