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# Animal models: A powerful tool for the study of human diseases

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**Abstract.** The application of animal models is an alternative approach to studying human diseases and developing new drugs without direct trials on humans due to ethical and technical restrictions. The animal model is a widely used approach to study human metabolic diseases since humans and animals share a high similarity of biological and physiological features. With the development of genetic engineering technology, its application has evolved to simulate human diseases in animals as human wills. This paper summarized the literature concerning animal models to provide an overview of the course of animal models application, the selection criteria of animal species and the limitations of their application. It can be concluded that animal models, at present, should mainly serve as a medical tool to provide clinical recommendations for the treatment of human diseases and new drug development as there are nonnegligible biological, financial and ethical problems associated with the application of animal models, for instance, different intolerance of chemicals, low input conversion efficiency, and animal welfare considerations.

**Keywords:** Animal model, Human disease, Animal testing, Animal welfare

## 1. Introduction

Metabolic disease is a great risk that compromises human health and life expectancy. Throughout world history, humans have been putting tremendous effort into understanding the mechanisms of diseases and developing new medicines and physical treatments. However, humans have not yet found out all the treatments to cure these diseases. Only a small portion of diseases has been overcome by humans and there has been a great blank in the treatment of a great number of diseases such as Human Immunodeficiency Virus (HIV) and cancer. One of the significant obstacles that restrain the progress of human medicine is the lack of human patients as experimental subjects due to human ethics and social security concerns. To overcome this challenge, animals have been used by humans as an alternative clinical approach to understanding human disease for more than 2000 years since they are highly similar to humans in terms of physical structures and physiological functions. Although they share similarities in certain aspects with humans, they are genetically different and grow up in different environments, which makes the animal test results less valid on humans. Thus, based on the existing literature, this paper aims to provide an overall picture of the application progress of animal models throughout history and discuss the main drawbacks of animal models in clinical research. It can provide background information and ideas for future research in animal models, particularly in the aspect of reducing the shortcomings of animal models.

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## 2. Overview of animal models

Metabolism plays a central role in maintaining the balance of essential nutritional substances and energy in and out of the human body. The research on human metabolism can not only facilitate a deep understanding of this process but also make great progress on the breakthrough of current medical treatment. However, there have been some long-standing challenges in studying human metabolism throughout history. One of the most significant challenges is the difficulty of conducting medical experiments or practices on real patients or volunteers due to human ethical prohibitions and technical limitations. Alternatively, animal models make it possible to run those medical experiments that are forbidden to be conducted on humans. They can provide a potentially effective approach for researchers to imitate aspects of human diseases caused by chronic or acute abnormal metabolism in non-human species to acquire important information for the prevention, diagnosis, and treatment of such diseases [1].

Among all animal species, mice, fruit flies, nematodes, pigs, rabbits, zebrafish, and guinea pigs are the common ones used as animal models to study human metabolism [1]. For instance, mammalian animals, particularly mouse models, have been widely used as study objects in modelling human diseases since they share many genetic and physiological similarities with humans [2-3]. Chowdhury et al. used a mouse model to study human congenital heart defects and revealed that the mice model can replicate the highly penetrant and progressive atrioventricular block phenotype discovered in human heterozygous missense mutations in NKX2-5 homeodomain by knocking in a comparable missense mutation [4]. Apart from common mice models, zebrafish were also utilized to model a wide range of human diseases. Poss et al. discovered that a zebrafish's heart can overcome the scar formation period and fully recover within two months after 20% of ventricular resection [5]. This discovery indicates that zebrafish models could be a powerful tool to study cardiac regeneration, which would be useful for heart injury treatment in humans. In combination with advanced genetic engineering, animal models can also become a powerful tool to study human diseases from a molecular perspective. Gene knocking is included in the gene edition. Also, in Yang et. Al's study, they used zinc finger nuclease as a gene editor to induce a defined mutation in peroxisome proliferator-activated receptor-gamma (Ppar-γ) in pigs which is the selective acceptor of Thiazolidinediones (TZDs) via the somatic cell nuclear transfer route (SCNT). Previous experiments on mice showed that cardiovascular diseases would benefit from the TZD-mediated activation of PPAR-γ, but it cannot be applied to the therapy of human patients as it would potentially bring adverse effects on the heart. Since its health risks have not been confirmed on other animals yet, the knockout pig model with PPAR-γ mutation, as a result, would contain huge values to provide further insight into the positive and negative role that PPAR-γ would play in the treatment of human cardiovascular diseases [6]. Therefore, genetic engineering technology reveals the possibility of artificially inducing mutations associated with human disease in animals to understand how this disease is potentially working in the human body, which is greatly significant for future medicine and drug development.

