CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

3rd March 2016

MINUTES

Present:

16/03-01 Apologies

Apologies were received

16/03-02 Minutes

The minutes of the meeting held on 21st January 2016 were considered by the Committee and were approved subject to amendments.

16/03-03 Matters Arising

The lay summary of the application discussed in minute 16/01-07-1 has been revised and this application is now with the Home Office Inspector for comment.

As discussed under minute 16/01-09, in an effort to improve the quality of Non-Technical Summaries they are now being screened within BMSU before being released to the Committee.

16/03-04 Chairperson's Items

There were no Chairperson's items for discussion.

16/03-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The new Home Office Inspector is now working with BMSU and its researchers and there are currently 7 draft Project Licence applications in the electronic system.

- Some problems have been experienced with the new electronic system for Project Licences and these have delayed the roll out of the system to the rest of the UK.

- Applicants are advised to allow sufficient time for the review and approval of renewals or amendments to avoid delays to their projects. Given the current workload of the Home Office Inspector, applicants are advised to start working on their applications approximately nine months before they will be required.

- Regarding the system of local 'hubs' and 'spokes' set up by the Animals in Science Committee, it was noted that BMSU falls within the Midlands West hub which is chaired by the University of Aston (not the University of Leicester as was previously thought).

- Work is ongoing on the development of an in-house IVIS system. Results obtained from the new system are being compared with those from the existing IVIS facility for validation purposes.

- The NACWOs within BMSU are rolling out a programme of training for researchers in saphenous vein blood sampling, which represents a significant refinement. New researchers will no longer be trained in tail vein sampling. Some concerns were expressed that the new method still needs to be validated against tail vein sampling and it was explained that this validation will be an ongoing process and any issues will be dealt with case by case.

16/03-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date and there are no outstanding issues.

16/03-07-1 Application Ref TBA – Adoptive T Cell Therapy for cancer

The objective of this project is to validate novel immune-based therapies designed within the PI's laboratory to target the tumour cells or the blood supply that serves them.

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

Further information was requested about the injection of tumour cells into the pancreas as detailed in protocol one. It was explained that this is a new model of pancreatic cancer which is being used by collaborators overseas. It is not yet clear whether it will be useful in relation to the current licence application. If the model will be used, a member of the research team will visit the collaborating institution where the model is already established to learn from their experience. It is understood that within this model a tumour is allowed to develop for a set period of time, the animal is then killed and the tumour is measured. It is anticipated that there may be adverse effects linked to the liver (e.g. jaundice) and that the model may need to be classified as severe. It might be possible to lessen the severity if the duration of the model is reduced via the use of blood markers to monitor tumour progression and/or the use of IVIS.

Funding is already in place for the proposed work using the RipTag mouse model. It was noted that particular care will be needed to determine appropriate humane endpoints. RipTag mice will usually die naturally by the age of 14 weeks; it was emphasised that death is not acceptable as an intentional endpoint for welfare reasons. Rather, the endpoints will be based upon levels of toxicity (to be reached before the animal reaches the point of death). Animals will be humanely killed whilst still within the boundaries of 'moderate' rather than allowing them to reach 'severe'.

As graft-versus-host disease can be anticipated after approximately 30 days, the Committee queried whether there is a sufficient window of time prior to this to allow measurable tumour growth. The PI explained that this will depend upon the number of cells injected.

Another research group carrying out similar work elsewhere has experienced problems caused by the development of thrombocytopenia. The PI will look into the risk of this; however, as there will be no need to irradiate the majority of the animals, it is considered less likely to be an issue.

It was clarified that immunocompromised mice are preferred for this work because irradiation of immunocompetent mice (which is the alternative) would not ablate the immune response sufficiently to allow human T cells to be put into the mice.

The application should be amended to include more descriptive humane endpoints. The explanation of the statistics behind the study design should also be improved and power calculations should be included.

The proposed wound healing studies are considered necessary because the development of new blood vessels during wound healing may have similarities to the process which occurs during tumour growth. If there are similarities it could be problematic because treatments for tumours which target the vasculature might also impact upon wound healing.

When T cells are injected it is not certain that they will 'find' the tumour. The Committee therefore queried the efficacy of the model. It was noted that the advantage of immunotherapy is that in theory the therapeutic agent will travel to all tissues; however, the efficiency of this needs to be tested. Previous related studies have indicated that T cells will travel to the required sites.

The Committee felt that further justification was required for the inclusion of the Apo-E model. The PI explained that there may be similar processes linked to toxicity in both vascular disease and cancer, and that there are relevant similarities between tumours and the clots seen in vascular disease.

All of the protocols will include some aged mice. This may be a concern because recent studies have shown immunotherapy to be safe in younger mice but more toxic as an animal ages. There are also inherent ethical issues in the aging of mice. It was explained that all treatments will be developed in younger mice and then limited trials with older mice may follow. This should be explained more clearly in the application.

The PI was commended on producing an excellent lay summary.

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

It was agreed that considerable further work was needed on the humane endpoints before this work takes place.

The RipTag and pancreatic tumour models are new to this research group and the latter model is also new to BMSU.

