Introduction

The emergence of transgenic species in research models began in the early 1980s, after a team of Harvard geneticists was able to successfully transfer the hybrid MMTV-*myc* oncogene into a colony of mice to breed the tumor-prone species that became known as OncoMouse.[1] OncoMouse became the first transgenic animal to be patented by the U.S. Patent and Trademark Office in 1988,[2] sparking widespread controversy in the United States and eliciting bipartisan support in Congress for a moratorium on animal patents.[1] The development and increasing inclusion of transgenic models has transformed the face of biomedical research and engineering. However, the ability to create novel species harboring human DNA, whether for purposes of research or economic advancement, raises critical ethical questions as to the moral obligations of those who endeavor to bioengineer new genetic lineages.

To create a novel transgenic species, uncleaved fertilized eggs must first be harvested from a super-ovulating female and injected with the desired transgene. The resultant embryos are then transferred into a pseudopregnant female, who gives birth to a founder lineage of transgenic animals that are heterozygous for the transgene of interest. Founders are then sequentially mated until a strain of homozygous transgenic animals has been obtained. On average, between 15 to 30 percent of the injected transgenic embryos are carried to term, with only 10 to 20 percent of the resultant offspring showing integration of the transgene into the DNA germ-line.[3]

To date, such research methodologies have been used in the creation of transgenic sheep, cattle, goats, chicken, fish, and mice.[3] These animals serve as living, non-human genetic models of various human diseases, facilitating comprehension of underlying pathology and guiding the developmental process of novel therapeutic interventions.[2] Transgenic animal models have been used successfully in the study of Alzheimer's disease, Huntington's disease, neuromuscular disease, HIV/AIDS, Diabetes Mellitus, cardiovascular disease, angiogenesis, cancer, and metabolism.[2]

An array of recombinant proteins (e.g. antibodies, growth factors, hormones, cytokines, etc.) are harvested from transgenic species in the hopes of human pharmaceutical use; currently, a vaccine found to restore neurologic function in transgenic mice is undergoing phase two clinical trials in patients with Alzheimer's disease.[2] In January 2009, transgenic goats were responsible for the first recombinant animal protein (ATryn – recombinant human antithrombin III) to receive approval for use by the U.S. Food and Drug Administration. Additionally, transgenic species have been utilized in the development of unique biopolymers that may prove useful as suture for advanced facial or orthopedic reconstructive surgical procedures. Transgenes may also be used to facilitate the success of xenotransplantation in porcine-to-human surgical transplant models, with transgenic species offering the alluring promise of a potentially effective alternative to human byproducts that could be made available on demand and en mass.[2]

Principles for Laboratory Animal Use

In December 2012, the Council for International Organization of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS) released the *International Guiding Principles for Biomedical Research Involving Animals*. This document, first published in 1985, was revised by an international cooperative of veterinarians, scientists, and biomedical experts spanning over thirty professional societies and organizations. The goal of the revision was to address the expanding scope of animal research, technological advancements in the field, and increasing societal attention to the welfare of laboratory animals.[4]

The revised document set forth ten guiding principles for use by the international scientific community when incorporating vertebrate animals in scientific and educational endeavors. The principles emphasize the moral responsibility and obligation owed to laboratory animals by individual scientists and researchers, stressing ethical action and proper consideration of both societal values and the impact upon animal welfare and well-being. Reliance upon the Three R's – Replacement, Refinement, and Reduction – is underscored as a method of avoiding animal usage unless justified scientifically and ethically.[4] However, the word 'transgenic' is absent from the document, as is any discussion whatsoever of the myriad technologic advancements since the original publication that now allow for the genetic manipulation of vertebrate animals and their ethical use in the laboratory. Principle VII states only that there is a 'moral imperative to prevent or minimize stress, distress, discomfort, and pain in animals, consistent with sound veterinary practice,'[4] leaving the details of such practice to be determined by individual investigators and institutional regulatory boards.

