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THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

23rd May 2016

MINUTES

Present:

16/05-01 Apologies

16/05-02 Minutes

The minutes of the meeting held on 14th April 2016 were considered by the Committee and were approved subject to amendments.

16/05-03 Matters Arising

In relation to minute 16/04-07-3 it was reported that the PI had since provided a comprehensive response to a query about whether he could adopt techniques developed in a recent NC3Rs-funded project which used optic neuritis as a marker of Multiple Sclerosis.

16/05-04 Chairperson's Items

- The Chair recently met with the Director of BMSU and the Establishment Licence Holder to update the latter on the work of the Committee. The Establishment Licence Holder intends to observe a meeting of BERSC later this year.

- It is hoped that the West Midlands regional hub for AWERBs will soon become active and the Director of BMSU and the Chair have had discussions with the Chair of the ASC about this. It was explained that one of the ASC's functions is to support AWERBs and the 'hub and spoke' system is intended to facilitate this. The Chair of each hub (in this case, from the

University of Aston) will meet directly with the Chair of the ASC and then hub Chairs will meet with each of the Chairs of the spoke organisations.

- In relation to the above, it was noted that there are currently two separate strands of work intended to support AWERBS; one led by the ASC and one led by AWERB UK (a forum for UK AWERB members organised by the RSPCA, LASA, LAVA and IAT). It was noted that the activities of the ASC and of AWERB UK appear to be taking place in parallel, and it was suggested that it may be helpful for them to be merged at some point.

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

Report from the Director of BMSU:

- The Director of BMSU recently went to a meeting of AWERB UK, which was useful and well-attended.

- An RSPCA Lay Members' Forum meeting will take place towards the end of 2016 and BMSU can provide support for two members of BERSC to attend. Interested members are invited to contact the Director of BMSU.

- An advertisement has gone out to recruit an NC3Rs outreach worker for the Midlands. This two year post is being funded jointly by the NC3Rs and the Universities of Birmingham, Nottingham and Leicester. 20 applications have been received and interviews will be held in early June 2016. It is intended that the holder of the post will attend BERSC meetings and will work closely with the Chair of BERSC, the Director of BMSU and the Academic Lead within the Medical School.

- The Home Office Inspector assigned to BMSU is working very hard but the current workload is such that a backlog of Project Licence applications has developed (there are currently 12 Project Licence applications from University of Birmingham awaiting consideration). Senior Home Office representatives have been made aware of the workload issue and the Director of BMSU will reiterate the problem at the Establishment Licence Holders' Committee. Whilst 3 additional Inspectors are due to start work in September 2016, it is currently unclear whether they will be assigned in such a way as to alleviate the workload at Birmingham.

- The Home Office is currently considering its approach to compliance, with the intention of increasing transparency and being more open about how non-compliance events are handled.

- Regarding the retrospective reviews due to be carried out by BERSC this year, it was suggested that it would be most efficient for them to be looked at by a sub-group reporting to the main Committee. Any concerns or issues would be escalated for consideration by the full Committee. Members agreed that this approach would be appropriate.

Report from the Named Veterinary Surgeon:

- An outbreak of pinworm has been detected in two cages of mice within BMSU. It was noted that so far this is on a much smaller scale than a past outbreak and it is hoped that it has been contained. Affected animals are being treated with a spot wormer and nearby animals will also be treated in an effort to prevent further spread. Internal and external health screening procedures have been increased. If the outbreak does spread further a more widespread treatment administered via food may be required.

Report from the Named Animal Care and Welfare Officers:

No further items to report.

16/05-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date. However, a number of amendments are currently sitting with the Home Office (see discussion in previous minute about the Home Office backlog).

16/05-07-1 Application Ref TBA – Modulation of murine lung injury by hormones, cells and growth factors

The objectives of this project are to establish whether alterations in certain hormone levels can influence animal models of lung infection (pneumonia), abdominal infection (sepsis) and severe lung damage (known as ARDS) that can occur following these infections.

The PI gave a presentation explaining the application to the Committee. It was noted that the previous Project Licence covering this work has now expired.

Given the failure of several new therapies for these conditions in the clinical setting, the predictive value of mouse models for these conditions was questioned. The PI explained that whereas in the past, pharmaceutical companies tended to move straight from proof of concept studies in animals to testing in the clinic, success is now more likely because initial 'first in human' trials are carried out to prove that the proposed new treatment works in humans before going on to undertake phase 2 and 3 clinical trials.

The Committee asked the PI what would be considered to be the 'state of the art' animal model in this field. It was explained that the American Thoracic Society has recently issued guidelines on the use of animal models of lung injury and sepsis; it is understood that no one model is suitable for all purposes and at least two relevant models should be used where possible.

The Committee asked for further information about the limitations of the *in vitro* work which has already taken place and about why animal studies are necessary in light of this. The PI explained that the availability of patients from whom samples can be taken for *in vitro* work is limited and the yield of cells from such samples is low; there are also difficulties relating to the purity and viability of samples. It was agreed that the application should be amended to clarify that one way in which the number of animals is minimised is via the *in vitro* work taking place in parallel.

It was explained that where possible the techniques used have been refined to minimise the impact upon the animals involved. For example, in the CLP model just one puncture to the caecum is required to produce measurable effects for experimental purposes, whereas a greater number of punctures have been used by other researchers. The timeframe of experiments is kept as short as possible and appropriate scoring is used to minimise welfare issues. The Committee felt that further work was needed to the 'refinements' section of the application to reflect this.

