G. NON TECHNICAL SUMMARY (NTS)

Project title: Mechanisms and Therapies in Musculoskeletal Cancer
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants: YES
   (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants: NO
   (iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes: NO

(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 paragraph (b): NO
(d) protection of the natural environment in the interests of the health or welfare of man or animals: NO
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work: NO
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills: NO
(g) forensic inquiries: NO

Keywords:
Cancer, Therapy, Musculoskeletal, Bone, Metastasis

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):
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.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the 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.

What types and approximate numbers of animals do you expect to use and over what period of time?:
Model validation studies: 100 mice. Project timeframe is 5 years.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels 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.

Application of the 3Rs
Replacement:
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.

Reduction:
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.

Refinement:
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.