In Europe, the task of policy formulation for the ethical use of laboratory animals has largely rested upon the European Science Foundation (ESF) in recent years.[5] This organization, composed of scientists and research councils from twenty-three member countries, publishes position papers and directives at the behest of the European Parliament and Council on the Protection of Animals Used for Scientific Purposes; their most recent directive was adopted by the European Parliament on September 22, 2010, and will officially redefine the minimal national standards of laboratory animal use in EU member nations effective January 2013.[6]

In contrast to previous versions, the new ESF Directive is more definitive and frank, providing clear-cut descriptions of the animals and life stages available for laboratory use, permissible research procedures and purposes, educational and training requirements, and the establishment of national 'animal welfare bodies.'[6] Currently, only a handful of countries (e.g. Germany, Sweden, and the Netherlands) have national laws requiring prior revision of all laboratory animal protocols by an animal welfare or ethics committee.[5] Furthermore, a separate panel was convened on the topic of the ethical implications of genetic modification prior to the current ESF Directive revisions, resulting in the submission of a position paper on the ethical use of transgenic technology to the European Committee in May 1996.[7] At present, no national regulations exist in the United States or China limiting the use of transgenic species in research.[8]

Ethical Implications of Transgenic Research

Supporters of transgenic animal development site their fundamental use in the biomedical field as models of human disease, function as alternative sources of human tissues and organs for harvest during xenotransplantation, and production of biologic proteins with therapeutic and pharmacologic potential as reasons for their continued creation. With the ever-expanding human population, transgenic mutations may also be used to produce or enhance disease-resistant and high-yield animals among food production species. Transgenic technology offers such enormous potential benefit to the welfare of both mankind and animals that the research is ethically and scientifically justified, as long as the methods employed do not cause unnecessary suffering or harm to the animals involved, the public, or the surrounding environment.[7]

However, accurate knowledge regarding the public perception of the creation and use of transgenic animals is fairly limited. On July 22, 2011, the Academy of Medical Sciences in the United Kingdom released a government-commissioned report entitled *Animals Containing Human Material*. Composed of an international panel of experts in philosophy, ethics, social science, law, and biomedicine, the group conducted a series of focus groups and surveys among lay Britons in order to determine underlying feelings about this subject. Results were mixed at best, revealing broad acceptance of some transgenic species creation among those who understood the rationale, yet a general discomfort about the potential introduction of human traits into the appearance, neural, or reproductive tissue of animals. In total, public support for transgenic research was highest when the experiment in question involved human blood (55%) and skin (51%) cells, and lowest when human neural (45%), optic (45%), or reproductive (42%) cells were being introduced into an animal model; additionally, twenty-six percent of respondents (N=1,046) indicated that it was never acceptable to introduce human cells into living animals.[9] Ultimately, the report stressed the need for the establishment of a national expert body to supervise the use of transgenic animal species, and recommended a ban on two classes of experiments deemed categorically unethical: (1) the combination of human and animal embryonic stem cells, and (2) the creation of a non-human primate or animal with enough human neural tissue to make it capable of 'human-like' function.[9]

This latter category has been a focus of concern among investigators in the field of comparative genomics studying human-lineage specific (HLS) sequences thought to underlie the characteristic traits of the human species (e.g. self awareness, higher order cognition, complex vocalization, etc.).[8] Although it may be possible to clearly elucidate the function of many as yet undefined HLS sequences via their introduction into apes and other non-human primates, Coors et al. (2010) feel that the creation of such transgenic species would be highly unethical and absolutely unjustified in apes due to their increased likelihood to experience harm as a result of such interventions. Although the author acknowledges the potential clinical benefits of such research (HLS variants are disproportionately implicated in human disease) and the limited utility of mice in transgenic HLS investigations (due to vastly different anatomic, genetic, and neural composition), she argues that the uncertainty in the outcome and the potential for harm to the animals involved far outweigh the potential benefit.[8]

Coors et al. (2010) posit that scientific advancement and the pursuit of knowledge must always be weighed against the animals whose welfare and best interest may be sacrificed in the process, and that not all animal research is ethically justified by these standards. The researcher sets forth five minimum criteria for determination of the ethicality of any investigative model, including the research goals, probability of success, species to be used, expected effects upon research animals, and presence of alternatives. By this logic, it would be wholly unethical and unjustifiable to create a transgenic ape with an HLS sequence that may lead to the expression of a humanized phenotype; this animal would have no opportunity for a normal existence outside the laboratory, and would likely be deemed unacceptable by members of its own species, placing it at increased risk of both physical and emotional harm.[8] In contrast, transgenic studies of animals with a reduced risk of exhibiting human-like phenotypes or comparative genetic analyses of HLS sequences within varying segments of the human population provide potentially safer, more ethical alternatives to this complex field of research.[8]

