NON-TECHNICAL SUMMARY

Mechanisms and Therapies in Musculoskeletal Cancer

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.

Key words

Cancer, Therapy, Musculoskeletal, Bone, Metastasis

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is required, and should be submitted within 6 months of the licence's revocation date.

Reason for retrospective assessment

This may include reasons from previous versions of this licence.

- Contains severe procedures
- Required at inspector’s discretion
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?

Bone cancer is a potentially devastating condition affecting young adults and companion animals. The most common primary bone cancers – cancers that originate in bone - are osteosarcoma and Ewing’s sarcoma. As these tumours grow, they destroy the bone, cause significant pain, and increase the risk of the bone subsequently breaking. If left untreated, the cancer will often spread (metastasise), usually to the lungs, and kill the patient. Current therapies for these cancers are reasonably good but survival rates have now levelled off at around 60% and there is a real need for better and safer therapies. In the work described under this project license, we will start by validating two published and clinically relevant mouse models for studying OSA metastasis, as a foundation for future studies on the molecular drivers that control OSA metastasis.

A retrospective assessment of these aims will be due by 03 October 2022

The PPL holder will be required to disclose:

- Is there a plan for this work to continue under another licence?
- Did the project achieve it's aims and if not, why not?

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 first phase will provide data that clarifies which model is most clinically relevant and where refinements can be applied. When this first phase has been completed, the results will serve as a foundation for additional experiments that will be used to develop safer and more selective therapies for treating and ideally preventing the progression of these cancers. The data collected will be used to guide clinical care in canine and human patients with osteosarcoma. In the longer term the aim is to develop/identify new approaches that will lead to measurable improvements in both quality and quantify of life for bone cancer patients.

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?

Model validation studies: 100 mice. Project timeframe is 5 years.

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 most significant effects on animals from this work relate to the formation of tumours under the skin or in the bone, and subsequent spread to the lungs. In the latter, potential adverse effects relate to risk of fracture, pain and lameness. In both models there could be signs of difficulty breathing (due to lung metastasis) and weight loss/anorexia. We mitigate most of these risks through the use of clear, measurable humane end points. One of our protocols involves surgical removal (amputation) of the hind limb in order to reduce the risk of bone fracture – this protocol is classified as severe, but the effects on the animal will be mitigated through the use of effective pain relieving drugs. Additionally, we will be actively exploring (under this license) a less invasive model that does not require amputation.

A retrospective assessment of these predicted harms will be due by 03 October 2022

The PPL holder will be required to disclose:

- What harms were caused to the animals, how severe were those harms and how many animals were affected?

**Replacement**

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

We make use of non-animal alternatives wherever possible, including cell culture models for studying the effects of therapy on isolated cells, and computational models for predicting the likely effects of cancer (and cancer therapies) on bone strength and risk of fracture.

A retrospective assessment of replacement will be due by 03 October 2022

The PPL holder will be required to disclose:

- What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

**Reduction**

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

For each cell line, pilot studies will be performed to establish the minimum sample size required for robust statistical analysis. Study design will be optimised to allow sharing of controls across multiple experimental groups. Within each experiment, we maximise data collection from individual animals by
using non-invasive imaging and blood tests that can be used repeatedly in the same animal, without the need to kill small numbers of animals at multiple time points.

**A retrospective assessment of reduction will be due by 03 October 2022**

The PPL holder will be required to disclose:

- How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

**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.**

Immune deficient mice provide a reproducible genetic and immune background against which we can study the effects of cancer cells and therapies without the animal’s immune system rejecting the foreign cancer cells. The adverse welfare cost to the mice will be minimised by (1) using established anaesthesia and analgesia protocols and (2) monitoring the animals using validated measures of lameness and bone destruction, and (3) using sensitive, validated imaging techniques to identify metastasis, allowing us to remove the animals from the study before they become severely clinically affected. We will also be working to validate a new model for bone cancer that does not involve injection into a long bone and that does not appear to cause pain or lameness.

**A retrospective assessment of refinement will be due by 03 October 2022**

The PPL holder will be required to disclose:

- With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals?