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Balancing the welfare: the use of non-human primates in research

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Until now, there have been no ideal alternatives to replace non-human primates (NHPs) in biomedical research, yet the debate on whether it is appropriate to sacrifice NHPs for research never stops. With recent advances in genomics and the appearance of new technologies, the time is right to return to the problem of finding solutions to balance the welfare of both humans and NHPs.

Similarities between NHPs and humans

NHPs are the closest neighbors of humans on the phylogenetic tree. Taxonomically, NHPs can be classified into apes, monkeys, and prosimians (lower primates). Monkeys can be further grouped into New World monkeys and Old World monkeys. In contrast to the impression given by their names, New World monkeys are phylogenetically older than Old World monkeys. Most New World monkeys have prehensile tails, whereas Old World monkeys are genetically closer to hominids (apes and humans) and their tails are no longer prehensile [1].

The initial genome-sequencing results revealed that the genetic difference between humans and chimpanzees, at the DNA level, is only slightly higher than 1%, which is approximately 60 times less than the difference between humans and mice [2,3]. Although the degree of difference between humans and NHPs may increase slightly with detailed comparisons at the RNA, protein, and epigenetic levels, the sequencing results affirmed that NHPs are genetically closer to humans than any other species. In addition, anatomically, chimpanzees are also the closest species to humans in terms of skeletal composition and brain structures.

Contributions of NHPs to human biomedical research

Owing to the genomic and physiological similarity to humans, NHPs have been the preferred model organism for many cognitive and neurological experiments, as well as for mechanistic studies and preclinical drug trials for a wide range of diseases and therapies. The contributions of NHPs to human biomedical research dates back to the early 1900s, with the discovery of blood and plasma components, and a therapy method for pellagra [4,5]. Following that, over 50 major medical achievements have been made with the help of NHPs, including the development of the polio and hepatitis B vaccines, the discovery of the toxic effects of alcohol to the liver, and the mechanistic understanding of many neurological and infectious diseases (Primate Info Net: http://pin.primate.wisc.edu/factsheets). Moreover, much credit should be given to NHPs for their contributions in drug safety and efficacy tests.

Still irreplaceable heroes?

Although much biomedical research can be conducted at the *in vitro* cellular level or using non-primate animal models, such as rodents, dogs, and pigs, until now, there have been no ideal alternatives to completely replace NHPs as model organisms. In particular, NHPs are essential for research on drug safety testing for diseases related to neurology and recognition, reproduction, AIDS, and other infectious diseases. For example, studies of latent tuberculosis (TB) can be carried out using the crab-eating macaque, which will develop sustained TB infection and pathological changes to the lungs similar to humans, yet rodents and other non-primate animals do not develop these symptoms [6]. In addition, research on certain types of cancers related to primate-specific carcinoma genes also rely exclusively on NHP models, such as prostate-specific antigen (PSA)-related prostate cancer, as PSA has only been detected in Old World monkeys but not in marmosets or rodents [7].

Although there have been a few cases where drugs that were safely tested in NHPs caused severe side effects or deaths in humans, the number of drugs successfully developed through NHP models greatly exceeds that of the problematic ones, or those tested via other animal models. The emerging demands for organ transplantation to cure cancer as well as regenerative medicine-related problems also rely greatly on NHPs, as artificial organs generated in NHPs have similar sizes as those of humans, and are likely to cause less immune rejection than those from pigs or other animal models.

Can we do better?

It is understandable that the close relationship between humans and NHPs makes it difficult for humans to accept the use of NHPs in experiments. It is difficult to imagine whether those NHPs that have been used experimentally would be proud of themselves if they knew how substantial the contributions are that they have made to human health. I would like to believe that the hero-like feeling is not human-specific, but one cannot believe that without also

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believing that pain is not human-specific either. Thus, the use of NHPs in biomedical research should strictly follow the 3R principles, which aim to replace and reduce the use of NHPs, and refine the related methodologies as far as possible (National Center for the Replacement, Refinement, and Reduction of Animals in Research: http://www.nc3rs.org.uk/the-3rs).