Nevertheless, there remain those who feel that the use of transgenic animals is never justified, and that their creation represents a skewed view of animals as mere commodities available for human exploit. Dalton (2010) stresses the importance of considering the ethics of transgenic species within the framework of Charles Taylor's 'social imaginary,' a term used to describe the dynamic ways in which the members of a human society live, interact, and view one another.[10] In the modern Western world, the social imaginary is dominated by themes such as human rights, democracy, and capitalism. There is an emphasis on technological and scientific advancement, and a sense of entitlement through which members expect ready access to worldly goods.[10]

Within this framework, it becomes possible to understand how the modern Western individual has come to view himself as superior to animals. Religious teachings that place mankind in a position of dominance over the ‘lesser’ creatures, the rapid development of and preoccupation with technological advancement, and the emergence of the rationalist school of thought have each contributed to an instrumental view of nature that extends to non-human animals. To this end, the creation of transgenic animals for biomedical research, while seemingly a dramatic departure from previous norms, is not terribly at odds with currently accepted societal standards such as factory farming for human food production, the keeping of wild animals in zoos, or the testing of products intended for human use on animals. As the current ethical standard against which animal research models are judged appears to be whether or not the use of animal contributes to the improvement of human life, it is easy to see how the use of laboratory animals for nearly any purpose has come to be viewed as normal within Western civilization.[9]

However, when the lens through which one views the world is changed such that both humans and animals are seen as being part of what Thomas Berry once described as a ‘communion of subjects and not a collection of objects,’ it becomes more difficult to discuss animals in terms of their instrumental use in service of mankind. Such a viewpoint represents a radical departure from the current social imaginary, as it requires recognition of the individual consciousness, integrity, and rights to life of all creatures. Nevertheless, it is critical to remember the dynamic nature of societal schemas; in much the same way that the definition of human rights has expanded over time in the United States to include women and individuals of varying races and social classes, it remains possible that the social imaginary could be similarly reframed to include a broader definition of the rights afforded to animals and the ethics of altering their genetic lineage.[9] The appearance of such ideas within the social consciousness have already begun to exert an influence on the scientific community, as seen in an ESF Directive dating back to September 2000 which explicitly states that laboratory animals are to be recognized and respected for their intrinsic value as sentient creatures, and not only as instruments available for human use.[11]

Conclusion

In the past thirty years, the ability to produce transgenic animals has revolutionized the biomedical field and paved the way to untold advancements in both human and veterinary medicine. However, the mere existence of a technology does not necessarily mean that it should be utilized, particularly when its use involves the creation and sacrifice of life. Furthermore, there remains the unpleasant fact of the suffering endured by many transgenic species created.

One must consider not only the visible distress of those animals produced as models of painful diseases such as mammary cancer or cardiovascular disease, but also the more insidious question of those transgenic species for whose deficits there exists no objective measure. For example, how does a researcher assess the cognitive function, quality of life, or distress of an animal bred to exhibit a human neurologic condition such as Alzheimer’s or Parkinson’s disease? In many cases, it can be difficult to make precise quality of life measurements on humans suffering from these illnesses, and there exist few if any validated cognitive assessment measures for laboratory animals. Despite the obvious need for research in these fields, it seems difficult to ethically justify the sacrifice of animals for such work when there exists no adequate method in which to gauge the extent of their suffering.

However, this is not to say that transgenic research should be discarded altogether. Rather, the author would like to see transgenic research used as a method of last resort to supplement current research techniques instead of replacing more traditional animal models. As long as transgenic animal production remains limited to a well-regulated scientific community whose data remains publically accessible, with the animals produced being protected from exploitation or release into natural habitats, it seems possible for such research to continue within an ethical framework.[7] Ultimately, the protection and preservation of animal and human well-being, as well as a keen regard for potential environmental impact, must always be prescient when determining the ethical nature of any animal research project, particularly that which involves the genetic alteration of a species.

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