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Review Article

Exploring the Landscape: Advancements, Challenges and Future Perspectives in Rodent Models for Biomedical Research

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ABSTRACT

Biomedical research, a subfield of science examines life processes, the causes, symptoms, prevention, and treatment of diseases, as well as the genetic and environmental components of health and illness. Biomedical research requires, animal experimentation research which attempts to solve issues in clinical practice and provide novel techniques and strategies for the prevention and treatment of illness and incapacity. Preclinical research using animals has improved medicine over the past century and is still improving it now by increasing our understanding of a wide range of diseases and providing doctors with new, secure, preventative tools. In this review, we have focused on the use of rodents in the field of biomedical science, including genetic engineering, humanization, and immunology. We have also discussed the current state of the art of animal models and their applications in the fields of biomedicine.

INTRODUCTION

Biomedical research is the branch of science that studies life processes, disease understanding, prevention, and/or treatment, as well as the genetic and environmental factors linked to health and sickness [1]. Characterizing genes and proteins, studying anatomical and physiological processes, and characterizing normal and diseased states in a range of animal species are all aspects of basic biomedical research [2]. An animal model used in biomedical research is described as "a living organism with an inherited, naturally acquired, or induced pathological process that in one way or another closely resembles the same phenomenon in human". Experimental research with animal models ultimately aims to address problems in clinical practice and develop new methods and approaches for the treatment and mitigation of disease and disability [3]. For more than a century, many species like non-human primates, zebrafish, fruit flies, roundworms are employed in biomedical research, but rats and mice are the most common model organisms that are used [4].

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Rodents, including mice and rats, can cause inconveniences in our daily lives, such as harming home objects, rotting food, and transmitting illnesses. However, they can also be useful for scientific study, as they are essential components of bioresearch [5] and have contributed to the development of almost all prescription medications in the market today. Animal research also rescues animals, leading to the development of therapies that can save or prolong the lives of various species, including cats, dogs, farm animals, wildlife, and endangered species [6]. The order Rodentia, which includes about 2200 species, is by far the largest order in the class Mammalia and includes rats and mice. The Muridae family, which includes the Old-World rats and mice (a sub-family of the Murine that includes rodents found in Eurasia, Africa, and Australia), is the biggest family within the Rodentia with over 700 species. Of these, the vast majority of animal studies utilized for biomedical objectives employ strains derived from Mus musculus and Rattus norvegicus [7]. Unquestionably, the use of animals in biomedical research has advanced medicine over the last century and continues to do so today, expanding our knowledge of a wide range of illnesses and giving medical practitioners new, safe, and preventative tools. On the other hand, moral questions brought up by animal research have traditionally ignited heated discussion and produced a wide range of public opinion [8]. Both scientists and the general public generally agree that using animal models in science, and especially in biomedical research, is essential to the development of practical information that alleviates suffering. It is, however, unclear to those outside the biomedical research community why these animal models are considered significant [3].

1. HISTORICAL CONTEXT

1.1 Early utilization of rodents: Before 1850, work on the rat was conducted, making laboratory rats the first domesticated mammal species used for scientific study [9]. Since then, the rat has taken the lead in several scientific domains, including pharmacology, physiology, neurology, genetics, and medical sciences [10]. Studies of physiological processes and disease pathways have long been conducted using rat models [11].

1.2 Advancements in genetics and strain development: The biology of over 500 laboratory rats, primarily used as models for complex illnesses, is the rat species' greatest biological asset. Inbred strains of rats have been used to create useful models, with recombinant inbred strains created by outcrossing two inbred strains and inbreeding for at least 20 generations. Each recombinant inbred strain has a distinct, fixed genome, combining the original parental genomes [12].

1.3 Rodent as models for human disease: Due to the shared homology between rodents and humans, rodents are widely utilized as animal models for investigating human diseases [13]. The fundamental understanding of human disease is mostly gained through the use of mice models, and this understanding is then applied to preclinical research using the same animals as models [14].

2. APPLICATIONS OF RODENT MODELS

Rodent models have been core for discovering many therapies and underlaying mechanism in diseases. It has been widely used in various biomedical studies (Table-1).

2.1 Neuroscience: In its broadest sense, neuroscience studies how the brain learns and remembers at all levels, from molecules and cells to brain systems (such as the network of cerebral pathways and areas that support our ability to speak and understand language) [15]. Rodents are the most common small laboratory animal used in the study of human brain diseases and possible treatment approaches.

