The Role of Transgenic Animals in Biomedical Research

The Issue

Transgenic (or genetically modified) animals are proving ever more vital in the discovery and development of new treatments and cures for many serious diseases by helping scientists to characterise the newly-sequenced human genome. Without them, the pharmaceutical industry's ability to discover new treatments would be significantly reduced.

However, the development and use of transgenic animals understandably raise a number of concerns, and the term "genetically modified" needs to be properly explained. This paper therefore seeks to explain the multiple roles of transgenic animals in biomedical research, considers the current usage levels and discusses the issues surrounding transgenic animals in general.

GSK's Position

- Transgenic animals are proving ever more vital in helping to discover and develop new treatments and cures for disease.
- Developments with transgenesis in mice will contribute to the further reduction in the use of "higher" animals, such as dogs and non-human primates, in biomedical research.
- The animal welfare issues associated with the use of transgenic animals are fundamentally no different from those associated with other animals in biomedical research. It is the minimisation of any pain or distress to individual animals in medical research that is important, not the manner in which the animals are bred.
- The development and subsequent use of transgenic animals is subject to stringent internal GSK review and government regulations and oversight. Regulations that control animal research permit the use of animals only when no alternative exists.
- GSK recognises that there is public concern regarding transgenic animals and is committed to addressing these concerns.

BACKGROUND

1. The Importance of Animal Research

A major part of biomedical research is aimed at understanding human biology at the cellular and molecular level in health and disease. Whereas certain human characteristics are shared by no other species or only by primates, there are many other characteristics that are shared with many species of animals. The use of animals has therefore become fundamental to all aspects of modern biomedical research from the study of basic biological mechanisms, to the understanding of disease pathology and the development of new medicines for both human and veterinary use.

Virtually every medical breakthrough in the 20th century came about as a result of research with animals and many more treatments and cures still await discovery. The list is almost endless but includes the discovery of insulin in the 1920s (research involving dogs), the successful polio vaccine developed in the 1950s (research involving monkeys), and the prevention of measles during the 1970s (research involving monkeys).

(Specific information concerning GSK's use of animals in research can be accessed on http://corp.gsk.com/tomorrow/animals.htm.)

2. What is a Transgenic Animal?

A transgenic animal is one which has been genetically altered to have specific characteristics it otherwise would not have. In animals, transgenesis either means transferring DNA into the animal or altering DNA already in the animal.

The earliest transgenic approaches involved transferring DNA, usually by injection into a fertilised mouse egg. However, since it is not possible to control the site of integration of the foreign DNA using this technique, it is a relatively imprecise tool. Mice resulting from this technique are generally called "overexpressors".

A more direct way to determine the function of a new gene is to alter the gene and then observe the physical manifestation (phenotype) of that genetic trait e.g., is the mouse obese, diabetic. These types of mice are often called knock-outs and for several years now, it has been possible to generate "knock-out" mice which carry specifically defined mutations in the gene of interest using gene targeting in mouse embryonic stem cells.

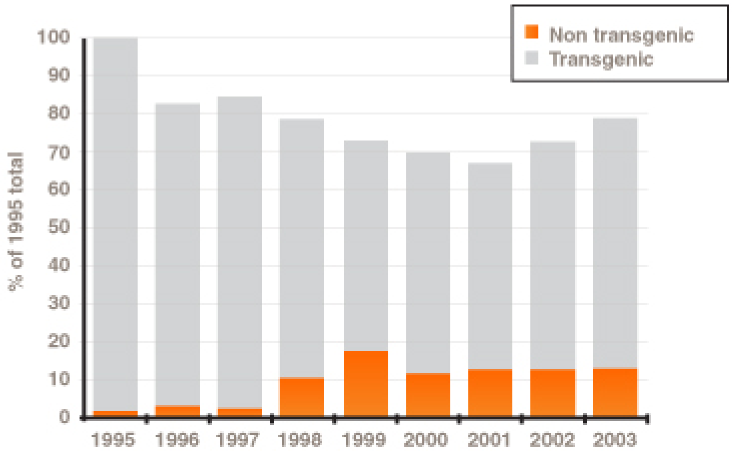
In conventional gene knockout and overexpression approaches, the genetic modification is present in the animal at birth. However, new molecular genetic techniques have been developed that allow a particular gene (in some cases in a specific organ or tissue) to be switched on or off for a short period of time in the adult mouse. This added feature of reversibility provides greater control over the timing and duration of a resulting phenotype, and more closely mimics the effect of pharmacological intervention. It also serves to minimise the physiologic consequences of specific gene modifications in the animal. GSK has begun to employ these new technologies for many of its mouse models.

