GSK Public policy positions

The Role of Transgenic Animals in Biomedical Research

The Issue

Genetically modified (transgenic) animal models, particularly those involving the mouse, represent one of the best methodologies for understanding gene function in the context of disease susceptibility, progression and response to therapeutic intervention. They are playing an ever more important role in the discovery and development of new disease treatments.

GSK recognises that there is public concern regarding the development and use of transgenic animals and is committed to addressing these concerns. This paper therefore seeks to explain the multiple roles of transgenic animals in biomedical research and summarises GSK's perspective on the issues surrounding their use.

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GSK's Position

– Transgenic animals provide value in helping to discover and develop new treatments and cures for disease.

– The animal welfare issues associated with transgenic animals are fundamentally no different from those associated with other animals used in biomedical research.

– The development and subsequent use of transgenic animals in research is subject to stringent control including government regulations and oversight as well as internal GSK overview. The 3Rs principles (Replacement, Reduction & Refinement) and ethical review are rigorously applied.

– GSK is committed to minimising animal usage within its own operations and those of the worldwide scientific community by sharing the models and technology developed in-house with others.

– GSK does not clone animals. We do not use cloning technology with the intention of replicating entire animals.

Background

The Importance of Animal Research

GSK's aim is to discover and develop medicines and vaccines that will prevent, treat and help alleviate the suffering caused by disease. Animal research forms a small but essential part of this discovery and development process. Animals are used to understand disease mechanisms, discover novel ways to treat disease, and evaluate the efficacy and safety of potential new medicines and vaccines before they are tested in clinical studies and approved for marketing.

Types of Transgenic Animals

A transgenic animal is one which has been genetically altered to have specific characteristics it otherwise would not have. Generally speaking, transgenic animals have either DNA added (generally with a view to expressing an additional gene) or have their existing DNA altered (generally with a view to abolishing or modifying the expression of an existing gene).

Currently over 95% of transgenic animals used in biomedical research are rodents, overwhelmingly mice. The mouse is the model organism of choice because of: the extensive analysis of its completed genome sequence and its similarity to our own; the availability of robust and sophisticated techniques which enable the genetic manipulation of their cells and embryos; the ability to perform physiologic and behavioural tests that can be extrapolated directly to human disease; and their short reproduction cycle.

Other transgenic species such as pig, sheep and rats also exist. Their use in pharmaceutical research has so far been limited due to technical constraints.

Recent technological advances should soon allow the transgenic rat to be adopted as a more robust translational model to humans in therapeutic areas where the rat is a better model than the mouse.

The Importance of Transgenic Animals to GSK Research

Transgenic rodents have a number of critical roles in drug discovery & development, some of the most common within GSK being:

Identification of new drug targets

– Transgenic rodents allow the function of specific genes to be studied at the level of the whole organism. In addition to revolutionising the study of physiology and disease biology, the technology has facilitated the identification of new drug targets through the correlation of alteration of specific gene function with disease-associated phenotype. A particularly valuable approach in this context is mouse 'knockout' technology, in which a specific gene function is removed. A retrospective evaluation of the knockout phenotypes of the targets of the 100 best-selling drugs revealed a close correlation between the phenotype and known drug efficacy (1).
– Knockouts therefore show huge promise for identifying & validating new drug targets among the tremendous number of potential targets revealed by the sequencing of the human genome. In recognition of this, national funding organisations have recently established two international consortia whose remit is the centralised & systematic generation & characterisation of mouse knockout models (2, 3). The anticipated output, an 'encyclopaedia of gene function', is expected to lay the foundations of a profound understanding of mammalian gene and physiological systems leading to greatly enhanced understanding of the genetic basis of disease states. This should in turn help to accelerate identification of novel drug targets allowing more effective treatments to be developed.

Disease modelling and drug development

– Due to the similarity in physiology and gene function between humans and rodents, critical aspects of disease pathology and disease processes can be experimentally recapitulated in transgenic rodents. This has greatly enhanced our understanding of underlying disease mechanisms and has enabled the development of novel therapeutic strategies. Furthermore these models have proven invaluable in the preclinical evaluation of potential therapeutic interventions, facilitating the development of more effective treatments by enabling drug candidates to be tested for potential efficacy and toxicity early in drug development. This allows focus on only those most promising drug candidates thereby saving on subsequent animal usage during the later development phases. See references 4, 5 and 6 for reviews of transgenic model value in cancer, Type 2 diabetes and Alzheimer's disease research and drug development.

Replacing non-human primate (NHP) models

– Transgenic mice can be generated which express human versions of target genes, which can in some cases obviate the need to use animals such as NHP for testing drugs that interact specifically with the human & NHP version of the target gene product. For example WHO has approved the use of a transgenic mouse model for neurovirulence testing of GSK's oral Polio Vaccine which previously had to be tested in NHP.

GSK's Use of Transgenic Animals

GSK fully appreciates the value of transgenic animal models in drug discovery and development, whilst recognising that there is public concern regarding their development and use.

As the Royal Society concluded in its 2001 Report "*The Use of Genetically Modified Animals*" (Vet Rec. 2001;148:703-4), 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 pain or distress to the animal.

As with the use of any animal model, all transgenic model activities within GSK are subject to stringent internal ethical review and government regulations and oversight. Moreover, all GSK's transgenic animal model activities adhere rigorously to the principles of the 3Rs - Replacement, Reduction & Refinement.

Examples of GSK's commitment to upholding these principles include:

- **A stringent review process for the approval of transgenic model usage**. GSK only approves the use of transgenic models when their use is critical to drug discovery & development programmes, and there is no suitable non-animal based alternative.
- For each new transgenic model approved for use, GSK conducts **a thorough review of breeding & study design** to ensure the minimal usage of animals and the minimising of any anticipated pain & distress associated with the study.
- GSK has a very active technology & process review programme, involving the **systematic and critical analysis of our entire transgenic animal model operations**. This ongoing initiative ensures that GSK's transgenic operations remain state-of-the-art from an ethical perspective.
- GSK ensures **the optimal usage of existing internal & external transgenic model sources** for its own research interests and those of the broader scientific community. Around half of the transgenic models in use within GSK are obtained from existing external sources, and GSK allows access to its own internally generated models to external colleagues (GSK has a rigorous review procedure which ensures external research colleagues meet the standards which GSK demands of its own research community). Both these activities obviate the need for duplicate model development in GSK and the broader scientific community. This will be further enhanced by GSK's engagement with the recently established international transgenic mouse model consortia (2, 3) whose activities are anticipated to greatly reduce animal use in future model generation & analysis in the worldwide scientific community.
- Finally, GSK adheres strictly to national and international regulations which 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.

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. We must be clear that there are currently 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 demonstrated significant medical benefits. GSK is committed to work with governments, scientific partners & society to ensure that transgenic research continues to be sensitively carried out for proper medical ends in a suitably balanced regulatory environment.

References

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