Transgenic Primate Research Paves the Path to a Better Animal Model: Are We a Step Closer to Curing Inherited Human Genetic Disorders?

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While the advancement of transgenic primate models has led to a new era in modeling human conditions and has a clear impact on elucidating the mechanism of human genetic diseases, some thoughts should be considered if non-human primates are the appropriate model.

Transgenic animal models are powerful tools for biomedical research. They play a crucial role in advancing and developing diagnostic protocols that may lead to cures for human diseases. Although transgenic rodents have been the most widely used animal species in research laboratories, there are undeniable limitations to a rodent modeling system, including lifespan, metabolism, genetic constitution and numerous physiological differences than humans (Chan, 2004). This strengthens a need for an animal model that is closer to humans to better predict the efficacy and toxicity of novel treatments.

The ability to genetically modify the genome of non-human primates opens the door to better modeling of human inherited genetic diseases, not only because primates share a high similarity in genetic blueprint and physiological functions with humans, but also that they can carry the same defective gene that leads to human diseases. Transgenic primates are likely to develop comparable anatomical brain structure with humans (Chan et al., 2001; Wolfgang et al., 2001; Yang et al., 2008). However, there are physiological limitations with rhesus macaques such as a long gestation time (150–160 days), singleton pregnancies and their 3–4 years pubertal development. As a result, the generation time for rhesus macaque is relatively longer than some other primates such as marmosets. The establishment of germline transmission of the transgene in rhesus macaques represents a physiological challenge due to their long pubertal time that perhaps makes rhesus macaques more like humans.

Sasaki et al. (2009) have made an important step in transgenic primate modeling by first demonstrating that the transgene can be transmitted to the next generation through the germline. Although the transgenic rate and the method of creating a transgenic marmoset is comparable with other published work, the ability to effect successful germline transmission is a remarkable achievement that may impact the future role of non-human primates in modeling human inherited diseases such as Parkinson's, Alzheimer's and Huntington's diseases. Successfully passing the transgene to the next generation also suggests the likelihood of establishing a cohort of transgenic animals that will enable the biomedical community to advance our knowledge in human diseases and finding cures.

Although the research community is excited about the creation of the first transgenic marmoset and the ability to pass its transgene to the next generation of transgenic primates; of equal importance, their success will bring public attention to primate research and the modeling of human genetic diseases in higher primates. This attention could prove to be a mixed-blessing. It could impact future development positively, or it could draw negative attention, especially to animal research. Therefore, extreme care should be taken when developing an animal model by either a genetic approach or other methods, especially with non-human primates. It is important to point out to the public that our interest in developing a better animal ‘Model’ is to mirror human diseases, in order to better understand how disease evolves and develops. Also, a better model could eventually lead to using fewer research animals to validate new treatments or cures, because the right model would more accurately predict possible side effects as well as determine the efficacy of treatment protocols.

Since transgenic primate models may not be the solution for all questions of human diseases, it is important to learn and compare different model systems...
before considering a transgenic primate approach. Researchers have to decide if transgenic primates will advance our knowledge when no other model could. Some basic criteria are: (i) Does another existing model system develop comparable human conditions? (ii) Could a primate model significantly advance our knowledge? (iii) Is the genetic component of the disease known and have transgenic rodents proven to be insufficient? (iv) How many animals will be needed for the study and is a germline transgenic approach necessary? and (v) Are downstream analysis plans in place and available?

There is no perfect animal model regardless of how close it is to humans in genomic constitutions and physiological functions. Neither marmoset, nor rhesus macaque, nor chimpanzee is identical to humans. As animal models have different strengths, it is important to match specific research questions with the best, most appropriate animal model. We have to carefully choose the animal model, and higher primates may not always prove to be the best. Caenorhabditis elegans and flies have led us to the microscopic world of RNA that regulates normal physiological activity as well as human diseases (Ambros, 2003, 2008). However, we cannot evaluate their cognitive behavioral functions even if they were to express the mutant gene and develop phenotypes related to human inherited diseases. It has been well documented that transgenic rodents do not always replicate human diseases. Even transgenic HD monkeys only replicate some human clinical features that no other animal model can achieve, and how close they are in mirroring human patients has yet to be determined (Yang et al., 2008). Thus, a similar result is to be expected in transgenic marmosets. Nonetheless, all of these model systems are important in advancing our knowledge and have led us to better understand ourselves as human beings. Medical advances have been made through studies on these diverse but unique models.

Although higher primates hold great promise in mirroring human conditions such as response to new medication, efficacy of new treatment and pharmacokinetics of drugs, they are not without limitations. The high cost of primate research often governs our interest in applying primate models in critical studies. But it would be a tragedy not to develop a transgenic primate animal model that could potentially help us clarify the underlying mechanism of Alzheimer’s, Parkinson’s and Huntington’s diseases, since other animal models may not be able to replicate key clinical and pathologies alterations because of their physiological differences (Yang et al., 2008). Due to the limited resources of primates and prime facilities as well as the high cost involved, only work with those diseases that could clearly benefit from a primate model system should be considered.

The choice of primates is also important. There is no doubt that transgenic marmosets are likely to be better models than rodents for modeling human neurodegenerative diseases, but whether they can mirror human disease has yet to be determined. The availability of cognitive behavioral tests for marmosets is limited, and its small head size may also make it difficult for non-invasive imaging. Its short pubertal time is an advantage for future establishment of colonies and investigating the impact of inherited diseases via future generations.

The report by Sasaki and colleagues on their success in creating a germline transmitted transgenic marmoset has pushing transgenic primate modeling to a new level after the development of transgenic HD monkeys in 2008. These advancements will accelerate the modeling of human inherited genetic disorders that may lead to insight on how genes function at pathogenesis intercrosses in higher primates. Although primate models have been largely developed in the areas of reproductive sciences, neuroscience and immunological studies, being able to manipulate the genome of higher primates opens the door to other research areas that desperately need a better model for mirroring human conditions.

Significant advances have been made in transgenic primate research in recent years. These exciting breakthroughs open the door for researchers to seriously consider the role that primates can provide in modeling unique human conditions when other animal models may fall short. Although there is no perfect animal model for humans, it is important to embrace the value of comparative medicine in bringing us a step closer to curing inherited human genetic disorders.

References