CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

15th January 2015

MINUTES

15/01-01 Apologies

15/01-02 Minutes

The minutes of the meeting held on 13th November 2014 were considered by the Committee and were approved subject to minor amendments.

15/01-03 Matters Arising

Attendance at recent LASA conference and RSPCA Lay Forum

It was reported that the Chair of BERSC attended the recent RSPCA Lay Forum, and found it extremely helpful. Learning points from this will be shared with the Committee.

Members of BMSU attended the recent LASA conference, and a report on this will be provided to the Committee. A presentation about AWERBs included some useful ideas relating to retrospective and interim review.

15/01-04 Chairperson's Items

No Chairperson's items were reported.

15/01-05 Verbal Reports from the Director of BMSU and Named Persons

Report from Director of BMSU:

A recent case of non-compliance has resulted in the relevant PI being required to undergo retraining before undertaking any further licenced work. The PI's competence in Schedule 1 culling techniques will also be reassessed.

In a separate and unrelated incident, a researcher has been issued with 'formal advice of non-compliance' by the Home Office. It should be noted that this is not classified as a recordable instance of non-compliance for Home Office purposes. In this case, at the end of an experiment intended to be conducted under terminal anaesthesia, a rising concentration of CO_2 was used for the purpose of culling. Unfortunately, the animal regained consciousness as a result of this, and the researcher has therefore been advised to select a more appropriate method by which to cull animals for such experiments in the future.

The Committee was informed that one of the larger colonies of animals within BMSU will shortly have to be closed with minimal advance warning, because the researchers involved have insufficient funds to continue their work. It will be necessary to cull 450 animals as a result of this. Maximum use will be made of the animals' tissue, but unfortunately it will not be possible to transfer live animals to other project licences as they are a strain which is not commonly used. In relation to this it was noted that researchers should be encouraged to plan ahead to avoid the unanticipated closure of colonies, but such closures cannot be prevented entirely as BMSU does not have advance information about researchers' funding streams.

A new cryostorage bank was delivered to BMSU late in 2014, and it is hoped that it will be installed by the end of January 2015. This will make it possible to resume cryopreservation work, and it is anticipated that additional support will be available to help clear the backlog in this area.

A survey has been circulated asking for researchers' views on the Home Office Inspection process, which users of BMSU are being encouraged to complete.

The use of SharePoint to host the fast track procedure and to hold BERSC documentation is working well. Feedback from the Committee was invited on this, and it was noted that it is unfortunately not possible to order discussions by 'thread'.

It was reported that Harlan, a key supplier of laboratory animals, has experienced a serious outbreak of mouse parvovirus. In connection with this, BMSU does hold some potentially infected animals and these are being tracked and tested. The Committee will be updated on this once the full implications are known.

Report from Named Veterinary Surgeon:

There is an ongoing review of how animals are tracked through BMSU systems, and the relevant SOPs and guidance materials are being revised.

A termly BMSU users' forum is to be held at the end of each term, and it is proposed that a session will be included in these forums on the functioning of BERSC.

The Home Office Inspector will be visiting the University on 27/1/15, and the visit will include the Inspector's annual meeting with the Registrar and Academic Lead.

15/01-06 Report from the Fast Track Procedure (including SharePoint drive)

It was reported that the fast track procedure is up-to-date, and that there are no outstanding issues.

It was reiterated that the online SharePoint drive is proving useful.

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15/01-07 Project Licence Proposals

15/01-07-1 Application Ref TBA – Blocking autoimmunity by targeting CD4 T cells

The aim of this project is to test in vivo the requirement for OX40 and CD30 signals in autoimmunity and whether blocking these signals, using reagents analogous to those developed for clinical use, successfully blocks autoimmune disease.

The PI's original licence has been split into two, more concise licences in line with the new guidance. This application is concerned specifically with autoimmunity. It has not yet received comments from the Home Office Inspector.

The PI gave a presentation explaining the application to the Committee.

