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Perspective

Mice Matter

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Introduction

There has been a long-standing debate in the biomedical research community over the utility and importance of animal models. Although there are many opinions on this issue, a recent high-profile study demonstrated markedly different genomic responses of humans and mice to inflammatory diseases, such as sepsis, burns, and trauma.¹ Although this by itself would not be that surprising (because mice are not humans and vice versa [Fig 1]), *The New York Times* used this study as the basis for publishing an article that took the difference between humans and mice one step further, actually suggesting that mouse models are unacceptable tools for research.² In fact, the article strongly argues that medical research should be focused solely on humans and human source material.² The rationale provided was that blockade of specific mediators from animal models, which were found to be critical for disease progression, failed to ameliorate human disease. It appears as if the pendulum has swung strongly against animal models for medical research. We disagree with the premise that animal models are irrelevant. In fact, we believe that much misunderstanding lies in misinterpretation of what information animal models provide. Used properly, animal models should and will continue to play an essential role in human biomedical research.

Mice Modeling Human Disease

There remains a general problem in the scientific (and lay) community on exactly what animal models actually model. Many people assume these models are the disease, which they are not. Both the genetics study published in the *Proceedings of the National Academy of Sciences of the United States of America* (PNAS) and *The New York Times* article make this mistake; they assume that mouse models are mouse versions of human disease. Most emphatically this is not the case; mouse models of a human disease do not

equal human disease. These models are specifically developed to phenotypically appear like the human disease. However, the various ways in which the phenotype is created may have little to do with what occurs in humans. Or, to put it a different way, the way in which the mouse (or any other animal) is treated is to generate a final product that appears grossly similar to the human disease. There is no guarantee that the means are anything similar to what happens in humans (eg, in food allergy, does anyone really think that cholera toxin administration with food is the mechanism through which

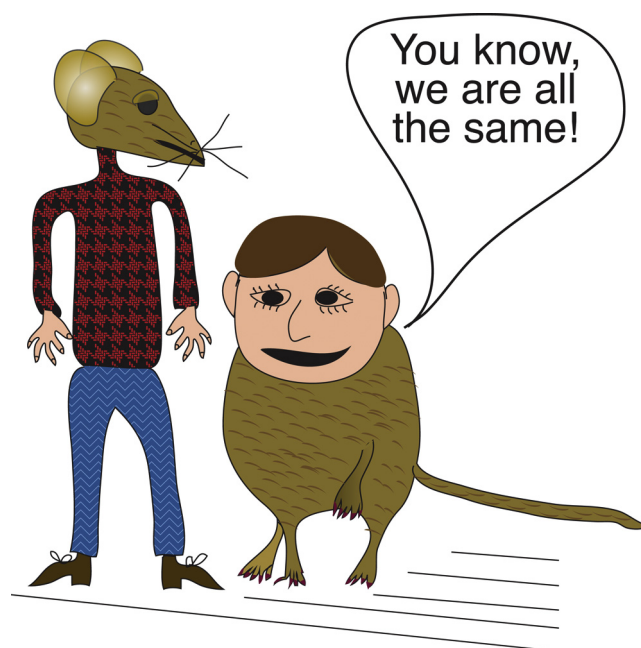


Figure 1. Mice and humans are not the same, but they are not completely different either. Animal research is designed to identify potential mechanisms that may underlie human disease. It is inappropriate to assume that all of these pathways will be operative in humans. Nonetheless, this limitation does not disqualify the use of animal models, it just requires validation of pathways in humans and the acceptance of multiple pathway approaches to therapy.

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food allergy develops?). These models are designed to begin to explore *potential* mechanisms that may lead to clinical disease in humans. When used appropriately, these models identify novel pathways, cellular subsets, and mechanisms that all lead to the final outcome of a phenotype that matches what is seen in human disease.

Mouse Research as a Benefit to Humankind

There are many examples of the use of animal models to identify important mechanistic and cellular components of human disease. For example, the initial descriptions of CD4⁺ T_H subsets (eg, T_H1, T_H2, and T_H17) came from studies focused entirely on animal models.^{3–5} Subsequent studies found similar cell subsets in humans, but the initial identification and characterization all were from mouse studies. It is true that these same subsets would have been identified in human studies eventually; however, animal research greatly accelerated their discovery. As a direct result, a more timely development of therapeutic drugs that interfere with key cytokines involved in T-cell differentiation occurred.

