IQP-43-DSA-8263

TRANSGENIC ANIMALS

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

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August 26, 2009

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ABSTRACT

Transgenic animals are genetically modified organisms whose genomes have been integrated with foreign DNA to provide a new phenotype. This project informs the reader of various uses for this technology, and discusses the impact of this controversial technology on society. This IQP weighs potential benefits of specific transgenic animals against legal and ethical concerns regarding their use. The author concludes that transgenesis could provide enormous benefits for society, and should be allowed to continue under tight NIH and FDA oversight.

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PROJECT OBJECTIVES

The intent of this project was to describe the applications for transgenic animals, and examine the impact of this new and controversial technology on society. This IQP explores the potential medical, industrial, and educational benefits of transgenic animals. The research also illustrates various relationships between the technologies, the ethical concerns of society, and the legislation that regulates the use of transgenic animals. Chapter-1 describes how transgenic animals are created and categorized their uses. Chapters-2 and 3 investigate the ethics and legalities surrounding this contentious technology. The author concludes that these experiments should be allowed to continue with tight NIH and FDA oversight to ensure careful consideration for the well being of the transgenic animals involved, and that patenting transgenic animals provides necessary legal protection to allow further transgenic research to continue.

Chapter-1: Transgenic Applications

A transgenic animal is a type of animal engineered to incorporate a foreign gene into its genome for the purpose of giving it new properties. This technology resulted from the explosion of molecular biology techniques in the 1970's and 1980's, and has created a variety of new animals that benefit society. The purpose of this chapter is to categorize the types of transgenic animals created to date, as an introduction to subsequent chapters on the impact of the controversial technology on society. Transgenic animals can be divided into five main categories: disease models, transpharmers, xenotransplanters, food sources, and scientific models.

Disease Models

Disease models have been engineered to mimic some aspect of a human disease, to allow a better understanding of disease formation, and to test potential therapies. These models hold great promise for the study of human pathology, and in some cases are required intermediate steps for testing therapies prior to human testing. These animals provide a living system that can be used to acquire new information about a disease, with the ultimate goal of testing new vaccinations and treatments on laboratory specimens before moving onto human trials. A number of human diseases have been successfully been mimicked in laboratory animals, including Alzheimer's disease, cancer, Parkinson's disease, ALS, cystic fibrosis, and AIDS. Some of these are discussed below.

Alzheimer's Mouse

Named for German physician Alois Alzheimer, Alzheimer's disease (AD) is the most common form of cognitive degeneration. In November of 1906, Dr. Alzheimer presented the case of Frau August D, a patient with memory loss, delusions of suspicion, and a diminishing capability of verbal communication. She became a patient of Alzheimer in 1901, was bedridden only a few years later, and died in spring of 1906. In simple terms, Alzheimer's disease results in a progressive destruction of brain cells, and is ultimately fatal. While the complete mechanism of cell death has not been uncovered, scientists have noticed two hallmarks in those afflicted with the disease, senile plaques and neurofibrillary tangles. Senile plaques contain remnants of a toxic β-amyloid protein (Aβ) that accumulates between nerve cells in the brain to initiate the disease. Neurofibrillary tangles are composed of a τ-protein that forms within the dying cells, and result from cell death pathways activated by the Aβ. While plaques and tangles occur at low levels in those without Alzheimer's, they tend to develop rapidly in those with the disease, especially in parts of the brain responsible for memory and learning. Currently, an estimated 5.3 million Americans live with Alzheimer's, and the disease has no cure. (Alzheimer's Association, 2004)

In 1995, Professor David S. Adams of the Worcester Polytechnic Institute (in partnership with the former Transgenic Sciences, Inc.) became the first team to successfully replicate Alzheimer's disease in a mouse model. The mouse was designed to express amyloid precursor protein (APP) that forms toxic Aβ, in the same areas of the brain affected in Alzheimer's (Games et al., 1995). In addition, the form of APP used mimicked an early-onset family in Indiana (the Indiana mutation) that develops the disease in their 40's. The experiment proved that Aβ

formation is sufficient to initiate the disease, and provided a convenient model to test drugs for blocking or reversing disease formation.