Resolved that:

The revisions discussed above will be made and feedback will be sought from the Home Office Inspector and incorporated into the application. The revised application will be recirculated to the Committee for information. Once the Chair is happy with the changes,

a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

16/03-07-2 Application Ref TBA – New Treatments for Heterotopic Ossification (HO)

The objectives of this project are i). to establish a way to reliably cause the animals to develop HO, to assess the bone formed and to compare it with equivalent human samples and ii). to treat the animals with an experimental chemical to test whether or not it can prevent the problematic bone forming or if it can dissolve the problematic bone once it has formed.

The PI and a co-researcher gave a presentation explaining the application to the Committee.

It was explained that when this project is up and running it is likely that it will be transferred to another researcher who will take over as PI. Rather than developing an entirely new model, this licence application is to establish a model which is already in use elsewhere within BMSU.

It was queried why the injection of biomarkers is an option in protocol one. The PI clarified that it may be necessary to inject biomarkers in order to carry out post-mortem imaging.

The Committee asked why it will be necessary to maintain the animals for up to sixteen weeks after surgery and the PI explained that this length of time is stated in the application to ensure that enough time is allowed for HO to develop, although it is likely that ten weeks will be sufficient. Sixteen weeks also allows time to administer therapeutic agents after HO has developed. It was emphasised that in previous similar studies very minimal suffering has been observed; the only significant effect on the animal is likely to be that it will be unable to forcibly jump, but it should be able to walk normally and it is unlikely to experience significant pain. Animals will be kept in single layer cages to remove the need for them to jump any distance.

The number of anaesthetic events listed in the application is incorrect and will be amended. A maximum of one anaesthetic per animal will be required.

It was queried whether the type of HO which will be induced in rats is comparable to that which occurs naturally in humans. The PI explained that rats have very similar bones to those of humans. Mice have a quite different bone formation and are therefore not suitable for

this work. Young adult rats will be used which is analogous to the age at which HO is usually a problem in a human clinical setting.

Regarding controls, it was explained that the delivery vehicle alone will be used and that some animals may receive no treatment at all.

Dose testing will not be carried out as part of this study as the dose is physically limited to the volume of the therapeutic gel which it is reasonable to inject into the relevant site and to how much of the active substance can be suspended within the gel. The gel will be of a neutral acidity/alkalinity and so should not cause irritation. It was suggested that bilateral surgery could be included within the application to allow a vehicle, internal control which would help to reduce the number of animals necessary.

Various techniques for measurement are mentioned within the application and it was clarified that these will all be carried out post-mortem.

Other similar studies elsewhere have utilised in vivo imaging (e.g. CT scanning) allowing the animals to be humanely killed at an earlier point. However, this equipment is not available within BMSU. It was suggested that if the work shows progress it may be possible to collaborate with a nearby institution which does have CT scanning facilities.

Opiate analgesia will be used rather than NSAIDs.

In relation to protocol one, it was queried why the animals are killed once HO has developed rather than going on to test therapeutics on such animals. It was clarified that the purpose of protocol one is to prove that HO has developed (which will be done post-mortem). This initial stage is needed to establish that the required disease state is present before it is possible to test therapeutics. This should be made clearer in the licence application.

Resolved that:

The revisions discussed above will be made and feedback will be sought from the Home Office Inspector and incorporated into the application. Once the Chair is happy with the changes, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

16/03-07-3 Amendment application Ref TBA – Podoplanin-CLEC-2 in thrombo-inflammatory models

Although amendments are usually reviewed via the fast track procedure, it was explained that this amendment was being considered by the full Committee because it will increase the severity of the work to 'severe'.

The work described in the original licence requires the formation of stable thrombi. 55 mice have been used to date. The original licence was of moderate severity and the requirement to remain within the endpoints associated with moderate severity has so far meant that experiments have resulted in mild liver and kidney damage rather than the stable thrombi required for the research.

This application for amendment will raise the severity of the application to severe and it is hoped that it will allow the development of stable thrombi by allowing the animals to be maintained for a longer period of time. As it is not certain whether this will prove successful the number of animals stated in the amendment has been limited to 40. If the work is successful a further amendment will be submitted to increase the number of animals. Initially only two animals will be used at a time.

A statement on the scientific necessity of the amendment and the importance of the research question was requested and will be forwarded on by the PI.

Resolved that:

Once the Chair is happy with the additional information requested, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

16/03-08 Any Other Business

The Committee was informed that it has become difficult to book rooms within the University for both the Home Office training modules and for AWERB meetings as neither is considered to be a teaching activity. As they are both essential University functions, this matter will be escalated within the University by the Committee Chair.

16/03-10 Date of Next Meeting

The date of the next meeting is 14th April 2016.

GLOSSARY

Apo-E	Apolipoprotein E
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CT	Computerised Tomography
HO	Heterotopic Ossification
IVIS	In Vivo Imaging System
NACWO	Named Animal Care and Welfare Officer
NSAID	Non-Steroidal Anti-Inflammatory
CLEC-2	C-type lectin-like receptor 2
PI	Principal Investigator
RipTag	A strain of mouse which spontaneously develops tumours
T cells	A type of lymphocyte that plays a central role in cell-mediated immunity.
TBA	To Be Announced
UK	United Kingdom