Psychiatric disorders including obesity, depression, and anxiety are included in rodent models of human brain illnesses, along with the major neurodegenerative diseases and stroke. Rats may be used for a wide range of tests using either in vivo or ex vivo techniques; in humans, these measurements are not feasible, and in nonhuman primates, they would be prohibitively expensive [16].

2.2 Oncology: The term "cancer" refers to a group of malignant illnesses that can affect various bodily organs. The hallmark of these disorders is the fast and unchecked proliferation of aberrant cells, which can aggregate to form tumors or growths, or they can spread throughout the body and trigger aberrant growth at other locations [17]. In terms of morbidity and mortality cancer has become the second most dangerous disease and has always gained human attention due to this. This makes cancer a focus of intense medical investigation. The use of animal models in cancer research can aid in our understanding of the genetic basis of the disease and the function of particular genes and gene mutations in the onset and progression of cancer. It also makes the creation and testing of anti-cancer medications easier [18]. The mouse genome is extremely similar to the human genome, offering the benefits of easy gene modification, affordability, and straightforward feeding. It can also mimic a number of biological characteristics, including the incidence, development, and metastasis of human cancer cells in vivo [19]. It offers a useful platform for drug development and validation in addition to being a helpful tool for cancer research. Pigs provide excellent animal models for cancer research because of their close resemblance to humans in terms of anatomy, physiology, and genetics. Mitchell et al. used diethyl nitrosamine (DEN) to establish hepatocellular cancer in pigs and discovered that partial hepatotic embolism might aid in the model's development [20].

2.3 Immunology: Mice research has made significant contributions to our understanding of the adaptive immune system, including the identification of the T cell receptor and the major histocompatibility complex genes, as well as the regulation of antibody synthesis and numerous other immune system functions [21]. For instance, studies on mice produced the first descriptions of the T cell receptor, the major histocompatibility complex, and antibody production [22].

2.4 Cardiovascular research: cardiovascular disease, which is primarily caused by a mix of environmental and hereditary factors, is the primary cause of morbidity and mortality in affluent nations [23]. Because of their robust reproductive ability, simplicity of detection, and ability to simulate human cardiovascular illnesses, experimental rodent models are frequently employed in cardiovascular disease research [24].

2.5 Genetic and Genomics study: Over the one and half decades, the use of rats for genomic and genetic research has steadily increased, despite the fact that they are still predominantly used as "physiological" models. Positional cloning and transgenesis are the main approaches in genetics research [12]. Pronuclear injection has been the standard method for transgenesis of rats since 1990, with over 200 transgenic rats created [25-26].

2.6 Drug development and toxicology: When it comes to fundamental pharmacokinetic factors including medication effectiveness, safety, and toxicological research, animal models are seen to be the most significant in vivo models because these pre-clinical data are necessary before translating into human trials [27].

Among animals, rodents are essential to any program aimed at finding and developing new drugs [28]. The study of poisons and toxins, as well as how to treat them, is known as toxicology. The creation of novel medications and the expansion of the therapeutic range of already-existing compounds both heavily depend on toxicological screening [29]. Numerous animals are used in toxicological testing to determine a drug's overall toxicity, mutagenicity, carcinogenicity, and teratogenicity as well as whether it irritates the skin or eyes. Before moving further with medical studies, both in vitro and in vivo models are typically validated [30]. Rat, mouse, and hamster are the most commonly used rodent species in toxicology, with rats and mice being the most commonly used in experimental biology and medicine. They are crucial in identifying toxicities linked to drug, industrial, and agricultural chemical exposure, assessing potential hazards, and understanding their underlying processes [31].

2.7 Aging and age- related studies: The aging process is linked to a steady, time-dependent increase in vulnerability to illness. Although the maximum life span varies throughout creatures, almost all known organisms age. Significant advances in our knowledge of the mechanisms underlying aging and the development of therapies aimed at extending life and improving health have resulted from research on the causes of aging. Model organisms have yielded important insights, including the identification of conserved mechanisms that might control human aging. Common models used to investigate aging and age-related disorders are laboratory rats and mice. An explosion of aging-related research has centered on these models due to their abundance of background knowledge, ease of use, ability to control environmental conditions, genetic manipulability, and cost. Furthermore, compared to long-lived animals, they are easier to research due to their shorter life duration than humans [32]