Less than four years later, researchers in San Francisco used this mouse model to develop a vaccine against Aβ to prevent senile plaque deposition (Schenk et al., 1999). The vaccine decreased the concentration of existing plaques, even in older subjects with severely advanced pathology, and was later shown to improve cognitive function. To confirm the vaccine's effectiveness, the control group (mice who received an unrelated vaccination) showed advanced neuritic dystrophy and astrocytosis. Subjects who had been treated from a young age onward contained non traces of Aβ, and showed no apparent health or behavioral complications after immunization (Jones, 2000).

Oncomouse

In the early 1980s, researchers from Harvard Medical School produced one of the world's first transgenic animals with funding from Dupont. Appropriately named Oncomouse, the specimen had been genetically altered to rapidly develop cancer (Stewart et al., 1984). A recombinant activated oncogene sequence was introduced into the somatic and germ cells of mice for the purpose of studying different treatments of tumor formation (Bioethics and Patient Law, 2006). This mouse line received additional publicity in 1988 when Oncomouse received the first animal patent (discussed in Chapter-2). Philip Leder, of the National Institute of Health, one of the Oncomouse inventors, described Oncomouse as "the key model system for studying cancer, and for testing the effectiveness of novel cancer therapeutics" (Stern, 2000).

AIDS Mouse

Another important disease model is the AIDS mouse. The HIV virus that causes AIDS normally only infects humans and chimpanzees. But limiting factors such as high maintenance costs, and a dwindling population in their natural habitat, made primates ill-suited for laboratory research. Additionally, the virus does not cause full blown AIDS in chimps.

Although mice are easily maintained at a low cost, they naturally lack the CD4 and CKR5 receptors that HIV binds to enter cells to cause infection (Science News, 1988). A transgenic rat AIDS model was created at the Baylor College of Medicine in 2001 by injecting newly fertilized eggs with a mutated version of HIV (that could not replicate), and implanting the modified eggs into the uterus of a foster mother. The subsequent offspring showed evidence of HIV expression, and the characteristic immune dysfunction of AIDS (Reid et al., 2001).

The creation of AIDS mouse provides a huge opportunity for researchers, and provides hope to the estimated 30.8 million adults and 2 million children across the globe currently living with HIV/AIDS (AVERT, 2007). Not only is the specimen completely safe to handle (due to the inability to transmit the virus), its use as a biological model can aid in finding new treatments for AIDS, and could eventually lead to a cure.

Transpharmers

Transpharmers are genetically modified to express a specific protein in their blood, eggs, or milk. Since milk is easy to obtain from female animals, and the secreted produce does not enter the blood to affect the animal's physiology, the mammary gland (classified as a "natural secretion organ") is more frequently used for production. A special promoter is used to help ensure the inserted transgenic DNA will only be "turned on" during milk production, and not

expressed in other tissues, thus a transpharmer host should remain normal and healthy while expressing the desired protein (GTC Biotherapeutics, 2006). Transpharmers could allow for the manufacturing of vital nutrients, enzymes, antibodies, and protein-based human therapeutics to become less cost prohibitive, thus becoming more available to patients in need of medication. Cows, sheep, goats, and mice, have all been successfully engineered as transpharmers, and are favored for their high milk output.

In 1991, scientists from GenPharm International engineered the world's first transgenic bull to carry the human gene for lactoferrin, an iron-containing protein that is vital to infant growth and development. The bull, named Herman, was created by microinjecting early bovine embryos with the gene encoding human lactoferrin, and culturing the cells *in vitro* until they reached the blastocyst stage. The blastocyst embryo was then transferred into recipient cattle. Herman was born, matured, and successfully bred (with no subsequent harm from the genetic implantation) to become the father of at least eight calves in 1994. This achievement could allow for Herman's female offspring (and others like them) to produce lactoferrin-rich milk, and become a vital source of nutrients for children in developing nations (Biotech Notes 1994).

