

**CONFIDENTIAL MATERIAL**

THE UNIVERSITY OF BIRMINGHAM  
BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

12<sup>th</sup> March 2015

**MINUTES**

Present:

15/03-01                    Apologies

15/03-02                    Minutes

The minutes of the meeting held on 15<sup>th</sup> January 2015 were considered by the Committee and were approved subject to minor amendments.

15/03-03                    Matters Arising

*Minute 15/01-07-2 – The pathophysiological roles of podoplanin and its receptor CLEC-2*

It was reported that since the last meeting, the research team working on this project have carried out a pilot study to see if softening the tamoxifen diet and making it more palatable, by adding water and sucrose, has any impact upon the animals' weight loss. No significant effects upon weight loss were seen as a result of this dietary manipulation, and it was highlighted that other measures, such as making food more physically accessible within the cage, seem to be more successful. A poster on these findings will be presented at the next LASA conference.

It was also highlighted that less than 20% of the animals involved in these experiments actually fell within the stated moderate severity banding, with the rest being classed as mild.

15/03-04                    Chairperson's Items

No Chairperson's items were reported.

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15/03-05

### **Verbal Reports from the Director of BMSU and Named Persons**

#### *Report from Director of BMSU:*

The Director welcomed a fourth year veterinary student to the meeting as an observer. It was explained that the student is working alongside the NVS as part of a LAVA scheme.

It was reported that four condition 18 notifications have been made to the Home Office by BMSU over the last few weeks. Condition 18 notifications are made when something inadvertently goes wrong during an animal experiment, and it is understood that the Home Office expect such notifications as routine, and do not necessarily view them negatively. Further information was provided about recent condition 18 notifications as follows:

- One notification has resulted in a new BMSU guidance document on expectations in the care of post-irradiated animals, which will serve as a useful reminder in an area in which BMSU has a long-standing good track record.
- Another involved a number of unexpected, unexplained deaths during a procedure in which all relevant care had been taken and protocol details had been followed.
- The most recent notification was associated with the euthanasia of a number of animals following a procedure, because of unexpected, unexplained hind limb paralysis. These animals will undergo post-mortem to investigate further, and the named veterinary surgeon will observe the next set of surgeries as a precaution.

An FOI request has been made in relation to nicotine research involving animals. A response was issued at the time of the request, correctly stating that no such research was undertaken. It was noted that the externally facing BMSU webpages have been very helpful in minimising the additional work generated by FOI requests.

New RSPCA guidance has been issued for lay members, and this can be accessed via the SharePoint site.

All new personal licences are now submitted via the electronic licensing system, ASPeL. From the summer, project licence applications will also move to ASPeL. The University is part of a working party on this, and will hopefully be early adopters of the new procedures. It was noted that there will be a six week period between July and August 2015 during which the ASPeL system will be shut down; it is not anticipated that this will cause significant problems, as

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summer is usually the quietest time of year. Potential applicants will be warned of the closure in advance and advised to submit in good time beforehand.

### *Report from the NVS:*

Regular meetings of named persons within BMSU have now been formalised and will take place quarterly. It has been agreed that academic leads will be invited to these meetings on occasion. This is in keeping with the BMSU Strategic Group's views on the need to reach senior project licence holders when issuing reminders about training, compliance, etc, and the need for ongoing CPD for all licence holders.

It was reported that within BMSU, the xenopus frog colony has recently shown signs of skin worms and bacterial infections. There have also been some issues with their eggs, which are used for experiments. These problems will be kept under review and the Committee will be kept informed.

As anticipated, BMSU has been affected by the recent outbreak of mouse parvovirus at Harlan, which supplies animals to the University. The infected animals have been isolated and some experiments will need to be repeated, but it is not anticipated that the impact of this will be significant.

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### 15/03-06                      Report from the Fast Track Procedure

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

### 15/03-07                      Project Licence Proposals

#### 15/03-07-1              Application Ref TBA – Function of tetraspan complexes in carcinogenesis

The aim of this project is to reveal key elements of a specific molecular network that controls tumourigenesis and metastatic progression with a subsequent goal to target specific components of the network with newly designed inhibitory agents.

This is a renewal of a previous licence which expired in January 2015, and the Home Office Inspector has already provided positive feedback on the application.

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

In protocol 2, the administration of tamoxifen or doxycycline should be an optional rather than a compulsory step. Also, in the protocol it is stated that tamoxifen may be administered via intraperitoneal injection “typically once a day for 5 days”, whereas in the section on adverse effects, it is stated that there will be “a single injection every 5 days” – this inconsistency should be corrected.

