Home Office

NON-TECHNICAL SUMMARY

Sex chromosomal control of development and disease

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Infertility, sex chromosomes, male-female differences

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Men and women are genetically the same, with the exception of their sex chromosomes. Men are XY and women XX. The sex chromosomes have a special role in making sperm and eggs. Abnormalities in these chromosomes are thought to be responsible for many cases of infertility, a condition that affects

15% of couples. Evidence suggests that sex chromosomes are also responsible for other differences between men and women, for example in their likelihood of developing cancer, their life expectancy and how they respond to medications. The overall aim of this project is to investigate how the sex chromosomes control these processes. More broadly, we also wish to understand how problems in chromosome behaviour in developing eggs and sperm give rise to conditions in offspring such as Down syndrome. Finally, many areas of medical research and agriculture require only animals that are male or female, and those of the opposite sex are therefore created needlessly. A good example is the dairy industry and egg industry, in which only female cows and chickens are required. We want to design a system for creating litters that contain only males or only females.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

Ultimately, our studies of sex chromosomes could give insight into the causes of human infertility and of sex differences in disease. They could also help us understand why chromosome abnormalities are so common in humans, affecting 7-10% of all clinically recognised pregnancies. In turn, the discoveries could lead to new ways of diagnosing or treating these conditions. Finally, a method to create single sex litters would have a huge economic impact on the medical and agricultural industries, and would be a major step forward for animal welfare.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

For most of our experiments we will use mice. These are an excellent model system because their genetic make-up is similar to that of humans. Also, egg and sperm formation in mice occurs in a manner similar to that in humans. We also use a marsupial, the laboratory opossum, which diverged from mice about 180 million years ago in evolution. The rationale for using both model organisms is that mechanisms common to both are likely to be of highest importance for understanding the diseases in which we are interested.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

Our objectives require the creation of genetically altered mice and opossums. In the majority of cases, the effect on the animal will be observed only in the testis or ovary, and so the severity level will be mild. Also, most of our experiments will be performed on material obtained from animals post-mortem.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

Our studies require the use of animals, because currently it is impossible to make germ cells (i.e. eggs and sperm) in a dish. This is probably because in order to form properly, germ cells require two-way interaction with other cell types in the gonad, as well as changing levels of hormones provided via the bloodstream. Nevertheless, one of our aims will be to try and make eggs and sperm types in the laboratory. If this succeeds, it could help replace the use of animals in the longer term.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We implement a number of approaches to reduce animal numbers. This begins with experimental design. Genes that we think are important for the processes we're studying are chosen based on published literature and data generated both by us and by other scientists. This vastly reduces the number of "false-leads". Genetically altered animals are only created if they not available from existing sources. If this is the case, the genetically altered animals are created in-house by highly trained personnel, and are usually maintained as small colonies. We plan our experiments so that each animal provides the maximum amount of material for analysis, and that tissue harvested post-mortem from a single animal can be stored and repeatedly reused in different experiments. This approach, together with statistical approaches, means we use few animals to address a specific scientific question. A major focus of our work is to design a system for creating single-sex litters. Many areas of medical research and agriculture require animals of a defined sex, and those of the opposite sex are therefore created needlessly. If successful, this approach would dramatically reduce the numbers of animals needed for our experiments, and for those of the international research community as a whole.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Our work focuses on sex chromosomes. Mice and opossums are ideally suited for this work, because unlike other model organisms, their sex chromosomes, and the mechanisms by which their eggs and sperm are formed, are similar to those of humans. The mouse is also useful because it is the most tractable mammal with respect to genetic manipulation. In the majority of our experiments, the genetic alterations we create impact only fertility, and thus do not appear to cause pain or distress. Furthermore, in most cases material will be acquired post-mortem. We use highly trained personnel to carry out protocols with moderate severity limits, e.g. induced ovulation, in order to keep animal suffering to a minimum. We cannot always predict the effect of a new genetic alteration. However, animals exhibiting any unexpected or detrimental effect will be killed by a Schedule 1 method, or in the case of new lines

or individual animals of particular scientific interest, advice will be sought from the local Home Office Inspector.