GTC Biotherapeutics, located in Framingham, MA, is responsible for the first transgenically produced protein to be approved worldwide. The protein, called antithrombin, is naturally found in human blood, and functions as an anti-clotting mechanism (blood thinner) to deactivate several enzymes of the coagulation system. Antithrombin can be used to treat deep vein thrombosis with potential applications in oncology, hematology, and various autoimmune diseases. Using pronuclear microinjection, GTC engineered a line of transgenic goats to "express a desired protein [antithrombin] in their milk in addition to the many milk proteins it already produces." The goats were subsequently screened for high levels of antithrombin

expression in the mammary gland during milk production. Goats have an average generation time of 18 months (compared to 3 years in cows) and produce an average of 800 liters of milk annually. After the goats are milked, the antithrombin is isolated and prepared into a formula commercially known as Atryn® that can be given to humans.

Over the past decade, GTC has published documents evaluating the health and wellbeing of all of it's transgenic animals, and receives regular inspection (minimum of twice annually) from organizations such as the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), and the Institutional Animal Care and Use Committee (IACUC) (GTC Biotherapeutics, 2006).

Xenotransplanters

Xenotransplanters have been engineered to provide organs for transplant into humans. The need for Xenotransplanters arose as the demand for clinical organ transplants greatly exceeded the supply of available human organs. An estimated sixteen patients die daily waiting to receive critical organ transplants (U.S. FDA, 2009). The prefix "xeno" stems from the Greek "Xenos", meaning stranger, and is used in biology to designate species difference (Wikipedia, 2006). Therefore, xenotransplantation involves procedures that replace human organs or tissues with those from an animal source.

In Blacksburg, Virginia exists a farm with over 200 pigs. Due to the chronic shortage of organs for transplantation, the DNA of these pigs has been engineered to lack a glycosyl transferase gene (alpha-1,3-galactosyltransferase) that encodes an enzyme that adds galactose sugars viewed as foreign to humans. Thus, the organs from these pigs are stripped of the sugars that would be recognized as foreign, enabling them to be transplanted into test monkeys. In

several testing facilities, the hearts from these pigs have been successfully transplanted into baboons, and are able to survive and function in the primates for up to 3-6 months (Fabregas, 2006). Genetically altered swine kidneys have survived in baboons as well.

Another potential application for xenotransplantation includes the 50 million patients worldwide who suffer from diabetes. With patients needing constant insulin therapy, and other treatments, the total economic burden caused by diabetes in the United States has soared an estimated 98 billion dollars annually. Using transgenic pigs designed to lack the genes responsible for triggering acute immune rejection, researchers are approximately 2 years away from islet cell (insulin producing cell) transplantation trials in humans (Revivicor, 2005). This technology is believed to be technically feasible, and could potentially change the field of diabetes treatment forever.

Food Sources

As the global population increases, so does food consumption. Transgenic food sources involve genetically modifying a species' genome to incorporate a growth hormone. In aquaculture, this process has been quite successful in several species of trout and salmon, and shows promise of helping to accommodate the growing needs of human food consumption.

In normal salmon, the gene that regulates growth hormone is activated by light such that the fish only grow during the sunny summer months. Aqua Bounty Technologies developed a genetically modified salmon that produces growth hormone year round by attaching a promoter sequence to its growth hormone gene. The transgenic fish look and taste identical to normal farmed salmon, but grow twice as fast as their counterparts, and eat less food. The company's owner, Elliot Entis, has stated that Aqua Bounty will only market sterile, female transgenic

salmon to prevent accidental breeding with native salmon populations, and any resulting negative environmental effects (Piquepaille, 2006). Sterilization in the transgenic fish can be achieved through a method called triploidy. The process works by introducing a pressure, temperature, or electrical shock to an egg immediately following fertilization, which alters the number of chromosomes retained by the zygote. While triploidy does not ensure sterility in males, female specimens produce non-functional ovaries that are completely absent of oocytes (Harper, et al., 2006). Entis is now seeking approval from the Food and Drug Administration that could pave the way for marketing his genetically engineered salmon.

