EDITORIAL

The need for compatible and more human-relevant animal models

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Animal research is always a vital part of our medical understanding and development of modern medicine, which contributes to a healthier world population and has saved millions of lives worldwide. There is a plethora of examples that show the contributions of animal research to human and animal health including the discovery and testing of vaccines, drugs, antibiotics, surgical techniques, organ transplants; and the development of diagnostic tests and techniques, immunotherapy treatments, etc. Animal research has also proven indispensable to the new field of biotechnology and its widespread applications of new biomedical innovations to the environmental and agricultural industries. These have saved millions of lives worldwide, ease the pain and suffering from, and enhance the quality of lives all over the world including the lives of animals.

Animals being used in research has been an issue debated for a long time, and it will get even more challenging with the new genetic manipulation of the animals experimented on. Another reason the debate will continue to increase is the loss of the credibility of the scientific community in the society, due to many factors but mainly due to the new era of social media, Google, internet, and news media. We need to explain exactly what is being done, why it is done and how it benefits humanity. We need to gain the public's trust.

Genetically modified animals have been recently used widely as farm animals to ensure enhanced food quality and disease resistance, and for biomedical research as animal models to producing biopharmaceuticals and as a target for testing genetic-based therapy. The creation and the use of these genetically modified animals (transgenically, cloned, or their genome edited by CRISPR) provide scientists with more accurate and valuable understanding of many diseases (1) and treatment for these diseases. It will be an important tool in providing transgenic organ donors that is safe for human transplant and solving the high demand for safe human organ transplantation. Interfering with the animal genome by inserting or deleting segments of DNA may result in alteration of the animal normal genome (2,3). This can give us a better understanding of the possibilities of outcomes in human studies.

The significant increase in using these new genetic modification techniques in the last 10 years raises the fundamental, ethical and controversial questions again: is the use of these techniques in animals a continuation of selective breeding which human practiced for thousands of years and should continue? Or is the use of these techniques abusive and interfering with natural processes and evolution and animals' welfare (3)?

In the face of new lows in societal trust in animal research contributions to human health and diseases, and to animals' welfare, the scientific community should increase vigilance and monitoring of potential animal welfare impacts (4). New approaches need to be explored to improve the ways that human diseases are studied and animal models are selected.

More and more recent studies showed that animal studies are limited in their application to human diseases. Even with the use of genetically modified models, many obstacles still remain that create a huge translational disconnect between animal models and human diseases. Briefly, human and animals have distinct gene regulations, distinct immune systems, different immune cells, and different signals (5). Even subtle genetic variation among humans can make a big difference in the susceptibility to different diseases and response to treatments. The nature of the immune system has to go through a learning process. Through life, the immune system it has the interactions between genes, epigenetics, antigens (pathogens, non-pathogens, organisms), environmental factors, food, drugs, care and stress (6,7). All of these can alter the genomic responses which will not be represented by the experimental animals' models. It is a dynamic system that changes from one day to another based on what a person is exposed to, what their stress (hormonal) level is, or nervous system status. Given all of these variables, it will be next to impossible to have good enough control over animal models in order to replicate human disease.

Various alterations to animal testing were proposed and alternatives being used in the last decade. These include cell and tissue culture, tissue on slides, computer simulations and modeling, bioinformatics tools, use of alternative organisms (lower vertebrate, invertebrate), and use of 'tissue chips' (miniature 3-D organs made with human living cells) (8-11). These integrated approaches would result in minimal involvement of animals (either genetically modified to have humanized immune systems or 3d human tissue chips) in scientific procedures.

The problem is not using animal models but the use of the correct model or the alternative if available. We need to have an open, constructive dialogue about animal genetic research, which will help the scientific community and society to have a better comprehension of the boundaries (ethical framework) we need to limit our endeavors. More efforts need to be undertaken for the effective implementation during experimental animal use. Limits to genetic engineering need to be established using the full breadth of public and expert opinion. Greater emphasis should be placed on developing better and more human-relevant models that advance science without harming animals, systematic comparison of the genomic and immunological responses between human diseases and animal models. The use of an alternative to the animal should be implemented.

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