The possibility of administering tamoxifen should feature in all protocols, not just protocol 2.

The possible adverse effects of tamoxifen and doxycycline should be explained in the relevant sections of the application. Generally, it was felt that the wording of all adverse effects sections should be tightened up. Also in relation to adverse effects, it was noted that in line with the guidance on the application form, some indication should be given of the likely incidence of any adverse effects.

It should be clarified in the application that pre-operative analgesia is given as standard.

The non-technical summary should be amended to replace or explain all technical terminology.

The Committee requested further information about the procedure involved in stripping the mammary fat pad, and it was explained that this is a quick and simple procedure in such young animals.

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It was noted that some of the protocols have a large number of optional stages, and considering cumulative severity, it was queried whether all of the stages were likely to occur in any one animal. The Committee requested some indication of the likely experience of an 'average' animal in these studies. The PI explained that the application has been written to give necessary scope, but it is very unlikely that all stages will be needed in one experiment. Where appropriate, the application will be amended to show stages as 'either/or' rather than all being optional. It was further explained that even if a particular animal underwent all of the procedures listed within a protocol, because of adherence to the stated humane endpoints, it will not be possible for the overall procedure to exceed moderate severity.

In relation to protocol 2, it was clarified that the reference to a weight gain of 10% of original body weight was in comparison to age-matched controls, and the animals are unlikely to be aged beyond a maximum of 4 months.

In relation to protocols 3 and 4, all animals will be immunocompromised, and this should be clarified in the application.

No terminal anaesthesia will be required for the administration of chemotherapeutic substances, and this should be corrected in the application.

In part D of the application it should be clarified that some animals will be killed via terminal anaesthesia, in addition to those killed by schedule 1 methods.

The NVS noted that new compounds will be administered as part of the study, and queried whether toxicology and dose ranging tests will be carried out for these. The PI confirmed that where necessary such tests will take place, and this will be clarified in protocol 6.

It should be stated that statistical advice will be sought prior to the commencement of the studies, as well as when needed as the work progresses. It was explained that the PI's department within the University has a dedicated statistical services unit.

The frequency with which the animals will undergo imaging (with general anaesthetic) was queried, and the PI explained that imaging will take place as infrequently as possible whilst still facilitating the science. The named persons, including the NACWOs, will be consulted as the frequencies are determined.

It should be clarified within the application that in relation to skin tumours, the humane endpoints will encompass tumour size, body condition scoring and a limit of 10% body weight – this will take into account the welfare effects of numerous small tumours, as well as larger individual tumours.

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It was suggested that the 3Rs section of the application could be strengthened by explicitly including relevant matters which are discussed elsewhere, such as the humane endpoints.

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

Generally, it was noted that the application should be checked for 'cut and paste' errors.

References to 'sedation' should be replaced with 'anaesthesia'.

*Resolved that:*

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

15/03-07-2     Application Ref TBA – Protecting and repairing injured retinal ganglion cells

The objectives of this project are to determine changes that occur after injury to the optic nerve that connects the eye to the brain and relays information about vision.

It was explained that a co-researcher would present the application to the Committee, as the PI is on leave. This application is to renew an approval which ran out in January 2015.

Comments have already been received from the Home Office and incorporated into the application.

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

The Committee discussed the proposed use of albino rats, asking whether it was a representative model if such animals do not rely on eyesight as their primary sense. The researcher explained that the model is valid as the eyes of the animals are still functional, and their neuronal responses are exactly the same as in pigmented, fully sighted rats. However, the welfare implications are believed to be lessened by using animals which rely on other senses more than sight.

It was noted that fish are included in the application, and concern was expressed as BMSU now has neither large fish holding facilities, nor fish surgical facilities. If these facilities are required, additional investment will be needed. No funding has been secured to date for the proposed work with fish, and the likelihood of it being necessary will be checked with the PI. It was suggested that it may be best to remove the fish work from the current application, and then to submit

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it as an amendment if later needed. Also, it was felt that as the application is currently worded, it is unclear which protocol steps apply to fish, to rats, or to both. Removing fish from the current application would make this much clearer.

If work will be carried out with fish, it will be a precursor to the work with rats, and the fish would be used to identify genes only, with all therapeutic work being restricted to rats.

Regarding the choice of rats versus mice, it was explained that there is no equivalent non-pigmented mouse. Another reason for the use of albino rats is that these have been the animals used in all previous relevant models; it is helpful to use the same animals for continuity. The researcher also reiterated the welfare advantage of using animals which do not rely upon sight as their primary sense.