Super Pig (Beltsville Pig)

The "Beltsville Pig" was genetically modified to carry human growth hormone (HGH) with the hope that the animal would grow faster and leaner than normal pigs without the gene therapy (Miller et al., 1989). The desired results were to increase growth rates and weight gain, reduce carcass fat, and increase feed efficiency. Some of these goals were achieved, in pigs weight gain increased by 15%, feed efficiency by 18%, and carcass fat was reduced by 80%. But the animals suffered from several unanticipated health problems, including kidney and liver problems, uncoordinated gait, bulging eyes, thickening skin, gastric ulcers, severe synovitis, degenerative joint disease, heart disease of various kinds, nephritis, and pneumonia (Rollin, 1996). The catastrophic failure resulted in a voluntary moratorium on growth hormone experiments in mammals.

Scientific Models

This very broad class of transgenic animals includes those animals engineered to study the function of a specific protein by over-expressing the protein, or by knocking out its expression, to observe the biological effects *in vivo*. Such animals have immensely added to our biological knowledge of protein functions.

Smart Mouse

In 1999, Joseph Tsien, a neurobiologist from Princeton University, performed an experiment to investigate the effect of overexpressing a NR2B protein believed to be responsible for improved synaptic function (Tang et al., 1999). Tsien and his colleagues found that overexpressing NR2B produces a type of NMDA receptor, similar to the type produced by the embryonic brain, that more efficiently responds to glutamate neurotransmitter. Earlier, Tsien had created mice that lack the NR2B gene in a small region of the brain, and observed their impaired learning and memory, formulating the hypothesis that NR2B is important in this process. Then he later performed the over-expression experiment to two mice he named "Doogie," (after the smart TV character Doogie Houser). The mice showed increased performance on maze tests and preserved certain features common to juvenile mice. This new strain of mice confirmed the NR2B gene's direct correlation to learning and memory, and in the long-term could be used to enhance mental and cognitive attributes in people, particularly those suffering from dementia and other mental disabilities (Harmon, 1999).

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Chapter-2: Transgenic Legalities

Introduction to U.S. Patent Law

A patent is an exclusive set of rights granted to a patentee to prevent unauthorized manufacturing, marketing, or distribution of a material. The first United States Patent Act of 1790 defined a patentable material as "any new and useful art, machine, manufacture, or composition of matter" (Ladas & Parry (2003). Over the next 220 years, patent laws were extensively altered to accommodate changes and advancements in technology, and our understanding of the term "composition of matter" has also changed dramatically. We know that a transgenic animal is one that is not found in nature, and must be "invented" or created by a third party (it is also comprised of matter). Under this context, is a transgenic animal considered patentable subject material? Legislation regarding transgenic animals has largely been shaped by ethical concerns. This chapter focuses on the effects of transgenic technology on society, via a discussion of the origins and development of transgenic patents.

Currently, the United States Patent and Trademark Office (PTO) lists its conditions for patentability pertaining to non-obvious subject matter. Section 35 U.S.C. 103 (3) of the U.S. Patent laws defines the term "biotechnological process" as:

> "(A) a process of genetically altering or otherwise inducing a single-or multi-celled organism to: (i) express an exogenous nucleotide sequence, (ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or (iii) express a specific physiological characteristic not naturally associated with said organism; (B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and (C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B)." (U.S. Patent and Trademark Office, 2008)

Thus, based on *current* patent laws (not in effect for the 1980's landmark Oncomouse court case), the *process* of creating transgenic animals to over-express a particular protein, or to not express a particular protein (knockouts) is patentable, as is the creation of a cell line expressing a specific protein, or the method of using a transgenic product.

Explanation of an Animal Patent

A company may require the protection of an animal patent to prevent customers from simply buying one animal and breeding as many others as they like. Such a practice could hinder biological research by taking away any profit incentive for a company to create transgenic animals. An animal patent covers animals whose genomes have been integrated with a particular gene sequence and who do not exist as any natural species. Once a company has been issued a patent, it can prohibit anyone else from using or selling the transgenic animal without the company's permission until expiration 17 years later. The patent can also extend to cover the pharmaceutical antibodies or proteins produced by the animal. If any offspring are proven to possess the particular gene sequences and exhibit the same traits described by the patent, they are also protected by the same restrictions (Andrews, 1993).