Over 80% of mouse genes function the same as those in humans. Mice also have a short reproduction cycle and their embryos are amenable to manipulation. Mice are therefore an ideal human surrogate in the study of most diseases. Currently over 95% of transgenic animals used in biomedical research are mice. Other transgenic animals include rats, pigs and sheep. It is hoped that the refinement of transgenesis techniques in mice will ultimately allow for a corresponding reduction in the use of "higher" animals, such as dogs and non-human primates, in biomedical research.

3. GSK's Use of Transgenics

The total number of animals used by GSK has been relatively stable over the last few years. However, as the chart below illustrates, the revolution in genomics has meant a rise in the proportion of animals used that are transgenic, or involved in the transgenic breeding process.

Relative use of transgenics in GSK UK 1995 - 2003



In the short term, the growing reliance on transgenic animals in research may result in an increase in the number of mice used. However, possible changes to Home Office reporting practices, to reflect a more accurate picture of the total number of transgenics actually developed and used for research purposes, should serve to reduce numbers. Furthermore, new emerging non-invasive imaging technologies, such as ultrasound and magnetic resonance imaging are being applied to evaluate mouse models. These imaging tools allow longitudinal measurements throughout the life-time of animals and reduce the number of animals required.

4. The Human Genome Project and the Role of Transgenics

Recent advances in molecular biology, and particularly DNA sequencing, means that the pharmaceutical industry can study most of the 30,000 genes - or potential drug targets - in the human genome. This compares dramatically with the 400 drug targets that the industry has worked on over the past 50 years. Parallel advances in high throughput in vitro screening have helped to match this new genetic knowledge more effectively with chemical compounds. However, in vivo work remains a fundamental element of the drug discovery and development process.

5. The Role of Transgenic Animals

Using transgenic animals gives rise to a number of highly significant benefits.

- Transgenic animals **enable scientists to understand the role of genes in specific diseases**. By either introducing or inactivating particular genes, researchers can often for the first time discover the root causes of diseases associated with gene defects. For example, GSK scientists engineered the overexpression of the human mitochondrial transporter protein, "uncoupling protein-3" (UCP-3), in skeletal muscle in mice. In this model, the transgenic mice were found to eat more than wild-type littermates, yet remain leaner and lighter. The mice also exhibit lower glucose and insulin levels and an increased glucose clearance rate, leading to the hypothesis that compounds that regulate expression of UCP-3 might be of use in treating obesity.

- Transgenic animals **allow more effective treatments to be developed**. Having found the genes implicated in a disease, scientists can then target these or design other therapies which act by influencing their expression. For example, studies in the 1990s suggested a role for the enzyme cyclooxygenase-2 (Cox2) in the inflammatory response. Targeted removal of the Cox2 gene in mice prevented development of autoimmune arthritis, thus validating the Cox2 enzyme as a good target for pharmaceutical intervention.

- Transgenic animals help **test the safety** of new medicines and vaccines. Because transgenic models can highlight specific characteristics such as certain mechanisms involved in the formation of tumours, they can demonstrate more clearly the possible side effects of new therapies. Their use in early toxicity trials may also serve to prevent the subsequent use of a larger number of animals in the development phase.