Previous studies on animal models have proved their potential and efficacy in understanding the mechanism of human diseases and developing their underlying treatments. However, since animal species and humans are genetically different, their responses to experimental interventions usually differ from humans. For instance, in clinical tests, the safety level of toxic chemicals for animals is usually harmful to humans [7]. Under current experimental conditions, it is impossible to completely overcome these barriers to make all the results of animal tests accurately reflect on humans. At present, the primary purpose of animal models is to provide insight into the pathogenesis of human disease and promote drug development. Finding suitable human substitutes was, is, and will continue to be a tough task in medical research.

## 3. Rules that should be followed to select appropriate animal models

The first step in building up an animal model is to select the most informative animal species. Since animal models have been widely recognized as an alternative approach to study human diseases, the selection of proper animal species in modelling a particular human disease becomes enormously

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significant. According to Veening-Griffioen et al., the process of selecting a specific animal model is mostly affected by three general criteria: the availability of animal species, the availability of expertise, and its pathological similarities to humans [8].

The availability of animal species is a fundamental trait for traditional animal model selection. It mainly refers to the reproductive capacity of a particular animal species and means that the quantity of an animal species should support long-term animal experiments which usually require tremendous animal sample input and massive repetitive tests. Common animal species used for animal models such as rats and rabbits generally have a strong reproductive capacity and can reproduce a great number of descendants in a relatively short period. Their strong breeding ability not only ensures sufficient experimental materials for current animal research but also makes future research more sustainable and ecologically friendly [8].

Apart from the availability of animal species, the availability of expertise is also an important indicator emphasized in the process of animal selection. Generally, the concept of expertise is correlated with the known knowledge of an existing animal model and the availability of relevant tools or equipment for the research on these animals. Adequate knowledge of a specific animal species would avoid unnecessary time and resource input to develop a brand-new model. With years of research experience, researchers would have established a full picture of the internal structure of a few animal species, as well as their metabolism performance or pathological mechanisms in their bodies, so that they can choose an appropriate animal species to study a particular human disease within a short period. Along with the known knowledge of given animal species, the matched tools and types of equipment that have already been in place also ensure that animal research can be smoothly conducted. Otherwise, researchers would need to overcome many knowledge and technical barriers for an undeveloped animal model before it can be put into real practice. It is time-wasting and would result in unnecessary financial and resource costs [8].

The pathological similarities to a human would also be an important indicator for the evaluation of the goodness of an animal model. Since humans and animals grow up in different environments and share significant genetic differences, it is impossible to completely replicate the way by which the human body responds to metabolic diseases in animals. Under such circumstances, those animal species that have the potential to produce similar illnesses to humans would be primarily selected as experimental targets. Their results, however, still have certain deviations from human diseases and cannot be accurately applied to human medical research. The common approach to improve the representativeness of animal-modelling results is to find animal species that can spontaneously perform a studied human disease or induce a specific disease on an animal via physical, chemical, or biological modifications. In combination with genetic engineering, inducing the modification of genes is also an emerging approach to produce highly similar symptoms of human disease in an animal body. Although these approaches could increase the accuracy of an animal model to some extent, developing new animal models that share more pathological similarities with humans is still of great importance and should be an ongoing task [8].

In addition to the three criteria above, the 3R principle has also been implemented in some animal projects. The core idea of 3R principles were defined by Russel and Burch in 1959 and mainly includes three aspects: replacement, reduction, and refinement [8-9]. Replacement is an attempt to replace experiments on live creatures with in vitro experiments based on the data mainly obtained from prior in vivo, in vitro, or ex vivo studies. Reduction is usually achieved by optimal experimental design and statistics, mainly through statistical power calculation. Refinement is achieved by reducing the discomfort of animals with the best pre-procedure and post-procedure care. However, most applicants' interpretation of the implementation of 3R principles in their animal projects is usually blurred and not in detail [8].