The PI was advised to read a recent paper in which the 3Rs are applied to sepsis and shock models. It was explained that this paper discusses acute models of sepsis under terminal anaesthesia, which may be useful to consider within this Project Licence. The PI clarified that the CLP model used in this project is relatively mild and therefore, the length of time required for disease signs to develop precludes keeping the animals anaesthetised throughout the entire procedure. The CLP model is considered to be the animal model most clinically relevant to human sepsis and is already established within BMSU.

Further information was requested about the mortality rates of the models used, and the PI reported that the mortality rate of the LPS

model is now almost 0%, whereas over the past 5 or 6 years, 2 animals have died during pilot studies of the CLP model. The mortality rate of the pneumonia model depends upon the strain of bacteria involved.

Stringent procedures are in place for the close monitoring of the animals involved in all of the models used, including overnight monitoring if required. The NACWOs within BMSU are happy with the scoring system used and the level of monitoring. Regarding the CLP model, the animals are checked every few hours after the puncture has taken place. For all models, fluids and opiate-based pain relief will be administered as required in line with current practice by the group (this should be clarified in the application, which currently states that fluids and analgesia may be given). The experiments are timed such that the later stages of the experiment occur during daylight hours, facilitating closer monitoring at the time when issues are more likely to occur.

It was noted that the monitoring of chest movements and sounds may be useful in the LPS model but is less useful in the other models.

Regarding refinements, it was suggested that oximetry may be useful in some models but not in all. The PI will explore this.

It was clarified that all lavages will take place post mortem.

Regarding the proposed use of cellular therapy, a phase 2 trial on the use of MSCs in human patients has shown this treatment to be safe, and those patients given the highest doses of cells had the best oxygenation at the end of the study.

The PI was asked whether human patients who are deficient in vitamin D are more likely to develop ARDS, and he explained that they were; the difficulty is that when a patient becomes critically ill their metabolism of vitamin D is altered and the direction of this relationship remains unclear. This is being investigated in another study.

It was felt that a better explanation should be provided within the application for the use of the pneumonia model. The PI clarified that in some, but not all cases pneumonia will lead to sepsis; the focus of this model is on pneumonia within the lung, rather than on sepsis itself.

It was queried whether the PI could make use of tissue from a related, ongoing study within BMSU. The PI agreed to explore the possibility that wild-type tissue from the related study could be used as a control.

Whilst a particularly virulent strain of pneumonia-causing bacteria is mentioned within the application, it was noted that the application is

currently of moderate severity; it was clarified that the use of more virulent strains of bacteria as part of this project is very unlikely.

The route(s) of administration, doses and thresholds for vitamin D should be clarified within the application.

In relation to the LPS model, it was explained that the animals will be culled at 9 days; in the CLP model, the animals will be culled within 24 hours. The PI explained that in the LPS model it is necessary to keep the animals alive over a number of days to study whether the consequences begin to resolve with and without intervention.

The PI clarified that bacteria in the pneumonia model are administered via nasal inoculation, with no anaesthesia required. It is not possible to administer LPS via nasal inoculation due to its very short half-life.

Efforts will be made to maintain each animal's weight during the experiments via dietary supplements and the use of a soft feed.

The explanation of the possible adverse events within the application should be revisited, as in the current wording there is potential confusion between strain of mouse and strain of bacteria.

The Committee queried whether it would be possible to use a non-recovery version of the CLP model (e.g. administering non-recovery anaesthesia at 16 hours) to allow the injury to progress further. The PI noted that the immunomodulatory effects of anaesthesia may preclude this (and determining such effects would be a project in its own right) but they will consider it for future work.

Within protocols 1-4, the 'and/or' between doxycycline treatment and cell transfer should be checked and amended as necessary.

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

The Committee commented that the non-technical summary should be redrafted using lay terminology and further attention should be given to the explanation of the 3Rs within the study.

Resolved that:

The application is still awaiting feedback from the Home Office Inspector. Once both this and the Committee's comments have been incorporated into the application, the application will be recirculated electronically to the Committee for consideration. An email of support will be sought from the lead researcher within BMSU who is already using the pneumonia models and who will be advising the research group.

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16/05-08 Publication lists from end of licences

It was explained that this is a standing item and that when a Project Licence expires a list of the publications arising from it will be included on the shared Collaborate workspace.

It was agreed that DOI links should be included to allow committee members to access the publications directly.

16/05-09 Any Other Business

- It was noted that a RSPCA presentation entitled 'More than Mice' had recently taken place within the School of Biosciences. It was agreed that it would be helpful if information about such events could be disseminated more widely and this will be followed up by the Director of BMSU.

- The Committee was informed that BMSU's NACWOs will be presenting a poster at the LASA Annual Conference, on the improvements made in-house to the PhenoMaster cage system.

16/05-10 Date of Next Meeting

The date of the next meeting is 7th July 2016.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
ARDS	Acute respiratory distress syndrome
ASC	Animals in Science Committee
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CLP	Caecal Ligation and Puncture
DOI	Digital Object Identifier
IAT	Institute of Animal Technology
LASA	Laboratory Animal Science Association
LAVA	Laboratory Animals Veterinary Association
LPS	Lipopolysaccharide
MSC	Mesenchymal Stem Cells
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research
NACWO	Named Animal Care and Welfare Officer
NVS	Named Veterinary Surgeon
PI	Principal Investigator
RSPCA	Royal Society for the Protection of Cruelty to Animals
TBA	To Be Announced