Table 1: Use of Rodent Models in Various Biomedical Studies

Applications	Description	References
Neuroscience	Behavioral studies: Rodents provide insights into learning, memory, anxiety, depression, and other behaviors.	[16]
	Neurodegenerative diseases: Transgenic models aid in studying Alzheimer's, Parkinson's, and other neurodegenerative diseases.	[15]
Oncology	Cancer modeling: Genetically engineered models facilitate the study of cancer biology and testing of anticancer therapies.	[18]
	Tumor immunology: Rodents are used to understand tumor microenvironment and test immunotherapies.	[18]
Immunology	Infectious diseases: Rodents help study host-pathogen interactions and develop vaccines and antiviral drugs.	[21]
	Autoimmune diseases: Models aid in understanding mechanisms and testing immune-modulatory therapies.	[21]
Cardiovascular Research	Heart disease models: Rodents help study myocardial infarction, heart failure, hypertension, and more.	[23]
	Atherosclerosis studies: Models aid in understanding plaque formation and testing interventions.	[24]

Genetics and Genomic Studies	Gene function: Rodent models allow for studying gene function, regulation, and effects on health and disease.	[25]
	Human disease genetics: Models help understand genetic factors associated with diseases and test targeted therapies.	[26]
Drug Development and Toxicology	Pharmacology studies: Rodents are crucial for preclinical testing of drugs, assessing pharmacokinetics, toxicity, and efficacy.	[28]
	Toxicology and safety testing: Models help evaluate the safety of chemicals, drugs, and environmental exposures.	[29-30]

3. ADVANTAGES OF RODENT MODELS

3.1 Genetic similarity to human: Compared to other non-mammalian models like C. elegans, Drosophila, and zebrafish, rodent models are more similar to humans in terms of genetic architecture, brain anatomy, and behavioral traits [33]. There are around 30,000 genes in each of the three species-rats, mice, and humans-of which about 95% are common genes [2].

3.2 Easy to handle: With short legs and a compact body, the majority of extant rodents are rather small. But compared to other mammalian orders, their size range is significantly wider [34]. The main advantage of compact size is that a group of 8-10 animals may be kept and cared for in a cage that is not much bigger than a shoebox. Additionally, tiny size is associated with rapid growth and aging [35].

3.3 Cost effectiveness: Using rodents for research has financial benefits because mice and rats grow to adulthood fairly quickly, have short life spans, require little space or resources to maintain, and have short gestation periods compared to the number of children they produce [2]. Rats are an economical animal to breed, raise, and study because of their short generation period and simplicity of breeding [11].

3.4 Well characterized strains: Rat strains come in a range of strain types, giving researchers a lot of alternatives when planning their studies [11]. Numerous rat strains have undergone selective breeding to achieve isogeneity after being polygenic with environmental influences, or multifactorial illness. The Rat Genome Database now contains 1015 rat strains, of which 538 (or more than 50%) are inbred strains for complex features. According to RGD's strain disease and phenotype ontologies, the disorders investigated in these strains include 168 distinct diseases, 393 phenotypes, and conditions ranging from seizures to multiple sclerosis to cancer. A single complex illness may have many inbred strains in some situations. For example, there is an elevated risk of multiple sclerosis (MS) in five distinct rat strains: BUF, DA, F344, LEW, and PVG [12].

3.5 Physiological and anatomical similarities: The anatomy and physiology of laboratory rats and mice are quite similar to those of humans, making them perfect animal models for biomedical research and studies of comparative medicine [2]. Rats, mice, and other rodents have significant physiological parallels to humans, which makes their use in preclinical research a powerful tool for advancing our knowledge of human illnesses and advancing the creation of novel treatment approaches [4, 36].

3.6 Behavioral homology: Current animal stress models only partially replicate the pathophysiological and behavioral changes that people experience as a result of stress [37].

3.7 Ethical considerations: The importance of scientific ethics in ensuring that experimental animals are treated humanely [38]. It's critical to adhere to ethical guidelines when doing animal research in order to prevent unnecessary suffering of the animals. From an ethical and scientific perspective, it is crucial to give these animals the finest human care possible. The results of experiments can be affected by poor animal care. Therefore, mistreatment of experimental animals has the potential to damage scientific information and conclusions drawn from the studies, making them difficult to replicate-a hallmark of scientific

research [39]. Currently, the majority of ethical guidelines operate under the premise that the substantial potential advantages to humans justify the use of animals in experiments.