First Patent on a Living Organism, 1930

The *Plant Patent Act* of 1930 (PPA) established the first patent to a living organism. The law granted regulatory rights for new varieties of asexually propagated plants (but not those which reproduce through seed germination). Thomas Edison and Luther Burbank were among the better-known early advocates of the PPA. With the enactment of the PPA, congress extended the same kind of protection to plant inventions that had long been available to industrial

inventions (Kjeldgaard, 1996). Writer R. Cook, in the *Journal of Heredity* commented on the passage of the PPA three years later. "It is a little hard for plant men to understand why [patent laws] of the Constitution should not have been earlier construed to include the promotion of the art of plant breeding. The reason for this is probably to be found in the principle that natural products are not patentable" (Cook, 1933). After the legislation passed to allow the first patent of a living organism, so began the controversy and ethical concerns that would continue to shape other such laws.

First Patent on a Microorganism: Diamond v. Chakrabarty, 1980

Genetic engineer Ananda Chakrabarty, an employee of General Electric, developed a remarkable bacterium in 1972 that was able to digest crude oil into simpler substances that could serve as food for other aquatic life. This bacterium has applications for efficiently treating oil slicks without creating environmental problems. Chakrabarty derived his bacterium from the *Pseudomonas* genus, and proposed a possible use in the treatment of oil spills. In 1980, Chakrabarty sought a patent for his bacterium, now known as *B. cepacia*, but was denied by a patent examiner who argued that microorganisms are "products of nature," and that U.S. patent law did not allow living things to be patentable subject matter (*Diamond v. Chakrabarty*, 1980).

Chakrabarty appealed his case to the United States Court of Customs and Appeals, who voted in Chakrabarty's favor, stating that patent law did apply to microorganisms. Sidney Diamond, the commissioner of Patents and Trademarks appealed to the Supreme Court, and *Diamond v. Chakrabarty* ensued in March of 1980. On June 16, 1980, the Supreme Court ruled 5-4 in Chakrabarty's favor. Chief Justice Warren E. Burger wrote that:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement

> thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." Under this context, "A live, human-made micro-organism is patentable subject matter under [Title 35 U.S.C.] 101. [The] respondent's micro-organism constitutes a 'manufacture' or 'composition of matter' within that statute." (*Diamond v. Chakrabarty,* 1980)

First Patented Animal: Dupont and Harvard's Oncomouse

Only four years after Chakrabarty's case, in June of 1984, geneticists Dr. Philip Leder and Dr. Timothy A. Stewart of Harvard University filed for the first American patent on a transgenic animal. Harvard University scientists Timothy Stewart and Philip Leder developed transgenic "Oncomouse" that was genetically predisposed to developing cancerous tumors. The researchers inserted an activated human oncogene into the mouse genome and observed increased development of neoplasms (Leder and Stewart, 1984). Harvard applied for a patent for Oncomouse in the summer of 1984, but received negative publicity from animal rights groups who observed the obvious suffering to the mice that developed tumors (PETA, 2008).

In 1988, the United States Patent and Trademark Office granted Patent 4,736,866 (filed June 22, 1984) to Harvard College. The document defined the extent of the patent's protection to include "[the] transgenic non-human mammal whose germ calls and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal…" (Bioethics and Patent Law, 2006). The patent claimed the methods used to copy the oncogene, the fertilized mouse egg containing the foreign DNA, and the fully developed Oncomouse and its descendants (Shorett, 2009).

Years later, Harvard and Dupont signed a memorandum of understanding, giving Dupont exclusive rights to Oncomouse, and allowed the company to control and restrict its use by researchers. Dupont allowed private organizations such as the Taconic Farms, Inc. to obtain licenses to handle Oncomouse, but scientists complained that the fees Taconic charged for the

mouse were so high it prohibited research, and the company was criticized for their aggressive licensing agreements (Taconic, 1998). As a result of Dupont's and Taconic's "anti-competitive practices", MIT, and the University of California ended research agreements previously made with them, and The San Francisco Chronicle wrote in 2002 that Dupont was "impeding the war on cancer by charging high fees to companies, imposing unusually strict conditions on university scientists, and pushing an overly broad interpretation of which lab mice the patents cover" (Shorett, 2009).

