Royal Veterinary College
University of London

Summary Minutes: AWERB PPLs meeting

Status: FINAL

Meeting held: 2nd August 2023 at 10am via MS Teams

Present: 12, plus 1 in attendance, 1 by invitation and 13 apologies

1 PPL AMENDMENT

The PPL Holder was welcomed to the meeting. She explained that she wanted to make an amendment to her licence in order to add a new disease model. This was to explore further and gain a better understanding of the molecular and cellular pathways involved in the pain phenotype associated with skeletal diseases, in particular Paget's disease.

A query was raised how the new model would fit into the overall objectives of the project licence, which was to understand the mechanisms of bone pain and how to manage those? The PPL Holder advised that the pain associated with Paget's disease had not been studied very well. With this disease, patients have bone lesions, usually on arms or legs, that can appear at any time but usually with ageing. Paget's disease disrupts the normal cycle of bone turnover causing bones to become weakened and possibly deformed and causing persistent pain. A mouse model of this disease had been developed by others which fitted in with the objectives of this licence. The model involved a mutation in a gene important for osteoclast activity, the cell that destroys the bone. The incidence of bone lesion in this model had been looked into but nobody had really looked at the contributions of these bone lesions to skeletal pain. This was the objective of this study to see whether the pain associated with the disease progressed with age.

The following queries were raised:

- **Why was there no pain phenotype associated with the model?**
- As far as the PPL Holder was aware, only two teams had previously used this model. They had kept the mice until they were 18 months of age and no signs of pain had been reported in their studies, only that the number of bone lesions increased with age.
- **Could this be a relatively short study if it was found that there was no phenotype in spite of the lesions, as then there would be no possibility of looking at mechanisms of pain because there was no pain to inhibit?**
- Yes. The aim was to confirm that the number of lesions do increase with age. An age limit of 66 weeks for the mice had been decided upon as most bone lesions generally occurred between 12 to 16 months. The plan was to quantify pain behaviours in these mice with the disease progression and to do some molecular analysis of nerve markers in the dorsal root ganglia of these mice and in the bone. If no changes were found though then further experiments would not be done.
- **The new protocol referenced using a general score sheet. Was it applicable to this model though?**
  The general score sheet related to all of the models.
- **The licence refers to evoked and behavioural naturalistic tests but it was not clear how frequently they would be done?**

The protocol would be amended to make it clear that there would be a maximum number of up to four tests (3 evoked and one naturalistic) carried out on any given animal, which would be done no more than once a week. This would still provide the flexibility to identify and use the most effective tests but without exposing the mice to too much intervention too frequently.

- **One of the behavioural assessments would involve food being withheld from the mice for up to 6 hours. What was the reason for that?**
- As this test used equipment that the researcher no longer had access to AWERB recommended that this test be removed from the licence and so consequently the requirement for food to be withheld.
- **According to the NHS website, in many cases there were no obvious symptoms for Paget's disease and the condition was generally found during tests carried out for other reasons. Was it therefore expected for mice to have a phenotype?**
  Some phenotype was expected. The PPL Holder had recently attended an international meeting on Paget's disease. As part of that patients had been interviewed who had advised that when they did have pain, it was severe. Although it was not expected for all mice to experience pain, the aim was to try and determine if the pain correlated with the numbers of lesions and if there was a particular lesion that could be painful.
- **Where there was pain in people, it had been suggested that some of the pain was due to the abnormal size of the lesion and therefore the effects that had on the joints and also nerve root compression. Would the mice also exhibit these effects or would they just have the microscopic bone lesions?**
- Currently no one had been able to show deformities in these mice that might explain the pain. This research was aiming to see if the pain could be coming from just the excessive bone remodelling.
- **The signs of the indicators of pain that were chosen would be crucial in identifying the pain. How validated were these measures? If none of the tests showed signs of the pain, it might not necessarily mean that there was no pain, but that the wrong indicator had been chosen?**
  The PPL Holder recognised this. She was aiming to use between three to four tests that represented the diverse types of pain.

AWERB recommended that once the study was underway and it was possible to assess whether pain could be detected and so able to decide whether further studies could be done, that the PPL Holder should report back accordingly to AWERB.

The PPL Holder was thanked for attending the meeting. The requested changes would be made and circulated for a final review.

After the PPL Holder had left the meeting AWERB discussed the amendment further and concluded that if it was granted, then initially the minimum number of animals should be used, so that it could be determined if there were any adverse effects and severity. A decision could then be taken on how to move forward with the project.

2 ANY OTHER BUSINESS

2.1 Bordetella Bronchiseptica

A study request application had been received involving the use of Bordetella Bronchiseptic, which was a very contagious bacterium to a lot of species (dogs, pigs and horses) that were

held within the BSU. Although B. bronchiseptica would be inactivated, concern had been raised about the potential risks.

It was agreed that a copy of the risk assessment would be requested. Advice would also be sought from experts at the RVC. A signed certificate would also have to be provided to say that tests had been done and that there were no viable bacteria present (like what was provided for any killed bacteria that was going into a vaccine).

3 MINUTES

The minutes of the meeting held on 11 July 2023 were confirmed as an accurate record.

4 DATE OF NEXT MEETING

This was scheduled for 23 August 2023 at 10am. It would be a standard agenda items meeting.

Secretary
21 August 2023