Another area where animal studies provided the initial insight into mechanisms of disease was transplant rejection and the idea of self vs nonself. In a series of elegant experiments, Dr Peter Medawar demonstrated that exposure to foreign tissue during embryonic development led to tolerance, which gave birth to the idea that embryonic and postnatal development of the immune system is disparate.⁶ He further demonstrated the role of T cells in graft rejection and pioneered the concept of graft-vs-host disease.⁷ Almost all of these groundbreaking studies depended on research in animal models. Today, there are literally thousands of people who are alive because of these studies (and many, many more!) that were based on animal models.

More recently animal models have proven critical to the discovery of the new cell class of innate lymphoid cells (ILCs). One such ILC is the ILC2, which is an innate leukocyte that mediates T_H2-like responses.⁸ These cells expand in response to interleukin (IL) 25 and IL-33 and represent the predominant source of IL-13 in helminthic infection.⁸ The identification of these cells required using mice in which all cells that made IL-13 were programmed to produce a fluorescent tag. When these mice were infected with *Nocardia brasiliensis*, a helminthic parasite, these ILC2s were found to be the predominant IL-13–producing cell 5 days after infection. Although these cells have been subsequently found in humans, the use of genetically modified animals greatly accelerated the pace of this research.⁹

We have provided only a small smattering of the types of studies in which animal models have provided important and critical advances to our understanding of human disease. There are many more examples in the literature, including such allergy-related issues as the role of c-kit and stem cell factor in mast cell development.¹⁰ As a result, it seems that mouse models should be a clearly acceptable method of deciphering the immunologic basis of human disease. However, it is important to remember that not everything found in animals will translate to humans. The example of mast cell development is a good one in this regard; the study by Saito et al¹¹ demonstrated that although IL-3 supports mouse mast cell development, in humans IL-3 generates basophils not mast cells.

How to Use Animal Models

Animal models are useful if there is a clear understanding of the limitations in what they tell us. The *PNAS* and *The New York Times* articles describe how none of the 150 drugs developed from mouse studies were found to be beneficial in treating human sepsis.^{1,2} These so-called failures do not negate the use of animal models in research; they simply prove that each of these targets are not primarily (or solely) responsible for the disease. In fact, the use of these therapeutics in human disease is based on the idea of a single

“silver bullet.” The therapies target specific proteins that in a given mouse model are critical for the development of disease. The failure here is more a result of misunderstanding the “ends justify the means” approach of animal research. A drug failing to work in humans does not mean that the target proteins have no role in the disease; it simply means that they are not critical for the illness. In fact, it is not at all surprising that human diseases are complex with no single “silver bullet” sufficing, as seen with anti-IL-13 in asthma.¹² Of course, the opposite sometimes happens, where inhibition of an animal model–based pathway leads to far greater improvements in human disease (eg, the use of anti-IgE in human inner-city asthma).¹³ We believe that the best approach is to validate target pathways from animal models in humans before starting any therapeutic trial. It is also critical to explore combination therapy directed at most if not all of the potential mediators, rather than discounting the entire lot simply because the pathways were identified in animal models.

In dissecting mechanism of disease, much of the initial explorative studies must be performed in animal models because the similar studies are often unethical in humans. We cannot in good faith inoculate humans with various toxins, infectious diseases, or experimental therapies, and we cannot make genetically altered humans. Until computer (ie, in silico) modeling is more advanced, animal models remain the only acceptable alternative—and even they are subject to strict guidelines and protocols.¹⁴ Animal research provides the foundation for studies to understand development and improve management of human disease without having to directly manipulate humans. Once the pathways are identified, they should be documented in humans (translation of the animal study into the human arena), and then therapeutic interventions can be planned. Until in silico approaches are improved or alternative approaches for human research are developed, animal research remains the most ethical way to define and manipulate mechanistic pathways that lead to disease. It is important that our politicians and decision-makers keep this in mind and do not allow themselves to be sidetracked by stories about the failures of single therapies, such as what appeared in *The New York Times*.

Conclusion

To be fair, we study animal models, but throughout our careers we have made every effort to translate our findings to humans. Nonetheless, we acknowledge that we are biased in this discussion. We still believe that our primary tenet is correct: our mice friends have aided in the advancement of medicine for many years, and suggesting that animal studies fall short in every regard is inaccurate and dangerous. Mouse models have contributed significantly to our medical knowledge by illuminating potential mechanisms underlying clinical disease. The utility of these models lies in their ability to identify pathways and cell types, not in directly mimicking human disease. Allowing people to equate animal models with human disease only furthers the misunderstanding and subsequent disappointment with single therapies. It is our fervent hope that animal model research will continue to be supported, not only to maintain a rapid pace of discovery but also to allow for greater identification of potential pathways to human disease. Today, the best and most ethical way for this to happen is through the use of animal models.

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