NON-TECHNICAL SUMMARY

Mice with transgenic immunoglobulin loci

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.
  - (iii) Improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
- (c) Development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in purpose (b)

Key words

Companion Animal, Antibody, Therapeutic, Immune

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?

Our pets are currently getting sick from the same conditions that we do, and that we can successfully treat in people with antibody medicines. The problem is that these medicines are species-specific (so we can't just give a dog or a cat the human drug). This is because antibody drugs are proteins and so the pet's immune system would recognise the human drug as foreign and get rid of it, stopping it from working.

We are developing a way to make sure these diseases can also be treated in our pets. We will use the same cutting-edge science used to make human therapeutics, but are building a version that can do it for pets. We will mainly conduct work that will benefit dogs and cats, but could potentially begin work to benefit other species, for example horse. It is unlikely that we would conduct mouse work related to more than three pet species over the five years of the license.

The best way to make antibody medicines is using mice that express the antibody genes of the species you want to treat (which to date has always been human). Our main objective is to generate mice that can express the antibody genes of a companion animal species (e.g. dog or cat). Once we have done this, we will immunise the mice (a process that is similar to a human having a vaccination) with the proteins or other substances that we want to make antibodies against.

We will then test these antibodies to see if they can be used as medicines. Most of this work will not involve mice, but once we’ve narrowed down some antibodies that have good properties based on our experiments, we will then want to test them in a mouse model of the dog or cat disease. This will allow us to see if they work like they are supposed to, and successful ones will be taken into clinical trials in dogs and cats (work that will not be carried out here or in any way related to this license, but which will be carried out by experienced professionals at licensed establishments).

In summary:

Aim 1 – Make mice that express dog/cat antibodies

Aim 2 – Immunise these mice to make antibodies

Aim 3 – Test these antibodies in mouse models

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?

The range of veterinary medicines available is much smaller and less advanced than for human medicine, and so dogs and cats are often being treated with drugs that we no longer really use in people, simply because there isn’t a better alternative. For example, we treat lymphoma, a type of blood cancer that’s very common in dogs, with the same chemotherapy we’ve been using in people for a very long time. The thing is, the dogs don’t understand why they are suddenly experiencing all of the side effects of chemotherapy and it can be very distressing for them and for their owners. As a result, they tend to be given a lower relative dose than people are, to reduce the side effects, but this also means it
doesn’t work as well. Lymphoma is just one of many diseases for which we have highly effective human antibody medicines that mean that people can have treatments that work, without the awful side effects of previous therapies. It is our hope that the antibodies produced in, and later tested on, mice that come under this license can be used to treat pet diseases in the future and to deliver the same benefit that we have seen in people. Given how little innovation there is in veterinary medicine (compared to human medicine), this new class of drugs could have an even bigger impact on pet health than it did on human health. And because we have thirty years of experience in making human therapeutics to work from, we have a very good idea of what will and will not work, and so we can make sure that we can deliver the maximum benefit with the fewest mice used. Part of the lack of innovation in veterinary medicine is because less fundamental research has been done in these areas. Therefore, as part of our project, we will need to conduct work ourselves, as well as with external collaborators, to learn more about how these diseases work and how best to treat them. This work will be published and made available to the rest of the field, so that we can all benefit from the greater level of understanding of dog and cat disease and its treatment. In the long term, it is our aim to move from just learning from human antibody medicines and to use these mice to help us learn what are good drug targets. We can then use this information to help improve drug development for people by giving more accurate information on what goes wrong and how we can treat it. So this project will go from our pets being benefited from what we know from human medicine, to being able to help the other way around, overall making the most of the advantages of each area. In summary: Short-term benefit – New veterinary medicines based on what we know from human health Mid-term benefit – Increased understanding of dog and cat disease Long-term benefit – Potentially this work could be used to gain insights that benefit human health.

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?

Members of our team have carried out, over the last ten years, almost exactly the same process to make mice that have human antibody genes. We therefore know exactly how many mice were needed for that project. Whilst the species (cat or dog) is different, the science is the same. We are therefore able to confidently predict, based on these past numbers and statistical predictions based on normal inheritance patterns, how many mice this project needs. This project will use mice, and we estimate that the project will need 85,250 mice in total over the five years of the project. All experimental work will be carried out on adults.

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?

