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THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

29th September 2016

MINUTES

Present:

16/09-01 Apologies

16/09-02 Minutes

The minutes of the meeting held on 18th August 2016 were considered by the Committee and were approved subject to amendments.

16/09-03 Matters Arising

CPD sessions for Project Licence Holders

The second CPD session for Project Licence Holders was held recently. Although the Establishment Licence Holder had encouraged all Project Licence Holders to attend one of the two sessions held, unfortunately not all did. Those who did not attend may be required to redo their Home Office module 5 training when they next renew their Project Licences.

16/09-04 Chairperson's Items

There were no Chairperson's items to report.

16/09-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The new quarantine room for initial exploratory experiments on animals from external sources is now operational and the availability of the room will be noted in next week's BMSU newsletter.

- Activities within BMSU are running smoothly and the number of animals in the facility has gone back up to the usual level after a brief reduction in usage.

- Several new members of staff have recently been appointed within BMSU.

- Two training courses have been held for new Personal Licence Holders. New Personal Licence applications are now usually being turned around by the Home Office within 24 hours.

- The next BMSU Strategic Group meeting will be held in October 2016.

- A BMSU Users' Forum will be held in the autumn term.

- The Establishment Licence Holder will be attending an annual risk assessment meeting with the Home Office Inspector next week.

- The Establishment Licence Holder has been invited by the Home Office to be part of a small focus group to consider how infringements are handled by the Home Office. This has been prompted by a number of concerns from other institutions about the handling of infringements by the Home Office. It was noted that the Home Office's handling of infringements within BMSU has to date elicited no complaints.

- A national 'Trainers' Day' was recently held within BMSU for those individuals running Home Office training courses. This was combined with a 'Trade Day' for suppliers.

- All Project Licence Holders will be invited to suggest the purchase of small items (e.g. trolleys, microscopes) which they feel would be of benefit within BMSU. Successful proposals will be included within the equipment budget for next year.

Report from the Named Veterinary Surgeon:

- The NVS updated the Committee on progress on the Project Licence discussed in previous minute 16/04-07-1. When the Committee reviewed this application earlier in the year, some concerns were expressed about the difficult nature of the procedures to be carried out and the potential for significant

animal losses. Since the review of the application, the researcher has been fully trained to carry out the necessary technique on cadavers and is now confident and ready to carry out the procedure on live animals.

- The Committee's attention was brought to a potential issue affecting BMSU's rat colony. During the recent autopsy of a rat, lung pathology was identified. All rats are purchased from suppliers rather than being bred in-house and as the infection does not seem to have come in from a supplier, the colony within BMSU will be closely scrutinised over forthcoming weeks.

Report from the Named Animal Care and Welfare Officers:

No further items to report.

16/09-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date.

CONFIDENTIAL MATERIAL

16/09-07-1 Application Ref TBA – Targetting IL-17 driven pathology

The overall objective of this project is to determine whether IL-17 driven inflammation can be effectively targeted and reduced through the use of small molecule inhibitors targeting key molecules in the IL-17 pathway.

The PI gave a presentation explaining the application to the Committee. Feedback from the Home Office Inspector on the application is due soon.

The PI was asked to provide further information on the project's timescales. In relation to oral gavage with C. rodentium, it was explained that the bacterial load will increase between days 5 and 14 and this analysis will take place on days 7, 14 and 21. In order to carry out these analyses it is necessary to cull the animals to physically inspect their intestines and to culture cells from the intestinal tract.

Some of the predetermined clinical endpoints as currently written may exceed the 'moderate' severity classification; it was felt that it was a matter of wording and the PI will consider this with the Inspector to ensure that the endpoints remain moderate.

The C. rodentium model is the only model within the application in which the animals are likely to be symptomatic. The PI was asked whether clinical scoring will be used for these animals and responded that the animals will be culled as soon as clinical signs are present.

The non-technical summary should be rewritten to ensure that it will be understood by a lay reader (e.g. explaining the terms IL-17, cytokines, etc).