4. LIMITATIONS OF RODENT MODELS

4.1 Genetic differences: Mice and humans are clearly distinct on many levels, despite their many similarities. Distinct species-specific factors influence how diseases develop, including size, architecture, neuroanatomy, longevity, heart rate, and treatment reactions. Even when it comes to genes, humans and mice do not quite have the same range; about 1% of mouse genes are absent from humans [40]. Furthermore, 3.4 splice isoforms on average per gene (3.4 isoforms per protein-coding gene) are found in humans compared to 2.4 in mice [41].

4.2 Physiological disparities: There are several anatomical, physiological, and biochemical distinctions between humans and mice that are connected with variations in metabolic rate. Mice possess comparatively greater quantities of metabolically active tissues, including the liver and kidney, and comparatively fewer inactive tissues, like bone. Moreover, mice have greater accumulations of brown fat, which is essential for heat generation and thermoregulation. In addition to their different mitochondrial density and metabolic rates, mouse cells also have different fatty acid compositions in their membrane phospholipids. Specifically, the polyunsaturated (and easily oxidizable) fatty acid docosahexaenoic acid is more prevalent in the membranes of mouse cells [42]. Compared to humans, mice produce more reactive oxygen species and experience more oxidative damage at greater rates.

4.3 Short life span: Although mice and rats have short lifespans, which would appear advantageous for lab animals, there is a significant drawback. Studying the fastest aging species may not yield all the answers needed, as the aim of aging research is life extension in humans, one of the slowest aging mammals [43].

4.4 Complexity of human disease: Animal models are commonly used to experimentally generate human diseases; nevertheless, their use is limited due to the great challenge of accurately replicating even the most complicated human diseases in these models [44]. An ideal animal model should mostly mimic the phenotypic of a human disease as well as its underlying causation; the latter should be achieved by a mechanism of action or mechanisms that closely resemble what is currently understood about the human disease. The distance between the patient and the model of their illness state is sometimes insurmountable as the latter is frequently not fully understood, which makes the usefulness of the animal model very dubious and in need of relevant context [45].

4.5 Size difference: Since humans are around 3,000 times larger than mice, their size has a substantial impact on their physiology and life history, which in turn affects how well-adapted they are to their surroundings [46]. With regard to imaging and radionuclide treatment research, the mouse's small size has significant ramifications. For example, it can limit the maximum amount that can be injected or the maximum volume of blood samples that can be collected. Another obvious consequence of mice's smaller size than that humans have is that, when it comes to imaging, far better resolution devices must be employed than in clinical settings [47].

4.6 Immune system difference: The immune systems of mice and humans are generally similar, but humans and rats exhibit distinct immunological and inflammatory responses. Dendritic epidermal T cells (DETCs) are found in the skin of rats and mice. These cells release a variety of cytokines that are involved in wound healing and skin homeostasis [48]. In contrast, Langerhans and CD8-positive T cells are present in human skin but DETCs are absent [49]. Furthermore, unlike human wounds, mice and rats do not show severe scarring. This might be partly attributed to their quicker pace of healing and the significance of wound contraction vs re-epithelialization in rodent wounds. Rapid immune system evolution occurs when pathogens and commensal bacteria coevolve with host species [50]. Given that humans and mice have distinct pathogen and microbiome compositions, it is not unexpected that coevolution

of the host-pathogen and host-microbiome has resulted in immunological disparities between the two species [22]. Mouse blood has a majority of lymphocytes (75-90%, 10-25% neutrophils), while human blood is neutrophil-rich (50-70%, 30-50% lymphocytes) [51].

5. IMPROVEMENT AND FUTURE DIRECTION

5.1 Genetic engineering and humanization: By inserting a human gene into transgenic rat strains, several strains have been "humanized," establishing a connection between human genetic linkage studies and the functional correlation of a mutant gene with certain clinical characteristics [12].

5.2 Use of humanized immune system: In biomedical research, immunocompetent mice are frequently employed, and their usage has aided several advancements in a variety of scientific fields. However, research on specifically human immune responses in mice has been hindered by significant genetic and immunological variations between human and mouse models. Conducting in vivo preclinical investigations utilizing immunodeficient mice engrafted with human cells or tissues, sometimes known as "humanized" or "human immune system" (HIS) mice, is one method to address these species-specific discrepancies [52].