We are going to edit parts of the mouse genome in some embryonic stem cells, and then put these cells into a 3.5 day old mouse embryo. All of the work up to this point is not regulated as it doesn’t work on sentient animals, only cells from them. We then take that embryo into a female mouse that will give birth
to mice that contain our edited DNA. This is a female that has been mated to a male that has had a vasectomy (which is an equivalent process for mice and people), undergoes a simple procedure under anaesthetic, and then is pregnant in a normal fashion. As such, it is a very mild, and largely natural process. The changes we make to the DNA are not expected to have any effect on the mice, and so they will be healthy and normal. This project involves changing the DNA at multiple sites in the genome, and so we will need to take mice that have each of these changes and breed them together so that we end up with a mouse line that has all of the relevant changes (i.e. dog and cat genes) in the same mouse. These mice can then be used to make antibodies. To do this we will inject them with an antigen - what we want the antibody to be effective against, such as a cancer protein, and this should only cause temporary discomfort for the animal – it's just like you or I getting a vaccination. The type of antigen will determine how it is given to each mouse, the majority will receive a dose through a mild injection using a hypodermic needle. Some antigens will need to be delivered by injecting a large volume of liquid equivalent to 8-10% of the bodyweight in a short period of time (8-10 seconds), for this mice will be anaesthetised during dosing and will be given suitable pain relief until they return to normal roughly 24-48 hours later. This process may be repeated at monthly intervals, typically twice but rarely up to four times to boost the response to make better and better antibodies. Mice recover well from being challenged with an antigen, but any mice which fail to recover as expected will be humanely killed. After the mouse has enough time to generate suitable candidate antibodies these mice will then be anaesthetised and humanely killed – at which point we will be able to collect their blood and spleens, and the antibodies in them. When it comes to testing the antibodies in mouse models, what they experience will depend on what the disease is. We only want to use very well-established models, and so our work will be routine for this area. For example, we may use a well known mouse cancer model, and try to treat the cancer in the mouse with our antibodies. This will carry the accepted thresholds for the mice with the cancer or other disease.

Replacement

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

The immune system is very complicated, and you need all of the parts of it working together in a healthy animal in order to make good antibodies. Over the past thirty years, hundreds of millions of pounds have been spent on trying to make a system that does not need live animal models to make antibodies for human medicine but none of them works well enough. Hence we are using live animals to make these veterinary medicines. Simply put, there is no non-protected animal alternative that works well enough.

Reduction

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

The main area of reduction is by maximising the amount of work that is carried out in cells so that we don’t need to use mice. This is both in the stem cells before we make the mice, and in the experiments, we will run to test the antibodies, before using them in mouse models of disease.
The stem cells we use will be extensively pre-screened to make sure we only use the ones most likely to work. We will also try to do as many of the genetic modifications in cells, rather than mice, as possible in order to reduce the amount of breeding steps (and therefore animals needed).

In the stage where we make antibodies, we will want to knock out the target protein in these mice. We will check available databases to see if someone else has done this before, and if so what happened, as we will only undertake this work if the mouse produced is healthy enough to be used. In other words, we won’t just make the model and see what happens, we will reduce numbers by not making bad models in the first place.

Then when it comes to the antibody testing, we will carry out a wide selection of non-regulated experiments in order to be sure that we only go into mouse models if we are really confident the antibody could work. We are also going to use the most up to date immunisation methods in order to use the fewest number of mice for this step.

Finally, given that we only wish to use established disease models, and therefore shouldn’t need to run pilot trials – reducing mouse numbers, there will be a lot of data available about how the model works, and so we can carefully calculate the statistically significant number of mice we need to see if the antibody works.

The team’s experience should also help, as it means we know what mouse experiments are actually required, and overall ways to be as efficient as possible, reducing mouse numbers.

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.

Choice of the mouse

The mouse has been the first choice means of producing therapeutic antibodies for thirty years. Using it for this project means we can benefit from that knowledge and experience, increase the probability of success, and not require extensive work (including the use of many experimental animals) characterising an alternative mammalian model system. The mouse is also a very well characterised model for the diseases we wish to treat, and so we can be confident that the data will be relevant and that we are using the right model and number of animals.

Minimising suffering

For this project to work, the pet genes we are putting in have to work in the same way as the mouse ones we are taking out. These mice will therefore be healthy and not different from normal. The other changes we might need to make for the project will also only be useful if the mice are healthy.

Group housing

Animals will be kept in socially compatible groups.
Enrichment

Mice will be kept in suitable environment as specified by the Code of Practice for housing and care of animals bred, supplied or used for scientific purposes.

We use a sophisticated animal tracking system to ensure welfare data on all animals can be readily accessed/analysed.