Despite significant public ethical concerns, Stewart and Leder subsequently received two more patents covering their methods of preparing and testing the transgene. Although dozens of new applications were submitted, the U.S. Patent office did not issue another animal patent until almost five years after the Oncomouse trial (Andrews, 1993). However, as of 2007, using the Oncomouse case as precedent, more than 660 patents have been issued on animals since 1988 (Letterman, 2007).

Transgenic Patent Policies of Other Nations

Oncomouse in Canada

With respect to the Oncomouse case in Canada, in 1993, patent 1,341,422 was granted to Harvard College allowing modified claims that covered the *process* of creating the mice but not the mice themselves. However in 2000, the Canadian Federal Court of Appeals overturned this decision, ruling 2-1 that *both* the process and the mouse were eligible for a full patent, although the court also asserted that this decision did not include patentability of animals higher than mice, including human beings (Ching, 2003).

By 2002, after public criticism of the 2000 court ruling allowing mouse patents, the Oncomouse case was elevated to the Canadian Parliament. During *Harvard College v. Canada*, the Supreme Court of Canada decided *against* allowing a patent on animals. The court defined the term "composition of matter" as materials and ingredients that had been mixed together by a person, so under this context the oncogene sequence that had been inserted into the mouse embryo could serve as patentable material, but the body of the mouse itself could not. The court described patenting of animals as " a radical departure from the traditional patent regime, and the patentability of such life forms is a highly contentious matter that raises a number of extremely complex issues" (Mitchell and Somerville, 2002).

The Canadian Parliament's ruling against Oncomouse dealt a heavy blow to Canadian biotechnical companies who were awaiting patents on plants and animals for pharmaceutical research. Harvard criticized the decision, stating the companies were being deprived of legal protection for their inventions leaving "Canadian scientists at risk of being left behind from their colleagues around the world" (Ching, 2003). To this date, Canada remains the only industrialized nation to openly ban animal patents.

Oncomouse in Europe

After a similar process of verdicts and appeals, the European Patent Office (EPO) eventually approved Oncomouse for a patent in October of 1991. While the case itself was very complex, it incorporated the concept of a utilitarian balancing test that weighed the *ordre public* (moral objections) against the possible societal benefits of an application (Bioethics and Patent Law, 2006), and this will be discussed further in Chapter 3, Transgenic Ethics.

FDA Approval of Transpharmer Products

The issues surrounding transgenic legalities are not limited to a debate over whether life should be patented. On February 6, 2009, the U.S. Food and Drug Administration issued its first approval for a biological *product* derived from genetically engineered animals. The advisory committee of the FDA declared ATryn (an anti-clotting drug from the milk of transpharmer goats) to be safe and effective. The FDA also sought advice from several outside sources, including the Center for Veterinary Medicine (CVM) who conducted a thorough investigation and assessed the stability of the recombinant DNA construct in the animals' genome. Following their investigation, the CVM Director stated: "We have looked carefully at seven generations of these GE goats; all of them are healthy and we haven't seen any adverse effects from the rDNA construct or its expression. I am pleased that this approval makes possible another source of an important human medication" (FDA, 2009).

Other companies, like AquaBounty Technologies have been seeking FDA approval for almost a decade for their strain of transgenic salmon for use as a food source. These salmon mature much faster than native salmon, which can take ten years to reach full maturation and begin breeding. Before granting approval for this controversial food-source, the Food and Drug Administration must conduct a full assessment of any risks associated with this product, including what happens if the aquafarmed salmon escape into the environment and breed with wild type salmon. The FDA staff includes experts in environmental science and biology who analyze hundreds of possible environmental impacts (AquaBounty, 2009).

