Royal Veterinary College
University of London

Minutes: Adhoc AWERB meeting

Status: Chair approved

Meeting held: 18 August 2020 at 2pm by MS Teams

Present
Attendees: 5 plus 1 in attendance, 2 by invitation and 11 apologies

1 **PROJECT LICENCE APPLICATION**

The Chair of the meeting explained that this was an additional meeting that had been scheduled to review a new project licence application, as the agendas for the next couple of AWERBs were already full.

The project licence was already in existence, but the project licence holder was seeking to either transfer the licence to the College or to apply to add secondary availability to it.

The project licence holder had a very broad experience of using transgenic, knock-in and gene trapped mutant mouse lines and zebrafish morpholino and CRISPR technology. The aim of this work was to understand the function of genes involved in human genetic disorders and their molecular function during development and organ degeneration. During the past few years, the focus had been on the use of therapy to restore gene function in murine animals, using viral derived vector as transduction tools to deliver the corrected copy of the gene. The aim now was to move the work that had been done into clinical trials and to develop new models for the syndrome.

The following queries were raised by AWERB:

- How common were these disorders? It depended on the disorder. For one it was 1 in 100,000; worldwide the incidence of another was 1 per 13,250-140,000 live births.
- What level of resources were available to run these sort of studies and what were the milestones? It was confirmed that the timelines and study designs for the programme of work had been set up. Funding to move the research into human clinical trials was available.
- What work was planned to be done at the RVC? The aim was to test therapies: the phenotype would be tested first and then the therapy. Once the tests had been done new animal models would be created.
- What training for the techniques would be provided as they were highly skilled techniques? The project licence holder advised that he had been working on the delivery for several years and he was very experienced in the training so would be doing the supervising. He was also working with experts in this area. No study would start until the equipment was in place and the staff were completely competent.
- A query was raised about why tail tipping was used for those animals that needed to be genotyped perinatally? This was not a method that was advocated by the RVC. Could not ear clipping be used instead? The project licence holder confirmed that if there were

technical problems during analysis a second sample would be taken using ear punching. Tail tipping was generally used though in order to help differentiate between the genotypes and then to determine the sex of the animals. They had been using this method for several years and it was carried out the morning that the pups were born. The RVC recommended that a less invasive method should be used first though rather than tail tipping.

- Protocol 1 mentioned that one of the adverse effects was the potential for the mice to develop harmful phenotype such as tumours. What was the likelihood of tumours growing as this information should be added to the project licence? The project licence holder advised that it was not common but could occasionally happen as developing new GM lines. It was less likely than neurological signs developing though. It was recommended that the project licence should be clarified to explain that tumours were less likely to occur than neurological signs, so that it could be looked at as part of the harm benefit analysis of the adverse effects.

- A query was raised about one of the protocols in relation to anaesthesia and analgesia. It mentioned that for one route of delivery, gaseous anaesthesia would be the anaesthesia of choice, however further down it mentioned that injectable anaesthesia would be used. It needed to be made clear what was intended to be used for what, as the way it was currently written was confusing.

- Repeat dosing: Appendices 2 and 3 in the project licence referred to potentially doing daily injections for up to 6 weeks. This was a lot to put the mice through. How often could this happen? The project licence holder did not think it would be very likely but had been included in case it was required to enhance the effect of therapy. An explanation should therefore be added to the project licence explaining when it was likely that this might happen and what the normal process was expected to be so that it was clear to the Home Office Inspector.

- Under adverse effects, the project licence referred to published papers that had the potential adverse effects listed, rather than setting them out in the project licence. These needed to be set out in the project licence though for several reasons: the Home Office Inspector when reviewing the project licence might not have access to the papers or the opportunity to read them to look for the adverse effects described; also the technicians and NACWOs when working on the project licence, would not have the time or the resources to go find the papers – they would be looking in the project licence for the information on adverse effects so they could quickly make the appropriate decisions. This information therefore needed to be in there.

- Also under adverse effects, the project licence made reference that if animals were showing clear signs of distress with any delivery route after injection, they should be monitored closely every hour until total recovery was observed. There was no guidance given on when improvement should be expected by and that if there was no improvement, what should be done next. How long should the animals be left not improving before being euthanased? A clear cut off point was needed.

- Endpoints: one of the endpoints that was mentioned was weight loss of <15% compared to its litter mates. It was recommended that this be changed to <10%.

- Intramuscular injections: A question was asked how often did they go up to 1ml? It was confirmed that this had not happened so far. Another question was asked how often they would be doing IM on a mouse as it was a painful method. This would not be the main route, but it was possible it might be required as a method of administration. It was recommended that an option of anaesthetising the mouse be included to make it less painful in particular

when it needed to be done more than once (recognising though that anaesthetising the mouse could also be very stressful). The same advice should be considered for repeated blood samples.

- For the oral gavage it was recommended that plastic needles be used rather than metal ones.

The project licence holder was thanked for attending the meeting. It was agreed that the project licence should be re-worded as requested by AWERB and then sent back for review and decision.

After the project licence holder had left the meeting, the Committee discussed the project licence further.

The following comments were made:

- It was important to observe the researchers carrying out the procedures to make sure they were expert in doing them as they involved complicated techniques. The training records for the researchers would also need to be reviewed.

- There was concern that a lot of extremes had been included in the project licence, where the extremes and the norms had not been defined. It was important for both to be set out: to know what a normal mouse would be going through and also what the extremes could be.

- The project licence had obviously been written quite a while ago and it was felt that potential refinements in the project licence had not been considered. It was important to refine processes and techniques to make sure they were of the best standard. It was also important to keep up to date in the latest developments.

- If it was decided that the current project licence should be transferred over to the RVC, a check would be needed on how long was left on the current licence.

Secretary
24 August 2020