5.3 Organoid and 3d culture system: Organoids are self-organizing, three-dimensional microsystems produced from stem cells. They have tissue-level functions, a variety of disease phenotypes, and a full three-dimensional architecture and physiology resembling an organ. In fact, they are regarded as in vitro generated tiny organs, offering researchers a plethora of opportunities [53]. Organoids are promise for researching human development, health, and sickness as well as for promoting regenerative therapy since they provide improved 2D models, are easy to manipulate, and can be transplanted. Research is promising despite difficulties with integration and reproducibility [54]. Preclinical medical research uses conventional 2D cell culture and animal models for drug testing, toxicity tests, cancer pathophysiology, disease modelling, and immunology investigations. However, these models lack in-vivo disease heterogeneity and are associated with costs, ethical dilemmas, and xenogeneity difficulties. Three-dimensional cell culture models, or organoids, have potential applications [55].

5.4 Microbiome consideration: Trillions of microorganisms, including viruses, fungi, bacteria, and other eukaryotic creatures like protists and parasites, surround and live inside humans as a species. These microorganisms are referred to as the microbiome [56-61]. Mice have distinct microbiome and have coevolved with distinct pathogen groups compared to humans. The two species have different gastrointestinal tract architecture [62]. The microbiota plays a critical role in immune-mediated illness models, and the phenotypic variations across rats from diverse settings must be taken into account in biomedical research. Scientists must take into account the viability of using animals and appropriately record their origins in accordance with ARRIVE (Animal Research: Reporting of In-Vivo Experiments) rules [63]. Since diet has a significant impact on the microbiota, suppliers need to disclose the health of their animals in response to this circumstance [64,65]. Microbiota sequencing approaches have become more cost-effective than bacterial pathogen production due to their rapid development and cost reduction. In the long run, routine sequencing will become more cost-effective in biomedical research because it will gain expertise in accounting for the effects of microbiota on animal models.

5.5 Integration of big data and system biology: Understanding biological things at the system level is the goal of systems biology, which has applications in synthetic biology, metabolic engineering, and medicine [66]. Even though systems biology makes use of standard methodologies, their applications to biological complexity present new opportunities as well as obstacles [67].

5.6 Personalized and precision medicine approaches: Precision medicine is an evidence-based medical practice that selects an individual's optimal course of action based on their genetic and

epigenetic composition as well as other factors including age, lifestyle, diet, microbiota, and certain biomarkers. The ethical and practical constraints associated with conducting research on humans, especially children, impede the potential to fully exploit precision medicine [68]. Before being implemented in a clinical setting, any medicines or treatments under consideration for "precision medicine" must undergo testing in preclinical models. Because of this, several researchers have resorted to using animal models as stand-ins for human immunology, each with pros and cons [69]. The most popular animal model for immunology research is the mouse, which has yielded many important insights into the development of mammalian immune systems and how they interact with various immune cells [70].

5.7 Advanced imaging technologies: Throughout the past forty years, imaging has transformed biomedical research, and advancements are happening at an accelerating rate. In an effort to find new structural and functional information specifically related to human pathobiology, scientists have developed state-of-the-art imaging technologies as a result of the enormous difficulty of annotating the whole mouse genome [71].

6. ETHICAL CONSIDERATIONS

6.1 Animal welfare standards: Animal welfare is a foundation for laboratory animal medicine and research, focusing on a measurable state in an animal's ability to cope with its environment. It is a branch of science that examines these measurable states in various areas of our interaction with animals, including agriculture, entertainment, and research [72]. Congress of the United States passed. The Animal Welfare Act (AWA), which guarantees that animals used for exhibits, pets, or research would be treated with dignity and compassion. Animal welfare encompasses taking into account the health and mental welfare of animals. The care and application of animals in biomedical research is governed by a number of bodies. Animal and Plant Health Inspection Service (APHIS) enforces the AWA, which is supervised by the United States Department of Agriculture (USDA). The Public Health Service (PHS) and the Animal Welfare Act (AWA) have policies on the treatment of animals used in scientific research in the United States, which vary depending on the kind of animal and the funding source [1].

6.2 Minimization of discomfort and distress: Both the welfare of study animals and the results of scientific tests can be significantly impacted by discomfort and distress, although in subtle but significant ways. Due to the significance of animal suffering and distress in the context of biomedical research, national and international authorities have passed laws and regulations aimed at reducing the suffering of research animals [73].

