Royal Veterinary College
University of London

Minutes: AWERB (PPL Reviews meeting)

Status: Chair approved

Meeting held: 26 May 2021 at 2pm via MS Teams

Present
Attendees: 10, plus 1 in attendance, 3 by invitation and 7 apologies.

1 NEW PROJECT LICENCE REVIEW

An application for a new project licence had been received. The applicant explained that this was his first project licence, but he had been working with rats and mice since 1992. He had been working with genetically modified mice since 2000, and had made his first targeted mouse in 2004 and since then he had been working on the same mouse model. The particular gene that he had deleted had turned out to have a profound effect on tissue homeostasis and function in mice.

The project was based on understanding the roles of growth factors in several signalling systems. The applicant had looked at quite a few different systems and recognised that there was a model that could look at cell cycle, regulation of tissue homeostasis and tissue size amongst other things. To that end most of the data had been got out of testis, muscle and cartilage. These were the main things that they would be eventually looking at to understand if there were degenerative or disrepair related disorders and whether this could be a mechanism or pathway to try to alleviate the symptoms of impaired repair (due to loss of progenitor cells) related disorders such as sarcopenia and osteoarthritis. First though they were trying to figure out how each of these growth factors and their regulation primarily affected the cell cycle differentiation.

The following comments/queries were raised:

- The licence was not complex, however the wording used made the licence seem to be more complicated than it was. Some of the areas needed more detail as the Home Office Inspector would be doing a harm benefit analysis and so would need to get an understanding of what the animals would go through.
- NTS: This was used by the public to understand the aims of the project and what was going to be done with the animals. The current version needed to be revised as it was very complicated for members of the public to understand.
- The licence referenced 20% body weight loss as a potential adverse effect. AWERB recommended that this be changed to a maximum 15% weight loss. The licence should also include the steps that would be taken to combat that weight loss.
- Clarity was requested about the substances being given by which route and how each route would be done (such as anaesthetic) as the weight loss would also need to take that into account.
- There was a possibility that novel compounds might be used. These would initially only be used in small cohorts of animals (6 or less) in order to verify the absence of significant adverse effects. AWERB recommended that this be expanded on to include information about the possible adverse effects that could be experienced from giving an unknown, such as body weight loss,

coat condition, behaviour or any sign of discomfort, so these could be looked out for. There should also be information about what would be monitored and what would be focused on, similar to a scoring sheet. It was also important to define the difference about whether it was part of the phenotype or administering a substance to the phenotype.

- The licence made reference to tail tipping. AWERB asked why tail tipping would be used. The applicant said that it was unlikely and that it would be removed from the project licence.
- It was noted that there could be intramuscular (IM) injections. It was recommended that these should be administered under general anaesthesia (GA) as IM injections were extremely painful, so this was kinder to the mice despite the risk of an adverse response to repeated GAs.
- The licence mentioned that some of the animals might be housed singly. AWERB asked why. It was explained that this related to procedural work rather than husbandry, in order to be able to monitor for weight loss over a couple of days for example. The applicant was advised that singly housing for monitoring purposes was really only acceptable for a couple of hours as only transient pain and discomfort was anticipated. If an animal did suffer for longer and showed no signs of improvement, then it indicated there was a problem and that the animal should probably be euthanased. It would not be fair on animal to monitor for longer just in case it improved, as it probably would not.

The applicant was thanked for attending the meeting. Further work was needed on the project licence and the Chair of AWERB offered to meet with the applicant to go through the licence in detail to help make the required improvements. It would then be recirculated for another review.

After the applicant had left the meeting, AWERB discussed this project licence further. Their consensus was that the project licence needed to be rewritten, with guidance from AWERB, for currently the licence was very confusing. The technicians would be using the licence when working with the colonies and needed clear cut steps of what could or could not be done and what the expected adverse effects were. It was also unclear what the benefits were from doing this work and it was difficult to understand the diseases in the context of the models that were being used.