Chapter-2 Conclusions

While some individuals may view animal patents as an infringement on the sanctity of life, others recognize that transgenic animals are created for the benefit of human health and thus deserve the protection granted by a patent. The author of this IQP believes that by creating and a patenting a transgenic animal that specifically benefits society (such as serving as a cancer model), research that benefits society gets protected. Ultimately the information learned from such transgenic animals will help minimize all animal suffering in laboratories.

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Chapter 3: Transgenic Ethics

Since the beginning of civilization, human imagination has dreamt beyond traditional species boundaries. Ancient Greeks imagined the griffin, with the body of a lion and the head and wings of an eagle. The Egyptian sphinx, perhaps the most famous example, had the head of a human on the body of a lion to represent wisdom and strength (Kimbrell, 1994). While transgenic technology is so powerful it may only be limited by the constraints of human imagination, ethical concerns limit what types of animals should actually be created. The purpose of this chapter is to discuss the ethics of transgenesis.

The Utilitarian Balancing Test

In order to make an argument in favor or against a specific transgenic animal, one must consider a utilitarian balancing test. The purpose of the test is to assess the potential benefits to society associated with a particular transgenic animal, and weigh that against any negative aspects or ethical objections. One could consider positive examples as advancement of our medical knowledge, or the development new pharmaceutical treatments to save lives. Negatives might include concerns like public unease regarding the ethical treatment of the animals, or potential pain suffered by an animal. If the likelihood of substantial medical benefits outweighs the moral concerns, then one can argue in favor of continuing to experiment with the respective transgenic animal (Christiansen and Sadoe, 2000).

Alzheimer Mouse Ethics

Alzheimer's Disease (AD) has been referred to as "the long goodbye." A nursing home staff member described AD in a New York Times interview as " a cataclysm" that "tests the human spirit" as caregivers helplessly watch victims fade into the incoherent fog of the disease (Gross, 2004). The Alzheimer's Association released a recent report that revealed some startling statistical information about the disease. An estimated 5.3 million Americans have AD, making it the 7th leading cause of death. The total cost of Alzheimer's and other dementias to Medicare, Medicaid, and private business amounts to 148 billion dollars, annually. A new case of the disease is diagnosed every 70 seconds, and 9.9 million caregivers, such as friends and family of the victims, are not paid for their services. (Alzheimer's Association, 2009)

From a utilitarian standpoint, the Alzheimer mouse disease model developed by Professor David Adams at WPI and his colleagues at the former Transgenic Sciences Inc (Games et al., 1995) (as discussed in Chapter-1) is a great benefit to society. The mouse line has taught us that the production of human β-amyloid protein in a mouse brain is sufficient for initiating the disease, and has provided a model for rapidly screening drugs for blocking β-amyloid production. Since the creation of the Alzheimer's mouse, Elan Pharmaceuticals Inc. (San Francisco) has already used it to develop five different vaccines and inhibitors capable of removing senile plaques from neurological tissue (Elan, 2009). They are currently beginning human clinical trials that will lead to a better understanding of AD, and may help uncover an eventual cure. The costs that would be saved from complete eradication of Alzheimer's are astronomical. 148 billion dollars is enough money to modernize the U.S. railway system. On a global scale, it's enough to maintain freshwater supply systems and sanitation systems for the 2.5

billion people who still do not have ready access to clean drinking water (Agence France-Presse, 2009).

With respect to the wellbeing of the transgenic mice, no signs of pain have been observed to date. They eat, sleep, and reproduce normally, and show no signs of physical suffering or abnormal behavior. Aside from slightly poor performances on maze testing, Alzheimer mice appear to be pain-free (Adams, 2009).

Superpig Ethics

Superpig was created to potentially benefit society by providing a means to increase meat production (Miller et al., 1989). Based on the classic 1982 experiment of Ralph Brinster of the University of Pennsylvania who engineered a "super mouse" to contain a human growth gene, because the mouse did not appear to suffer from the transgene, researchers assumed that what worked for mice would work for livestock, and that "super pigs" could produce more meat at a lower cost, in less time. But the first transgenic super pig was a disaster. Researchers were unable to accurately predict the effect of the extra production of growth hormone on the pig's metabolism, and critics called the resultant creation a "super cripple". "Excessively hairy, lethargic, riddled with arthritis, apparently impotent, and slightly cross-eyed, the pig rarely even stood up" (Kimbrell, 1994).