## 4. Cases of application of the animal model

Humans have had an over-2000-year history of using animals to understand the physical structure and physiological mechanisms of human bodies. In light of the summaries from Ericsson et al., as early as

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the sixth century BCE, the ancient Greek medical scientist Alcmaeon of Croton determined that the brain is the controlling centre of intelligence and sensory by his observation in dogs. Later on, in the fourth century BCE, Aristotle used chicks to study embryogenesis and ontogeny. Despite some great discoveries being born in this early era, these discoveries still had some mistakes when reflecting on human bodies. Animal models did not become a true paradigm shift in our understanding of human physiology until the Renaissance. During this period, researchers have been using different animal species to explore the different metabolic mechanisms in humans throughout time [10]. One of the most extraordinary application examples of animal models at the time was the research by William Harvey. During his career life, William Harvey studied multiple species including eels and other fish, chicks, and pigeons by comparing the similarities and discrepancies of anatomic and functional properties of the heart and vasculature among these different animal species. He then inferred them to the human circulatory system and made an accurate and specific description of his discoveries in a series of seminal texts including *De Motu Cordis* based on what he observed in these animals [10-11]. Although the use of animal models increased rapidly in this period, the research on animals was more conducted by observation rather than by experiments [10].

Since the commencement of the twentieth century, there has been a dramatically increasing trend of using animals as experimental subjects instead of as observational subjects [10]. For example, in the 1920s, Frederick Banting successfully isolated insulin from dogs and received positive outcomes in the treatment of diabetic dogs. His discovery of insulin made him win the 1923 Nobel Prize in Physiology or Medicine. Soon after his discovery, insulin started its commercial production and many diabetic patients improved their life quality with the benefit of insulin shots [10,12]. During the 1940s, John Cade made a breakthrough in the treatment of depression. He accidentally discovered that lithium can have a calming effect on guinea pigs. To verify the medical effect of lithium, he used guinea pigs as the experimental subjects to test the effectiveness of lithium salts as an anticonvulsant. The medicine successfully calmed the animals down as expected [10]. Following this accidental discovery, in 1949, he published his first clinical report in which he described the therapeutic effectiveness of lithium in improving mania in patients with mood disorders and calmness in psychotic patients [13]. In 1976, Rudolf Jaenisch created the first transgenic mouse which was not only a great breakthrough in history but also laid a solid foundation for the application of modern genetic engineering technology [10]. In the early 1970s, he first demonstrated that at the early stage of mouse embryos, the foreign DNA could be integrated as a part of their DNA. As these mice grew up, the integrated foreign genes would spread across all of their tissues. These genes were subsequently demonstrated that they could also be passed to the descendants of the transgenic mice when Jaenisch injected retrovirus into early mouse embryos and discovered that leukemia DNA sequences coexist between the parents and the offspring [14]. While a series of world-breakthroughs have been made in this period by scientists with the massive use of animals for experiments, the voice for ethical concerns of the animals, particularly in rodents, have also been on the rise [10].

Following the research paths from previous scientists, the modern animal model applications started with a shifting focus from the macroscopical dimension of the animal itself to the microscopical molecule dimension. In combination with advanced modern genetic engineering technology, it is possible to replicate a type of human metabolic disease in animals as humans will with the integration of foreign genes into the animal's original genetic materials [15]. For example, Yang et al. injected high-titer lentiviruses of the human huntingtin gene into mature rhesus oocytes to establish a transgenic animal model in rhesus macaque that mimics the characteristic pathologies of human Huntington's disease (HD). This approach may give a deeper understanding of the underlying biology of HD, which in turn, helps develop the therapies for this disease [16]. Due to the complex and tremendous nature of genetic resources, the development and application of transgenic animal models might become a central research focus in the future and could help us discover new ways to treat diseases and discover new medicines., At the same time, some researchers, however, have also pointed out that ethical issues should be given more consideration when applying this technology to animals as it can compromise the welfare

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of model animals [17]. This means that biological scientific research is not merely about experiments. It should be an ethical science as well.

