CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

2nd March 2017

MINUTES

Present:

17/03-01 Apologies

17/03-02 Minutes

The minutes of the meeting held on 19th January 2017 were considered by the Committee and were approved.

17/03-03 Matters Arising

There were no matters arising from the previous minutes.

17/03-04 Chairperson's Items

There were no Chairperson's items to report.

17/03-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The University now has two Home Office Inspectors and both will be visiting soon to meet with researchers and to look around the facilities.

- It was noted that all Project Licence holders with surgery included within their Licence are now required to have undertaken Home Office module PIL C, in addition to modules PIL A and B.

- There are approximately 8 Project Licence applications currently awaiting approval from the Home Office and there are also a number of amendments which are taking longer than usual. These delays are being addressed with the Home Office via the appropriate channels.

- A working group has been set up to consider redesigning the Project Licence and Birmingham is providing input.

- Users of BMSU were asked for their patience during the inconvenience caused by the refurbishment of the BMSU changing rooms.

- The University's Pro-Vice-Chancellor (Research and Knowledge Transfer) recently visited BMSU and was given a tour of the facilities.

- The Committee is in need of additional lay members. It is understood that some members of the University's School of Philosophy, Theology and Religion may be interested and suggestions from the Committee were also welcomed.

- All of the required returns have been submitted to the Home Office on time. Training will be provided to researchers on how to complete the necessary paperwork for next year's returns.

- The new intravital suite will soon be inspected and formally added to the Establishment Licence.

- Two of BMSU's animal technicians will be attending the forthcoming Institute of Animal Technology Congress.

- Regarding staffing, one animal technician has recently left and additional senior appointments are planned for the future.

Report from the Named Veterinary Surgeon:

- The density of frogs per tank has been reduced, which has inadvertently led to an instance of non-compliance due to a mistake about which frogs were ready for use. This has been self-reported to the Home Office.

Report from the Named Animal Care and Welfare Officers:

No items to report.

17/03-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date.

17/03-07-1 Application Ref TBA – Understanding Thymus Function and Immune Reconstitution

The aim of this project is to investigate the identity of the cells and molecules that control T cell development within the thymus and to understand how these impact upon T cell-dependent immune protection.

The PI gave a presentation explaining the application to the Committee. This application is to replace an existing licence which will expire later in the year.

It was suggested that the researcher consider transplanting tissue to the mammary fat pad rather than to the sites currently proposed, as a refinement.

It was suggested that more emphasis could be placed upon the reduction of the number of animals needed for breeding. The PI explained that while the *in vitro* culture system could potentially be used to reduce the number of strains needed, this research will still require the use of a large number of strains. The Committee queried how the number of animals per protocol had been calculated, and the PI clarified that a typical experiment will involve 6-8 animals and that all experiments will be replicated 3 times. It was felt that justification for this replication should be provided. The PI explained that previous experience and existing data was been used to calculate the required sample sizes. Additional information should be provided in the application to allow replication of the power calculation.

The Committee commended the PI's attention to matters of replacement in the presentation (e.g. the use of very early embryos), and suggested that this be fully explained in the non-technical summary. It was queried whether it would be possible to use *in vitro* systems for looking at T cells and the PI explained that there are such systems, but their use is limited, basic and is unlikely to be accepted by respected journals. Whilst *in vitro* work will be used where possible, it must be supplemented by in vivo approaches.

Much of the work will be beneath the threshold required to be considered a licenced procedure, but in the licence application it is necessary to state that such work will be of mild severity. Also, it is stated that work will be of moderate severity 'in some cases' which doesn't reflect the fact that approximately half of the work will be of

moderate severity. These matters should be better explained within the application.

The PI was encouraged to include more discussion of refinements in the non-technical summary. Developments in imaging techniques will be employed where possible, which would be considered a refinement.

It was explained that all researchers are required to include standard Home Office wording about the use of tail tipping in applications. However, this technique is not used within BMSU in any case and discussions are ongoing about removing the obligation to include the wording.

The same humane endpoints are stated for all protocols, but it was emphasised that local score sheets will also be used (these are not included as part of the application). These score sheets will be provided to the Committee via Collaborate, to give a better understanding of the humane endpoints.