There was concern that the project licence was too vague. It seemed to have been written to try and cover as many options as possible. The Home Office were trying to cut down on project licence holders doing this and to just include aspects of work that would actually be done. ASPeL had been designed to make it as easy as possible to submit amendments if additional work or changes were needed. Project licences were now seen as evolving documents that were built on over time rather than one large static document that tried to cover everything that might happen.

2 NEW PROJECT LICENCE REVIEW

This project licence had previously been reviewed at the July 2020 AWERB meeting but because it had been significantly rewritten it had been decided to invite the licence holder back to discuss her licence further.

At the initial AWERB meeting in July, AWERB had commented that there had not been enough consideration of the potential occurrence of adverse effects and describing them in more detail, nor had cumulative adverse effects been taken into account. These had now been addressed and AWERB were happy with what had been put in the application.

A query was asked whether the NTS had been updated, as there had been references previously to fasting the mice and rats overnight. It was confirmed that this had been changed so that food would be left in the hopper so that they could eat overnight. There would just be a short period of time where they would be without food before the surgeries. She would check that this change had been reflected in the NTS though.

A query was asked whether in the experimental design section, more information could be included about the power calculation. It was explained that it was not possible to do an effect size as they were putting in human proteins and so the control injected sheep would not be expressing any human proteins. They were going to be doing one of the following: control animals with nothing injected; or animals that received gene therapy that would express a human protein; or animals that received human stem cells for engraftment. Information had therefore been included explaining that they had historical data that suggested that n=5 per group was sufficient to be able to determine a therapeutic effect (for example evidence of functional human protein expression in the blood of fetal sheep). Generally, where they were using gene therapy containing a human protein, the animal did not express the human protein. Therefore, they expected an "all or nothing" response where either all animals expressed or none did.

AWERB asked whether the transfusions that were mentioned would just be in the mice. It was confirmed that was the case. They would be collecting blood from litter mates who were not anaemic, and the transfusion would be done via the superficial temporal vein, facial vein, or the peritoneal cavity (if less than 3 weeks of age).

The project licence holder was thanked for attending the AWERB meeting and for having addressed their comments so well. It was agreed that an updated copy of the complete project licence, including the revised NTS, would be circulated to AWERB. If they were happy with this, then AWERB were happy to approve the project licence submission to the Home Office.

3 MINUTES OF PREVIOUS MEETINGS

The minutes of the meeting held on 11 May 2021 were confirmed as an accurate record.

4 ACTION LOG

4.1 Item 1: DMD dogs – guidelines (11 May 2021 meeting)

Monthly meetings were now being held to discuss the dog colony. These meetings would be used as an opportunity to discuss ongoing projects, the breeding programme and any welfare concerns that there might be.

4.2 Item 11.1: Virtual AWERB meetings (08 April 2021 meeting)

Wording had been provided for the terms of reference to make it clear that virtual meetings were allowed. It was suggested that it should also include reference to the members that would need to be present (such as the Named People that should be there) to make the meeting quorate. This would be discussed further at the June meeting as part of the Terms of Reference review.

4.3 Item 3: Proforma PPL comments form (11 February 2021 meeting)

One of the AWERB members advised that she had used the guide that had been put together to assess project licences but had not found it that helpful, as there was too much information and it added more complexity. She suggested that perhaps it should be refined to make the format easier to follow. It was agreed this should be looked at further at the June meeting where people would have had more opportunity to use it.

4.4 Item 11: ARRIVE guidelines (14 October 2020 meeting)

A sub group of AWERB would be reporting back at the next meeting on their findings about gaps in the compliance with ARRIVE reporting in papers and whether there was a need to have a course on it. This would also include a discussion on PREPARE, as this had been raised as one of the questions in Concordat on Openness Annual Review and whether the College required that PREPARE guidelines were met for research that was carried out.

5 FUTURE MEETINGS:

- AWERB agreed that they were happy to continue with the current format of fortnightly AWERB meetings, with one focussing on standard items and one on PPL reviews as this was working well and was a much better format.

- AWERB agreed that there would be no meeting scheduled for August, though if there were any urgent welfare issues, they were happy to meet.

6 DATE OF NEXT MEETING:

This was scheduled for 9 June at 11am and would be the Standard agenda items meeting.

Secretary
4 June 2021