It was noted that mice entirely deficient in RORgt (RORgt-/-) are not very robust and the Committee queried whether it will definitely be necessary to use these as a control, and if so, how often. The PI explained that a positive control is definitely needed and that these are the best animals to use; otherwise, there is a risk that the results of the experiment cannot be properly interpreted. It is not sufficient to rely on the fact that the infectious agents have worked before, because as the agents are live they will vary over time. It was acknowledged that the use of such mice needs to be very carefully overseen and the mice will be culled as soon as they show clinical signs. It may be possible to use one animal rather than two for each control.

In relation to sample size calculation, the Committee felt that it was difficult to determine whether an n of 10 is appropriate on the basis of the information provided. The PI agreed to include additional information about effect size to make this clearer.

The Committee queried whether the background of the mice was important to the study, as mice from different backgrounds will carry different commensal bacteria. It was explained that because of the differences in commensal bacteria between animal facilities, only mice of the same strain bred within the same unit (BMSU) will be used to ensure that the data is valid.

Adherence to the ARRIVE guidelines should be confirmed within the application.

It was queried whether animals will be randomly allocated to the treatment and control groups. The PI explained that the experiments are not blinded. The animals are matched for age and sex and suitable animals are used as they become available. Whilst the PI is willing to consider blinding, it was noted that the nature of the experiments (e.g. flow cytometry) leaves no room for bias because the data is completely objective.

It was felt that the use of the two candida models requires further justification within the application. The mucosal model better mimics the relevant condition in humans and the systemic model may not be required. As the candida models are new to the PI, efforts will be made to learn from researchers already using these models elsewhere.

The researcher will revisit the explanation of the adverse effects and humane endpoints relating to the use of small molecule inhibitors to clarify under what circumstances an animal will be monitored and when it must be immediately killed.

The Committee asked for more information about the nature of the collaboration with pharmaceutical companies. The PI explained that discussions are underway with several companies that wish to better understand the effects of their small molecule inhibitors. The PI has access to genetic tools and models which the companies don't have, which is why they wish to collaborate. The PI will not undertake any collaboration which will limit freedom to publish.

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

Justification for the proposed use of irradiation should be included within the application.

It should be stated that if the knockouts don't show the effects anticipated by the researcher, the work will not progress to the testing of small molecule inhibitors.

A wider range of references should be included within the application.

Resolved that:

The revisions discussed above will be made and feedback will be obtained 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.

16/09-07-2 Application Ref TBA – Characterisation of anti-inflammatory virulence determinants; role in bacterial persistence, gastric cancer and secondary infections

The objective of this project is to understand how a family of bacterial proteins common to both H. pylori and S. typhimurium suppress certain cells of the immune system, thereby facilitating chronic infection. The project will also study how H. pylori infection in the stomach affects the diversity of bacteria in the intestine, to understand the mechanism underlying the link between H. pylori infection and protection against intestinal diseases such as IBD.

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

This will be the PI's first Project Licence as previous work was carried out under another researcher's Project Licence.

The PI was asked to explain the rationale for using IVIS for the helicobacter model but not for the salmonella model. It was explained that the helicobacter model takes place over a much longer timescale than the salmonella model. To ensure infection control, the IVIS machine in BMSU can only be used with infected animals by administering an anaesthetic and placing the animal in a sealed box. For each animal, it is only possible to do this once per day, with a minimum of 48 hours between each anaesthetic and a maximum of 6 anaesthetic events in total. Whilst the PI would prefer to use IVIS in the salmonella model in order to reduce the number of animals required, it is not possible because the timescale of the model is too short.

The non-technical summary should be amended to explain the use of IVIS for the helicobacter model.

The location of injections will be the heel rather than the plantar surface of the foot, to avoid direct inflammation to the surface of the foot whilst still allowing the injected substance to be drawn into the necessary lymph zone.

The reference to 'very moderate' severity should be removed.