Regarding the endpoints involving the loss of 20% body weight, the Committee queried the period over which this loss could potentially take place. It was explained that it would be over 6-8 weeks, but that it is very rare to reach 20% weight loss as other endpoints would be reached first. It was suggested that the wording of the endpoints should be revised to ensure they are useful to the staff working with the animals; some endpoints are quite vague and rely upon staff experience rather than specific details provided in the application. It was reiterated that best practice score sheets are used within BMSU, with very detailed information on endpoints.

It was queried how the progress of the project will be assessed. The PI explained that this is linked to the different sources of funding; some funding is at programme level, for ongoing work, whilst other funding relates to smaller targeted projects. Publications will act as a measurable outcome.

The PI explained that after ectopic engraftment under the renal capsule, mice are kept alive for 6-8 weeks and should experience no adverse symptoms once they have recovered from surgery.

In protocol 2, it was explained that imaging may take place up to twice per week, with a maximum of 6 sessions in total.

In relation to protocol 8, more detail is needed on the type of tumour cells to be used and the exact location of the injections.

The maximum age of the mice to be used will be 16 months. Tissue engraftment will be carried out at the earliest stage possible. Specific

maximum age limits should be included where appropriate in the application.

It was felt that as currently written, it is difficult to judge whether the use of GA mice is justified and whether any other options have been considered. This decision process for this should be further explained in the application and should be mentioned in the non-technical summary. It was noted that approximately half of the work is being carried out on genetically normal animals which are bought in, rather than being bred on this licence.

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

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.

17/03-07-2 Application Ref TBA – Avian productivity and climatic extremes in an urbanizing world

The overall aim of this research is to explore how the urban environment influences the extent and nature of fine-scale genetic structuring, alternative mating strategies and breeding success of a population of Blue Tits (Cyanistes caeruleus) living and breeding in the city of Birmingham.

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

The breeding season for the birds starts in late April/early May, so it is not yet clear whether the Project Licence will be granted in time to begin the work in 2017. If the work cannot begin in 2017, work will continue on other existing projects and this project will commence the year after.

The aims and justification for the project should be amended in the licence application to provide the same clarity as was included in the presentation.

Given that the Blue Tit is highly adapted to an urban environment and is not endangered, the Committee queried whether it is the most appropriate species to focus upon in this study. The PI explained that there is a fine balance between finding a species upon which

urbanization has impacted, and one which is resilient enough to withstand being the subject of a research project. Also, it was noted that there is no other suitable species in Birmingham with a large enough population.

The Committee asked whether weekly checks will be sensitive enough to determine the 10-14 day point after hatching at which trapping should take place. It was clarified that there will be many people carrying out frequent checks at each site to ensure trapping is carried out at the correct point and the application will be amended to reflect this.

Regarding the adult birds involved in the project, it was explained that the researchers only need to trap the social female and social male in a grouping. In the application, it is stated that samples from 2000 nestlings and 500 adult birds will be required; the researcher was advised to clarify the basis of these figures within the application.

The PI will amend the application to cite previous research which has established that catching the birds is unlikely to disturb their breeding success.

All relevant professional guidelines should be mentioned in the application, particularly in the non-technical summary. The ARRIVE guidelines should be cited in relation to reporting.

It was explained that the nest box traps will only be used when a Personal Licence holder is present, so that as soon as the trap is deployed, the birds will be sampled and then immediately released.

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

The Committee agreed that the application should be amended as already discussed to ensure that it is as clear and detailed as was the PI's presentation, before it is submitted to the Home Office for approval.

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.

17/03-07-3 Application Ref TBA – Understanding mechanisms of atrial fibrillation, sudden death and heart failure

The aims of this project are to enable identification of novel molecular pathways driving cardiovascular disease (including atrial fibrillation, heart failure and sudden cardiac death), the development and discovery of novel therapies to treat patients with cardiovascular disease and to assess the effectiveness of novel therapies in mouse models of cardiovascular disease.

The PI gave a presentation explaining the application to the Committee. This is the first of a number of new applications to replace the PI's existing Licence.

It was queried whether the shaving of an area of the animal's thorax will cause any thermo-regulatory problems. The PI explained that this is not a concern based on previous experience and that a thermal plate will be used during anaesthesia.