It was felt that the rationale for protocols 1, 4 and 5 should be clarified, and the differences between these and protocols 2 and 3 should be made explicit. The PI explained that protocol 2 enables the researcher to maintain genetically altered mice over time, when their phenotype is not yet clear. Protocol 3 allows the researcher to induce autoimmunity.

In relation to protocol 2, it should be clarified that the non-optional step is the aging of the mice and the adverse effects associated with aging should be included. In previous such experiments, the worst effects seen have been some mild eczema on the ears. Such eczema is considered a warning sign for other, systemic adverse effects, and any animals experiencing such eczema will be humanely killed.

The Committee queried what statistical support will be accessed, and the PI explained that it will be someone with relevant expertise within the University. It was agreed that from a welfare point of view, it is important that the number of animals should be minimised, but this must be balanced against the cumulative experience of the animals. It is important the animals used are humanely killed at the earliest stage possible, and the researcher clarified that animals will usually be culled within approximately 2 weeks. Most experiments will be repeated 3 times as standard; the absolute minimum number of repeats will be 2. The PI clarified that this means that 3 experiments will be carried out with the treatment group, and that results will then be pooled.

More widely, the Committee discussed the MRC's recent investigation into the quality of experimental design. During this, some significant problems relating to reproducibility and statistical power were discovered in a number of studies. As a result, it is understood that in the future funders will be paying more attention to matters of study design and statistics.

The lay summary should be revised to make the refinements more explicit.

It was explained that urine will be collected whilst the mice are being handled.

When administering tamoxifen food in previous similar experiments, the PI has not seen weight loss. It was suggested that this may be specific to his work (using these particular strains of mice) as weight loss associated with tamoxifen food has been seen in other projects. It was noted that the animals have tended to remain lean whilst on the tamoxifen food, but that there is no particular weight loss and body condition remains good.

Injections will be given up to 3 times per week, but usually twice weekly. IP injections will be used as standard, but mini pumps may be used and further advice will be taken if required.

The adjuvant LPS may be used if alum is insufficient. As LPS can induce an effect similar to toxic shock, a warming chamber (the animal's home cage, placed in a slightly warmer environment) will be used as a precaution if LPS is administered. However, the amount of LPS used is so small that adverse effects are unlikely to occur. The maximum dosage of LPS should be stated in the application, and it should be noted as a refinement.

The Committee requested further information about the researcher's approach to tumour measurement, and it was explained that for the tumour studies, the issue is not the relative size of the tumour, but is instead a matter of the existence of a tumour versus no tumour at all.

In relation to imaging, the PI explained that whilst many previous studies have involved imaging, now such data has already been collected it is not considered necessary to carry out further imaging experiments.

It was highlighted that the proposed work cannot be carried out in vitro, as it is concerned with systemic responses in live animals. This should be further explained in the non-technical summary.

Tail tipping is very unlikely to be used, but is included in the standard application wording in case it is for some reason necessary.

Footpad immunisations have been refined, such that they are administered on the ankle rather than the plantar surface – this should be added to the 3Rs section of the non-technical summary.

In the 'immunisation' section of protocol 2, it was felt that the use of the words 'intermittent' and 'continued' in reference to hunched posture should be clarified – in particular, the Committee queried

whether 'continued' meant that hunched posture must be continuously observed over a given period, or that hunched posture would be observed repeatedly at given number of observations.

In the adverse effects relating to exposure to ionising radiation in protocol 3, it is not necessary to state that 'humane endpoints will be determined', as they are already clearly defined.

Any risk of ulceration associated with the proposed injections should be clearly explained in the adverse effects. It was noted that any animals showing signs of ulceration will be humanely killed.

In the non-technical summary, the PI should attempt to describe the objectives in more lay-friendly wording. Also, the benefits of the study should be made clearer.

The PI was advised to include, in the main text of the applications, the refinements which are described in the non-technical summary.

After the PI left the meeting, the Committee continued its discussions. It was agreed that the issues already mentioned were relatively minor, and that once they have been addressed, the application will be fit for submission to the Home Office.