## 5. Limitations of animal models

The use of animal models has become a trend in the current study of human metabolism and disease. With the help of animals, humans have made great breakthroughs in the medical realm, which has led us to a new era of disease treatment and drug development. Animals are, after all, not human beings. Although they share many similarities in physiological features with humans such as similar cell structure and functions, similar organ construct, and metabolic processes, there are also differences between humans and animals and between different animal species. Inevitably, animal models are not capable of explaining all the risks that are threatening human health. To better understand and interpret the test results of animals and how they should be properly translated to human patients, we must have a good awareness of the limitations of animal models, namely what animal models can inform us and what they cannot.

Animals are physiologically different from humans and other species. Their physical responses to chemical exposure, such as how their body will ingest and digest these substances, usually vary from species to species. For example, rats, mice, and rabbits have higher absorption rates of chemicals on their skin than humans, which usually leads to the overestimation of the danger of chemical exposure to human skin when using these animals for tests [18]. In clinical tests, animals often show different physical reactions to drug toxicity from humans. The level of toxic chemicals in the drug might be a safe dose for animals but harmful for humans [7]. Furthermore, animals have shorter lifespans than humans. It is unlikely to predict the long-term effects of chemical exposure using animals as it usually works on humans. Although scientists usually increase the dose of chemicals that exceed the level that humans experience in reality, the results can only be interpreted as how animals will respond to overdose rather than the long-term effects [18]. This shows that animal models do not have high validity and should be mainly used to make guidelines for the treatment of human diseases at the current stage. Another problem associated with animal testing is its low input conversion efficiency. Animal testing is usually time-consuming and requires massive financial and animal inputs. For example, the registration of one single pesticide with the US Environmental Protection Agency usually requires one-decade time input and costs three million dollars to complete all of the animal tests. In this process, there will be up to 10,000 animals being killed, including mice, rats, rabbits, guinea pigs, and even dogs just for one single pesticide composition [18]. In addition, it was estimated to take around 5 years and cost 2 to 4 million dollars to develop the drug for cancer therapeutics using rodents as testing models [7]. At the same time, the failure rate in animal drug tests usually overwhelms the success rate. According to Van Norman, the failure rate of drug tests is 88% in preclinical trials and 88.3% in clinical tests. Even though the drugs on the market were tested to be safe for humans, they also have a risk of other side effects [7]. When there were numerous reports of their side effects, these drugs were all withdrawn from the markets [18]. Therefore, animal research is not economical-friendly as it is high in cost, requires a long term for drug approval, and has the potential of losing beneficial drugs for human use [7].

Additionally, there are more and more voices against conducting experimental tests on animals along with the dramatic increase of animal research in recent years. Millions of animals are sacrificed as experimental subjects every year. Most of them were suffering from unimaginable extreme pain and were treated in a distressful way. Thus, it has pointed out a clear need for animal research that the legislation of animal experimentation should be an important consideration for the regulation of animal welfare. Each scientific procedure from the research itself to the personnel and researchers, to the care and housing of animals, and the experimental procedures should be ethically accepted and meet ethical principles. In addition, the running of animal experiments should be licensed via an ethical evaluation process which is generally organized and conducted by ethics committees [19].

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## 6. Conclusion

The application of animal models is an alternative approach to studying human diseases and developing new drugs without direct trials on humans due to ethical and technical restrictions. Since they share many biological and physiological features with humans, animal models are widely used to better understand human metabolic mechanisms and the causes and treatments of human diseases. With the advancements in genetic engineering technology, it is now possible for humans to mimic the human conditions in animals as humans will. At the current stage, the results from transgenic animal models are however not highly validated to reflect on human patients and should be used as recommendations for human diseases as the result of the biological and physiological differences between animals and humans. This paper does not include further information that looks at the improvement of animal-model validity. Potential calibration methods such as establishing new animal models should be an important focus in future animal research so humans can adequately replicate human conditions and even create entire human systems in animal models. Due to the complexity of genetic resources, the exploration of genes will also open a new door for humans in the treatment of diseases. It can be expected that the current incurable diseases such as cancer and HIV will be eventually overcome by humans and human organ regeneration will become a foreseeable truth with the breakthrough of genetic technology.

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