In the case of the superpig, ethical concerns regarding the animal's suffering greatly outweighed any benefits that a larger, leaner breed of pig would have on society. No real purpose for the animal existed, since farmers could breed more pigs as an alternate method to increasing meat production. Since "super pig" scored unfavorably on the utilitarian balancing

test, scientists agreed on a voluntarily moratorium on growth hormone experiments in livestock (Adams, 2009).

Oncomouse Ethics

Not every transgenic animal can easily be balanced on a utilitarian scale. Specifically, the case of the Oncomouse falls into an ethical "gray area." On one hand, Oncomouse (discussed in detail in Chapter-1) could be used to screen new treatments for cancer, to help lead to finding a cure, and has already taught us large amounts of information on oncogenesis or why tumors form. But conversely, the mice can suffer considerably from their genetic modification.

Statistics show that one out of every three Americans will be diagnosed with cancer at some point during their lifetime, making it the second leading cause of death. In 2008, patients spent 78 billion dollars fighting cancer. Avastin, a treatment for colorectal cancer, costs $4,400 for a monthly dosage alone (ACS, 2009).

With respect to pain suffered by the mice, animals are unable to clearly communicate their levels of pain or distress, but many feel that their perception and tolerance is analogous to that of human beings. Since a cancer patient's levels of pain can influence morality as well as morbidity, one can expect that Oncomouse specimens experience significantly high levels of pain and suffering from their affliction, especially if the tumors are allowed to progress to advanced stages prior to euthanasia.

Because cancer affects so many people, this author believes that new treatments and preventatives should be researched at all costs, but scientists must also consider the wellbeing of the animals used for experimentation. Preventative steps must be taken to minimize the distress of the animals by using painkillers whenever possible to reduce suffering. In addition, university

and corporate IACUC committees should enforce the early euthanasia of the mice prior to advanced tumor formation. The author feels that the potential benefits of cancer research do outweigh the animals suffering in this case. By creating an Oncomouse, scientists have created a specific test subject specifically for researching cancer treatments, which eliminates the need to test on other species. This will ultimately reduce the amount of human subjects that will need to be tested in clinical trials, and thus minimize the total amount of suffering.

Chapter-3 Conclusions

This chapter describes the ethical concerns associated with three specific cases of transgenic animals. In some cases, like the Alzheimer's mouse model, vital research can be conducted without causing obvious harm to the mice involved. Therefore, the Alzheimer model passes the utilitarian balancing test, and research should be allowed to continue on that model. In instances such as the "super pig," significant animal suffering is caused for no real benefit, so that research was rightfully terminated. For more complicated instances, such as the Oncomouse, steps must be taken to reduce the animal's suffering whenever possible by administering pain killers, and humane euthanasia should be considered before the disease is allowed to progress to levels that would cause suffering to the mice.

Chapter-3 References

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PROJECT CONCLUSIONS

Transgenic research has lead to a much greater understanding of human disease, gene function, and methods for producing pharmaceutical proteins. The author believes that overall, the potential benefits of transgenic animals outweigh many of the ethical concerns regarding the treatment of the animals in laboratories. However, strict moral consideration should be given to the treatment of the animals used in each experiment, and precautions should be taken to minimize animal suffering (by using painkillers or euthanasia if necessary). Transgenic animals should only be created to benefit society, and cases that involve animal suffering for no real purpose, like the superpig experiment, should be promptly discontinued.

The author agrees with the new FDA guidelines for transgenic patents, and believes that legislation should be passed to ensure safe and responsible use of transgenic animals, while allowing patents to protect the interests of the biotechnology companies who developed the specific animal so that further research can continue. Transgenic animals should be eligible for patents, as strict governmental regulation of this technology will help prevent accidental environmental release of the animals, such as an unwanted breeding of aquafarmed transgenic salmon with native salmon populations.