It was reiterated that the wider issue of the lack of statistical support within the University is a problem, and that it would be helpful to include a statistician as a member of BERSC (although it is acknowledged that it will be difficult to action this due to a lack of availability).

Resolved that:

With revisions as discussed above, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

15/01-07-2 Application Ref TBA – The pathophysiological roles of podoplanin and its receptor CLEC-2

The aim of this project is to determine whether clot formation and inflammation in sepsis and haemolytic uremic syndrome is regulated by the podoplanin-CLEC-2 pathway.

The PI gave a presentation explaining the application to the Committee.

The Committee requested clarification on how the proposed work differs from the other thrombosis model being studied by this research group. It was explained that the other model is concerned with deep vein thrombosis and is inflammation-driven. In contrast, the

application currently under review is focused upon a systemic sepsis model.

A member of the Committee referred the PI to the work of another researcher in this area, and queried whether the proposed work could make similar use of in vivo imaging to reduce the number of animals required, to reduce severity and to obtain additional data. The PI explained that his model is fundamentally different, and as such, it will not be possible to use imaging to obtain the required information. The PI felt that the application under review is a more sensitive model looking at small systemic thrombi, whereas the other researcher's model is based upon the imaging of a relatively large, localised thrombus. The PI will discuss this with the other researcher, and if it does prove viable to adopt or learn from any of their techniques, he will do so.

The Committee queried whether the PI has consulted the most recent literature in the field in order to identify opportunities to refine the sepsis model. It was noted that there is a paper due out shortly on the refinement of models of sepsis and septic shock, and also a paper detailing a scheme for assessing the severity of sepsis models. The PI will obtain these papers and will pursue any viable refinements.

Within the application, the wording "Terminally bleeding by induction of general anaesthesia" should be corrected.

The frequency with which the animals are monitored during experiments should be consistently stated throughout the application. It was felt that 6-8 hours is too infrequent for the monitoring of a severe model, and the PI clarified that this was stated in error in the application and will be corrected.

The NVS reported that in relation to previous studies carried out by this research group, the researchers are to be commended on their proactive approach and excellent monitoring of the animals used.

The non-technical summary should be revised to ensure that it will be understood by a lay reader, and acronyms should be removed or explained. Also in the non-technical summary, the sentence "any animal that is only responsive to being handled will be humanely killed" should be revised to clarify that while such animals are unresponsive when their cage is opened, they will respond when handled.

It was queried whether it would be possible to monitor the animals' body temperature as an early indicator, and this will be explored by the PI.

Regarding weight loss associated with tamoxifen food, a pilot study is being carried out which involves softening and moistening the food to make it more palatable.

After the PI left the meeting, the Committee continued its discussions.

The Committee agreed that the researcher should consider other potential models and the work of other researchers as previously discussed, and should either adopt any relevant techniques, or should state in the application the reasons that such techniques are inappropriate for this work.

Resolved that:

With revisions as discussed above, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

15/01-08 Any Other Business

Swimming/exercise model

It was reported that the swimming model which had previously caused some concerns when BERSC reviewed it as part of a project licence application has now been developed and refined, and it is now seen as best practice to the extent that details have been requested from a Home Office Inspector to inform a study elsewhere. The revisions to the original model have meant that it is now much less severe and its validity is improved.

15/01-09 Date of Next Meeting

The date of the next meeting is 12th March 2015.

GLOSSARY

AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CD30	Type of molecule expressed by T cells during an immune response
CD4 T cells	Type of white blood cell playing an important role in immune response
CLEC-2	C-type lectin-like receptor 2
CO_2	Carbon Dioxide
IP	Intraperitoneal
LASA	Laboratory Animal Science Association
LPS	Lipopolysaccharide
MRC	Medical Research Council
NVS	Named Veterinary Surgeon
OX40	Type of molecule expressed by T cells during an immune response
PI	Principal Investigator
RSPCA	Royal Society for the Prevention of Cruelty to Animals
SOPs	Standard Operating Procedures
TBA	To Be Announced