In practice, I think the following aspects will be helpful in implementing the 3R principles in research involving NHPs.

Genetic necessity evaluation

The advances in genome-sequencing projects and genomic studies have revolutionized the mode of biological research. Now it is feasible to conduct homologous comparisons between humans, NHPs, rodents, or other model animals at the genomic, transcriptomic, and epigenetic levels to evaluate whether NHPs are necessary and sufficient for the designed experiments. For example, diseases involving primate-specific genes or epigenetic modifications could not be studied using rodent models, whereas diseases related to human-specific genes cannot be studied in any animal system and therefore NHPs should not be used in such instances.

Alternative model assessment

The developments in stem cell biology and genetic engineering technology have created many new cellular and animal models just in the past few years, and this pace is likely to increase, thus providing new models for many diseases. With these changes, whether NHPs will remain irreplaceable models may need to be reassessed in many studies, especially from the above-mentioned genetic necessity aspect.

Computational modeling assistance

Although computational modeling of gene functions or drug effects is still in its early stage, increasing the use of computational modeling should be a significant advance in the future of biomedical research and an important factor in the reduction of NHP usage. In this regard, efforts should be made to develop more comprehensive and accurate computer models to meet the experimental needs.

Prioritize human needs

The ultimate goal of biomedical research, whether it involves NHPs or not, is to benefit humans. Thus, in cases in which the necessity of using NHPs is urgent, such as the treatment of a new and acute infectious disease, human needs should be prioritized before the 3R principles. In other cases, legislative requirements for the involvement of NHPs should be obeyed under all circumstances, as required for drug development in some countries [8].

Provide good care for NHPs

As the beneficiaries of sacrificing NHPs, humans have an obligation to ensure that the quality of their lives is as high as possible. Good care is required for the captivity and breeding of NHPs. Investments are needed to provide suitable housing conditions for NHPs, as well as to meet the physical and social needs of NHPs while they are in captivity.

Take advantage of new techniques

Several recent studies have successfully generated genetically modified monkeys using the TALEN or CRISPR/Cas9 technology [9,10], which have created better NHP models for human disease studies. With these techniques, some of the problems of using NHPs as models could be partially solved by eliminating the genetic difference between humans and NHPs at the target sites. One clear application to such technology is in further reducing or even eliminating the risk of transferring NHP-tested drugs to humans. By contrast, these techniques can also be used to modify other laboratory animals, such as rats and mice, to make them suitable alternatives to NHPs for biomedical research. Together, these new technologies will reduce the amount of research that relies on NHPs and increase the success and value of the research that is conducted using NHPs.

The ideal future

Currently, NHPs remain the most effective and safest animal models for drug safety evaluation, vaccine development, and pathological studies of neurodegenerative or other primate-specific diseases. As stated in one of the National Institutes of Health reports in 2000, 'nonhuman primates are crucial for certain types of biomedical and behavioral research' [11]. It is improper to use NHPs as model animals without careful evaluation, yet it is also unwise to avoid using them when necessary.

Human society is being challenged by increasing numbers of aging-related neurodegenerative diseases, organ dysfunction caused by various types of cancers, more frequent prevalence of new types of acute infectious diseases, as well as other health-threatening medical problems. NHPs have been and will continue to be the heroes for human biomedical research and drug testing. The 3R principles for NHP usage should be applied whenever possible, under the prerequisite of effectiveness assurance. The ideal future will be to develop appropriate alternative animal models using an array of techniques, from 'humanizing' other model organisms through genome editing to computational approaches, thus reducing the use of NHPs as much as possible. For now, and in the future, though, we must recognize and treat NHPs just as we treat veterans from other wars, for they are surely soldiers in the battle against diseases.

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