It was clarified that almost all animals will undergo bilateral crushing of the optic nerves, with each animal acting as its own control.

The Committee queried whether optic nerve regeneration was possible, and the researcher explained that whilst for years it had been considered impossible, recent studies have indicated that some environmental factor blocks regrowth, with at least 10% of the relevant neurons actually being capable of regrowth. Researchers are now investigating this further.

In relation to both the previous licence and current renewal application, the Home Office has raised concerns about the need for contingency and succession planning within the research team, in particular the need to train more junior researchers in the relevant techniques. It was explained that there are now individuals within the team who have been trained in the surgical techniques required; there is still a need for additional individuals to be trained to undertake the techniques with the expectation that they will then carry them out. The Committee will be kept informed about this.

In response to a query from the Committee, it was clarified that funduscopy is a non-invasive procedure which involves looking at the retina using a very bright light. Funduscopy will be carried out under anaesthetic, and may require the dilation of the iris.

The Committee requested further information about the criteria for selecting either the intracranial or intraorbital route for the lesioning of optic nerves. The intracranial route is more invasive and will only be used occasionally, if necessary to answer specific questions – the routine technique will be intraorbital.

The procedures in the application include a number of optional steps with recovery anaesthesia. Given the focus upon cumulative severity, the Committee asked the researcher for some indication of the likely

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experience of a typical animal, and it was explained that each animal is likely to experience a maximum of two general anaesthetics per week over two weeks. The stated humane endpoints ensure the work does not exceed moderate severity. The Committee suggested that the application should be amended to clarify which steps are likely to be combined or 'either/or' (particularly under the same anaesthetic), and some indication should be given of the typical maximum number of recovery anaesthetics to be administered per animal.

The Committee queried the justification for using both rats and mice, and it was explained that rats are preferred because of their larger physical size, for continuity with previous studies, and because many monoclonal antibodies are suitable for rats but not mice. However, mice are usually the only option when a transgenic model is required.

Further information was requested about the proposed sham operations. The researcher explained that sham surgery will be avoided where possible (for example, where historical data can be used instead). Where sham surgery is necessary, it will consist of all elements of the experimental procedure except the optic nerve crush.

It was felt that the wording of the first stated objective, to 'complete the understanding....', should be amended to be more realistic.

It was noted that this research group has not previously included cannulation in their experiments, and if used, the cannula would be inserted at the shoulder blade to administer substances to the animal. The potential use of cannulation will be discussed further with the PI.

The proposed use of electrodes will involve the implantation of very fine micro wires under stereotactic conditions, with the wires being attached to a surface screw. The Committee emphasised the importance of ensuring appropriate competency and training for the proposed techniques, and noted that the group has considerable experience in stereotactic surgery.

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

It was reiterated that the Home Office require more junior members of the research team to be trained in the required surgical techniques, to remove the dependency upon individual senior researchers. Whilst some researchers have already been declared competent to carry out procedures, there is a need for the PI to be signed off as competent to train others and the Home Office has indicated that they will expect this to happen in the near future. This will be discussed further with the PI.

The NVS emphasised that further information should be provided about the potential adverse effects of the various procedures in the application, and that the humane endpoints should be tightened up.



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The non-technical summary should be amended to state that the application is of moderate severity, and all abbreviations should be explained in full.

*Resolved that:*

Once the revisions discussed above have been made, the application will be recirculated and subject to Chair's approval, it will be recommended that the Establishment Licence Holder submits the application to the Home Office.

15/03-08

### **Any Other Business**

*Named persons meeting with academic leads*

As previously noted, going forward there will be quarterly meetings of the named persons within BMSU, and academic leads will be invited to these meetings on occasion.

*Guidance documents – instructions for applicants to BERSC, and guidance on interim reviews*

The Committee was informed that two new guidance documents, instructions for applicants to BERSC, and guidance on interim reviews, have been placed on the SharePoint drive for review and comment by the Committee.

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### **Date of Next Meeting**

The date of the next meeting is 23<sup>rd</sup> April 2015.

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### **GLOSSARY**

3Rs	Replacement, Reduction and Refinement
ASPeL	Animals Scientific Procedures eLicensing
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CLEC-2	C-type lectin-like receptor 2
CPD	Continuing Professional Development
FOI	Freedom of Information
LASA	Laboratory Animal Science Association
LAVA	Laboratory Animals Veterinary Association
NACWO	Named Animal Care and Welfare Officer
NVS	Named Veterinary Surgeon
PI	Principal Investigator
RSPCA	Royal Society for the Prevention of Cruelty to Animals
TBA	To Be Announced