Regarding the diet used to mimic human obesity, it was explained that a high fat chow will be fed which will cause the animals to gain weight. These animals will not be used for breeding. From previous experience the diet will not affect behaviour but may make the animals prone to greasy skin and dermatitis; protocols will be in place to minimise the problems associated with this, including providing the chow on the floor to minimise skin contact, using a more appropriate form of bedding, etc.

It was felt that the PI needs to determine exactly what is achievable within the 5 year duration of a Project Licence and to ensure that the application reflects this.

Further information is required within the application about the models to be used, their advantages/disadvantages and the justification for their selection. The researcher explained that the choice of models will develop over time. Linked to this, the Committee felt that as currently written the application is at quite a high/strategic level and is amorphous in terms of detail – further work is needed to determine specifically what procedures will be included in the current application and then amendments can be submitted later as required. Without the identification of the specific models to be used, it is difficult to assess the relevant adverse effects, humane endpoints, etc. It was suggested that it would be helpful to include a decision tree showing the process for model selection/development.

Most of the mice will not suffer any side effects, nor will they develop spontaneous atrial fibrillation or sudden cardiac death. In the majority, the data will just reveal subtle differences but the animal will appear perfectly normal – it should be explained that most of the mice will remain within the mild severity banding. Some of the animals used for breeding will fall within moderate severity.

The PI explained the justification for the use of aged mice – primarily that in humans, the conditions being studied develop in old age and it is hoped that the research will identify the mechanisms behind this. This should be better explained within the licence application.

Regarding the measurement of blood pressure, the first readings for each mouse are likely to be abnormal due to the need to acclimatise it to the restraint tube. After it has been introduced to the tube several times, the blood pressure readings should normalise. The use of restraint tubes has been validated against more invasive blood pressure gauges. Tail handling is avoided when putting the animal into the restraint tube, due to the stress it may cause.

It was suggested that the PI explore the use of the Experimental Design Assistant. The Committee queried how effect sizes had been determined, and it was explained that this was mainly based upon historical data held in-house and previous experience. The same basis was used to determine the number of animals required for breeding. This should be explained within the application.

The total number of mice stated in the non-technical summary is incorrect and should be amended and the application should be checked to ensure consistency in relation to numbers throughout.

The reference to saliva sampling will be removed from the application, as the technique causes stress and will not be used.

The wording of the humane endpoints should be revised for clarity and where necessary timescales should be included.

It was felt that some of the information within the non-technical summary was too technical and should be reworded in lay terms. Also in the non-technical summary, under the heading 'Refinement' the reference to historical work with larger animals should be removed.

The diagrams used within the presentation should be included as appendices to the application. The appendices will also be included on Collaborate for the Committee's consideration.

References to the treatment of congestive heart failure with diuretics, etc should be removed from the application because they are not relevant to the application and are therefore potentially confusing.

It was explained that the single housing of mice will be minimised wherever possible and if it is necessary (for example, if an aged mouse has outlived its cagemates) additional enrichment will be provided to minimise the impact on welfare.

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

Care should be taken within the application to ensure that when discussing reduction, the wording used does not incorrectly imply that an animal will be reused.

It was felt that the background rationale for the work is currently unclear within the application and requires further work.

Resolved that:

The revisions discussed above will be made and feedback will be sought from the Home Office Inspector and incorporated into the application. If significant changes have been made, the application will be returned to the Committee; if the revisions are more minor, once the Chair is happy with the application a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office and the revised version will be circulated to the Committee for information.

17/03-08 Any Other Business

- The refurbishment of ground floor of BMSU is likely to take a little longer than originally anticipated.

- The 2016 animal usage statistics are now available on the University's external website. The numbers have increased since last year and this increase is largely due to the numbers of mice required for breeding.

17/03-09 Date of Next Meeting

The date of the next meeting is 13th April 2017.

GLOSSARY

ARRIVE	Animal Research: Reporting of In Vivo Experiments
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
GA	Genetically Altered
PI	Principal Investigator
PIL A, B and C	Home Office accredited training courses for Personal Licence holders.
TBA	To Be Announced
T Cell	Thymus lymphocyte, a subtype of white blood cell.