6.3 3Rs (Replacement, Reduction, Refinement): Replacement, Reduction, and Refinement are the "3 R's" that regulate the humane use of animals in research (Figure 1) and the 3Rs guidelines have gained international recognition as a best practice for researchers using lab animals throughout time. [74]

- Refinement - Refinement (of protocols, methodologies, research designs, and husbandry practices) can lessen the degree of impacts and lessen the suffering, agony, and long-term damage that animals endure. [75]
- Reduction - The concept of "reduction" suggests that scientists employ fewer experimental animals in their studies in order to collect only the minimum amount of data necessary to get conclusions that are adequately instructive. [76]
- Replacement - When beginning any activity involving the use of animals, it is important to evaluate the replacement or complementarity of animal testing with alternative approaches such as mathematical models, computer simulation, and in vitro biological systems. [77]

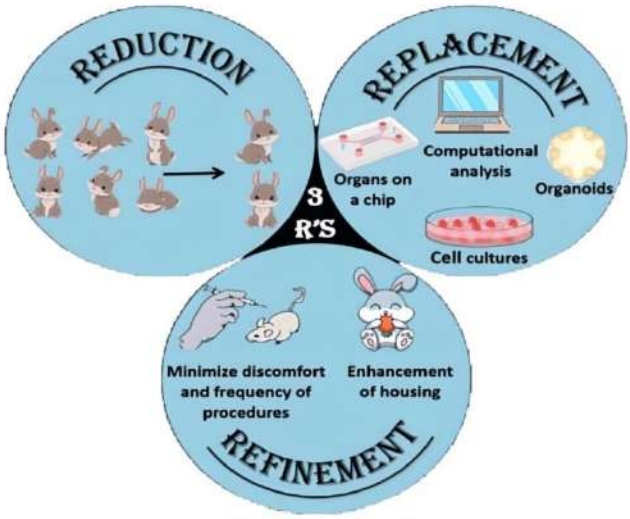

Figure 1: The 3R's of animal research- ethics and alternative ways

6.1 Institutional animal care and use committee-oversight: The IACUC is mandated by federal laws, rules, and policies to ascertain that staff members possess the necessary training and qualifications to provide care to animals or carry out research with them [78]. The IACUC is a committee that is qualified to manage its institution's animal program, animal facilities, and animal use protocols due to the experience and knowledge of its members. There are two principal roles for the IACUC. Assuring that its home institution (such as a university) continues to abide by federal laws, regulations, and policies regarding animal care and usage is the first and principal duty. Providing assistance in ensuring the wellbeing of animals used in research, education, and testing is its second role, which is closely tied to the first [79].

6.2 Alternative methods and technologies: In order to learn about disorders and provide safe therapies, animals are used in scientific and medical research. The possibility of animal suffering, however, makes this approach problematic and presents a question of ethics because the animals may suffer. For research reasons, replacement technologies like transcranial magnetic stimulation and magnetic resonance imaging (MRI) are being developed. Originally intended for therapeutic usage, MRI is currently being substituted for animals in some investigations. In healthy subjects, transcranial magnetic stimulation momentarily impairs brain function, making brain function research more precise and productive [80].

7. CONCLUSIONS

In conclusion, this comprehensive exploration of rodent models for biomedical research has shed light on the advancements, challenges, and future perspectives within this critical field. Rodents, particularly mice and rats, have played a pivotal role in advancing medicine and have significantly contributed to our understanding of various diseases. Their genetic similarity to humans, cost-effectiveness, and well-characterized strains makes them valuable assets in preclinical research. While these models have undeniable advantages, it's crucial to acknowledge their limitations, including genetic and physiological differences from humans, as well as ethical considerations regarding animal welfare. However, advancements in genetic engineering, humanization, organoid systems, and big data integration are paving the way for more sophisticated and targeted research using rodent models. Moving forward, it's imperative to maintain a strong focus on ethical standards, embodying the 3Rs (Replacement, Reduction, Refinement), and ensuring the highest level of animal welfare through oversight committees and the pursuit of alternative methods and technologies. As the landscape of biomedical research continues to evolve, it's essential to integrate state-of-the-art technologies, such as advanced imaging and personalized medicine

approaches, to further enhance the utility and ethical practice of rodent models. By embracing these advancements and upholding ethical standards, the future of biomedical research using rodent models holds great promise in advancing human health and scientific knowledge. This exploration serves as a reminder of the continuous need to balance scientific progress with ethical responsibility, ensuring that the invaluable contributions of rodent models in biomedical research are conducted with the highest standards of welfare and integrity.

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