CONFIDENTIAL MATERIAL

Within the 3Rs section of the application, it is stated that 'few animals may die prematurely'. It should be emphasised that this refers to deaths not linked to the protocols.

The in vitro work explained during the presentation should be explained under 'replacement' in the 3Rs section. It is not possible to use in vitro work to replace the proposed in vivo work – for example, in the helicobacter model the PI is looking at how T cells influence localised areas such as the lungs, and this has to be done in a live animal.

Saphenous rather than tail vein bleeding will be used, which is a refinement.

In relation to protocol one, the reference to 'prolonged subdued behaviour or unresponsiveness' should be reconsidered as this would take the licence to 'severe' rather than 'moderate'. Also, the reference to 'more than moderate severity' on page 43 of the application should be removed.

The numbers of animals stated within the protocols are inconsistent and should be corrected.

The non-technical summary should be revised to ensure that it will be understood by a lay reader.

In relation to protocol two, it was queried whether any particular adverse reaction is expected. The PI explained that no adverse reaction is anticipated within the six month timeframe of the experiment. In wild type mice, no incidence of severe gastric disease is likely before 12-24 months.

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

It was noted that the study is not randomised or blinded, and that increasingly funders want to see randomised, blinded data collection. It was felt that if a study will not be randomised or blinded, researchers should at least explain the reasons for this in their applications.

Regarding analgesia, the difficulties in using analgesia for this study should be explained rather than stating that it cannot be used.

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.

16/09-08 NC3Rs items

- The NC3Rs outreach worker for the Midlands has now started work and will soon visit the three Universities involved to meet with PIs and liaise with the AWERBs. Meetings will be set up with key people including the Named Persons and Academic Leads. The areas which the outreach worker will focus on initially have been agreed with the NC3Rs; the earliest project is likely to be workshops on the NC3Rs' Experimental Design Assistant. It is hoped that workshops will also be arranged on the refinement of chronic implant models.

- The next NC3Rs e-learning module will be on euthanasia, and will include videos on the relevant methods using live animals. It was noted that links to such e-learning modules are sent out to all BMSU users and are used alongside the required Home Office training for researchers.

- An NC3Rs video tutorial is available on mouse handling procedures, particularly the use of 'tunnelling' and 'cupping' rather than lifting mice by the tail. The use of both tunnelling and cupping is encouraged within BMSU. It was noted that lifting by the tail causes more stress to the animal than tunnelling or cupping, but is necessary in some circumstances.

- A new NC3Rs scheme to promote skill and knowledge transfer will shortly be introduced. This will provide funding of up to £75,000 for up to 12 months to allow researchers to establish an existing 3Rs technique within their laboratories, thus spreading best practice. The deadline for initial ideas will be 25th November 2016. It was suggested that it would be helpful to provide a list of the techniques supported by the NC3Rs for information.

16/09-08 Any Other Business

- The article "A Good Death? Report of the Second Newcastle Meeting on Laboratory Animal Euthanasia" is now available to Committee members via the Committee's online document repository. The Committee discussed some of the

recommendations of the report and the efforts within BMSU to ensure best practice in this regard.

- The Home Office has now appointed 3 new Inspectors.

- An FOI request has been received from Cruelty Free International, requesting animal numbers. The applicant has been directed to this information on the University's website.

- Interim reviews will be discussed at the next meeting of the Committee.

16/09-10 Date of Next Meeting

The date of the next meeting is 10th November 2016.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
ARRIVE	Animal Research: Reporting of In Vivo Experiments
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
C. rodentium	Citrobacter rodentium
CPD	Continuing Professional Development
FOI	Freedom of Information
H. pylori	Helicobacter pylori
S. typhimurium	Salmonella typhimurium
IBD	Inflammatory Bowel Disease
IL-17	Interleukin 17A
IVIS	In Vivo Imaging System
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research
NVS	Named Veterinary Surgeon
PI	Principal Investigator
RORgt	A transcription factor
T cells	A type of lymphocyte originating in the thymus
TBA	To Be Announced