- Transgenics may **spare the use of higher animals**. For example, GSK is currently awaiting approval from the WHO for the use of a transgenic mouse model (as an alternative to non-human primates) for neurovirulence testing of our Oral Polio Vaccine. Additionally, transgenic mice have been successfully bred to produce human CD4, a receptor found on the surface of white blood cells. Since successfully developing mice with this human receptor, GSK has been able to eliminate the need to use "higher" animals for testing drugs that interact with the human CD4 receptor. This was particularly important as chimpanzees, an endangered and protected animal, are the only other animals, other than humans, that carry the CD4 receptor.

- Transgenic animals can **produce biological products**. It may be possible to use transgenic animals to make rare biological products for medical treatment. Human alpha-1-antitrypsin, a protein used to treat the rare genetic disorder of alpha-1-antitrypsin deficiency, is just one example. Research is underway to breed transgenic sheep which produce the protein in their milk. GSK is not involved in this area of research.

- Transgenic animals are being developed by some companies to **provide new organs** for transplantation such as kidneys, livers and hearts. Transgenic pigs with human histo-compatibility genes have been bred in the hope that their "humanised" organs will not be rejected by a patient's immune system. GSK is not involved in this kind of research, which is still very much in its infancy. If successful, however, this research could transform the lives of the many patients awaiting organ transplants.

6. Some Perceptions around Transgenic Animal Experiments

Despite the importance of transgenic animals in biomedical research, there are some concerns and misconceptions raised about their use in research. Some of these are addressed below:

- **Transgenic animals suffer more abnormalities than regular research animals**. The introduction of DNA into an animal can be very complex and the possible side effects can be difficult to predict. Possible harms might arise from surgical techniques used to harvest and re-implant embryos; the collection of tissue from the tip of the tail for genotyping; and non-specific effects caused by damage to genes adjoining the altered area of DNA. Also reduced fertility and/or oversize foetuses may result from this technology. In most cases the mutations impact highly specific metabolic processes or cell receptors without actually causing disease, discomfort, pain or malformation in the animals. The legal controls for their use are very stringent and GSK devotes considerable resources to monitoring these animals.

- **Transgenic animals not expressing foreign DNA or not containing a particular gene modification are destroyed**. Because transgenesis is a complex science, it is not 100% efficient. However, new methods are being developed to increase the accuracy in transgenesis. Again, it should be remembered that such genetic alteration can only be attempted if the authorities are persuaded that there is no other way topursue important research.

- **The potential risks of transgenics to animals, humans and the environment is too great to justify their use.** The UK has stringent regulations which address these concerns. The Genetic Modification of Organisms regulations and the Environmental Protection Act (1990) address the risks to those working with animals and the impact on the environment of accidental or planned releases. For example, no transgenic animal is allowed to breed with wild populations thus ensuring no long-term change in indigenous populations.

- **The intrinsic worth of animals may be devalued and their integrity violated by genetic modification.** Transgenic animals have not chosen to have foreign DNA or other genetic modifications. However, this potential "cost" to the animals is routinely assessed under the ethical review of proposed procedures and weighed against the potential benefits. Medical researchers only employ this technology when no alternative research avenue exists.

As the Royal Society concluded in its 2001 Report "The Use of Genetically Modified Animals", the use of transgenic animals is fundamentally little different from the use of other animals in biomedical research. It is the degree of pain or distress that is important, not the manner in which the animal is bred. The presence of an extra gene or a gene deletion does not necessarily cause any suffering to the animal.

CONCLUSION

Gene-based biomedical research offers one of the best hopes yet for curing the major diseases which still afflict mankind. The use of transgenic animals is central to realising that hope and offers the potential for the use of fewer animals in more targeted experiments. We must be clear. There are only two alternatives to using animals. One is to use humans in basic research; the other is to delay or even give up the search for desperately needed new treatments and cures. The appropriate use of transgenic animals is a positive development with potential for significant medical benefits. The challenge is for governments, industry and society to ensure that transgenic research continues to be sensitively carried out for proper medical ends in a suitably balanced regulatory environment.

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