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NON-TECHNICAL SUMMARY

Understanding proliferation versus differentiation in cells and tissues.

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Division, maturation, cell fate, cancer

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?

We need to understand why cells divide and how they chose to stop dividing before maturing into a functional state, so we can manipulate these processes for making new cells for therapy, as well as stopping disruption of these processes in cancer.

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?

We will understand better how the normal nervous system, pancreas and gut form in development and how they maintain themselves in adulthood both at the level of tissue behaviour and by looking at the molecular mechanisms of control of these processes. We aim to enhance the ability of cells in the pancreas, gut and nervous system to adopt and maintain a mature state, which will aid in the treatment of diseases of these tissues where functionality is lost such as diabetes and cancer. Data generated will also benefit other researchers who work on cancer and development. They will be applicable to humans and to animals with these conditions.

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?

We will use mice. We expect to use up to 20,000 mice over the 5 years of this licence to achieve our scientific aims.

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?

The vast majority of procedures are expected to have no effects on the animals other than giving injections and taking blood samples. In a small number of cases we will be using mice that are genetically engineered to develop intestinal or pancreatic cancer and these mice may show adverse effects such as weight loss, and diarrhoea. These mice will be closely monitored to ensure that their welfare is not unduly compromised and any suffering is minimised as far as possible e.g. by enhanced monitoring and supportive intervention such as wet food. At the end of the experiments, animals will be humanely killed and tissues will be taken for further analysis.

Replacement

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

We are studying how embryos develop and how the tissues that form are maintained in adulthood. The complex network of genetic and cellular interactions that control these processes are, as yet, largely unknown and we cannot use any system other than a living animal to study them. Indeed, animal

studies are unavoidable if we seek comprehensive knowledge and understanding of gene function, physiology and pathology. However, where possible we will first undertake similar experiments using tadpoles under a separate licenced programme of work, which will allow us to establish biological principles in living embryos that are not mammals.

Reduction

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

Prior to embarking on animal experiments we will collect as much evidence as possible to determine whether our experimental hypothesis is likely to be correct. Indeed, much of the programme of work described here is based on many years of work using Xenopus frog embryos (under a separate licenced programme of work) so we already have evidence in frogs that the mechanisms that control cell division and maturation that we aim to study in mice are active in this “lower” species. Some of these experiments will lead on from experiments where we change the genes in cells that we can grow in the lab and see whether this changes their behaviour. We will then need to see whether the same thing happens in mice. We are also using mini-organs which grow independently of the body in culture dishes (organoids) to study as many aspects of cell division and maturation as possible, which reduces and replaces some mouse experiments, although tissue for these mini-organ cultures are originally derived from mice, and each mouse only produces tissue for a small number of organoids. When we have types of genetically modified mice of scientific interest but for which we have no immediate use, we will freeze embryos that can be thawed out at a later date.

When designing the experiments, we perform statistical analysis to ensure that we use the minimum number of mice per group that will be informative. We have many years of experience in determining the correct sample sizes for the sorts of experiments we undertake. To get enough statistical power, we generally need n=3-5 per group for our analysis, and we anticipate looking at, at least, 3 time-points per type of mouse. Advice will be sought from a collaborator who is conversant with the sophisticated mathematical and statistical analysis that will inform our experimental design. Indeed, our experience of analysis of a genetically modified mouse previously studied with another ofr our collaborators has told us that, in general, 3-5 of each type of mouse per time-point are the minimum that will be required for statistical significance for analysis when we are looking at changes in cell numbers and tissue organisation. We would aim to look at at least 2-3 developmental stages as well as adults, depending on the effects that we see, as this allows us to gain the maximum information about how tissues form during development and adulthood.

To maximise the information from a single animal, we will collect samples from multiple organs and tissues and share these with other scientists who are asking similar questions, so they do not have to breed their own mice for experiments.

We will remain alert to any advances that will enable the replacement of animals.

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.

We have undertaken extensive work in embryos of the frog, which has generated data underpinning much of this programme of work. However, we must now determine whether regulatory mechanisms found in the frog are the same in mammals.

The mouse is the most appropriate animal model for this study because: (i) it is a mammal; (ii) physiology is more extensively characterised in mice than in other mammalian species; (iii) mice are amenable to changing their genes; (iv) a large number of relevant genetically modified mice are already available. The experiments in this proposal will involve creating and analysing genetically modified mice and are classified as mild to moderate with respect to potential discomfort, stress or suffering.

Specifically bred mice will be maintained in a clean environment to decrease the risk of infection. During this project, some mice will receive substances including chemicals that can switch on genes, which normally do not harm mice. Those will be administered mostly by injection, the pain of which is considered to be mild. Alternatively, where possible, these substances will be administered in food and water, resulting in minimal, if any, discomfort. We are using well-established chemical substances to alter the genes of the mice, so potential bad reactions to the substances used are minimised as far as possible. Taken together the overall harm to mice that can be caused by performing our experimental plan is minimal and the obtainable knowledge and benefit for our society is significant.

We have chosen mice that are designed to develop cancer where the development of tumours is well established. We have safeguards in the form of limits to weight loss and the detection of signs of compromised health such as inactivity, hunched posture and diarrhoea that allow us to act at an early age to humanely kill mice to avoid unnecessary suffering. Moreover, when using new sorts of mice genetically engineered to develop tumours , we will seek training from other scientists who are familiar with how these cancers develop to make sure that we know what to expect and are alert to early signs of suffering.

Where possible, we will use “mini-organ” cultures from mice that can be grown outside the body to investigate molecular mechanisms of control of cell division and tissue formation. These often divide limitlessly in plastic dishes as well as mature into functional tissues when we change the chemicals they are grown in.