CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

ANIMAL WELFARE AND ETHICAL REVIEW BODY (AWERB)

13th October 2022 (via Zoom)

MINUTES

Present:

22/10-01	Apologies Apologies had been received
22/10-02	Minutes The minutes of the meeting held on 11th August 2022 were considered by the Committee and were approved.

22/10-03	Matters Arising There were no matters arising.
22/10-04	Chairperson's Items There were no Chairperson's Items
22/10-05	Verbal Reports from the Director of BMSU and Named Persons Everything is running as normal in BMSU and it is business as usual. BMSU is also up-to-date with training people, and the PIL AB course is running this week. New licence applicants need to register with Occupational Health to ensure their spirometry tests are undertaken prior to training. The routine animal health screens went out last week and BMSU are awaiting the feedback but there are no anticipated issues. Three apprentices are coming to the end of their training and they have been offered the opportunity to apply for a permanent position. Following this, there will be a call for new trainees. The use of the training and competency module within ARMIS is to go live shortly. It will be piloted with two research groups initially and a step-by-step guide on how to use the database is being produced to assist with this. Animal facility staff have attended two external meetings recently. One was 3Rs-focussed, and the other was organised by the University Training Group to provide an update on the current best practice with regard to training. The University of Birmingham also hosted the AWERB UK event with approx. 75 delegates from across the UK. There are no animal health issues or concerns and no problems raised by the NVS. The aquatic unit is running as normal and the xenopus colony is breeding well, avoiding the need to purchase xenopus externally with the associated concerns around health status. There has been a 15% increase on the price of diet and the Strategic Group have been alerted to this. The Home Office have announced an additional type of audit that may be undertaken. Facilities audits are designed to investigate day-to-day running and compliance in the facility; all Establishments can anticipate a facility audit in due course. In the meantime, PIL and PPL holders continue to ensure they have all the required documentation to demonstrate their compliance with the standard conditions of their licences.
22/10-06	Report from the Fast Track Procedure Up to date with Fast Track and everything is going through as would be expected. There is one issue relating to AWERB oversight of the collaborative use of animals at another UK Establishment – the AWERB has not yet received a response having requested to see the relevant protocol from the project licence **Action: Chair of AWERB to write to applicant requesting a response.** All outstanding amendments have all been approved by ASRU.

	Home Office have now provided written guidance on Project Licence Applications (54 Pages) and the Deputy Director of BMSU will review this guidance to ensure AWERB are providing the correct advice.
22/10-07-1	Project Licence Applications *a) Understanding the role of inflammation in stroke* Summary: The stated aim of this project is to explore the role of inflammation in causing tissue damage after a stroke. • Stroke is the second biggest cause of mortality worldwide, and can cause severe disability in those patients who survive. • Stroke develops when a blood clot suddenly occludes a vessel in the brain and limits the delivery of blood to the tissues. • There is only one specific treatment for stroke, tissue plasminogen activator (tPA). This drug dissolves the clot in brain vessels restoring blood circulation and oxygen supply to neurons. However, for tPA to be effective it has to be administered within a very limited time frame (about 3 h) after onset of symptoms. • One complication of stroke is secondary inflammation developing as a result of tissue death. Inflammation expands the dead tissue area leading to further deterioration of patient's condition even when the clot is already removed. • The central goal of this study is identification of new inflammation-related mechanisms of stroke that can be targeted to minimize tissue injury and neurological deficit. The Committee raised the following points: The chosen model requires a high level of skill to advance a filament from the carotid artery to temporarily occlude a small vessel in the brain, and subsequently remove the filament. It was therefore queried who would perform the surgery, and how many comparable surgeries they had successfully undertaken previously. It was stated that the applicant has experience in undertaking over 100 such surgeries. A concern was also raised about this being a severe model, and the amount of suffering that may be anticipated. It was explained that the majority of experimental work will be completed within 24 hours of the induction of stroke and so the animals will not suffer prolonged and increasing adverse effects. It was pointed out that this would be a pilot study for 2 years initially. The Committee expressed the view that a wide range of different types of substances, and several different routes and repeats of administration were listed within the protocol and that this list of options would benefit from being more focussed, alongside a more detailed experimental plan to assist the reader in identifying the types of treatments to be used. It was commented that further amendments need to be made around adverse effects and humane end points. The IMPROVE Guidelines (Ischaemia Models: Procedural Refinements Of In Vivo Experiments) will be used to help inform these as they outline best practice. The choice of a mouse model was discussed further, with a question raised about recent reviews showing that mouse stroke models have not been particularly successful in translation to clinic. However, it was stated that this model is used widely in the research field because it re-capitulates the development of stroke in people very well, and whilst not a model of the entire process, it is a predictable model of the aspects of stroke under investigation in this proposal. It was queried whether this application is still at a basic science level rather than a therapeutic level. The applicant argued that the aim of this project is to identify cells that might be targeted to treat patients and as such, it is translational rather than basic science. It was also acknowledged that initially there needs to be an understanding of the basic science to identify molecular pathways and to move then onto a translational focus. Having justified the need for a mouse stroke model, the method of inducing the stroke was queried as to whether there was a difference between surgical induction and other methods, and whether this surgical model represented the most translatable approach. It was argued that whilst other non-surgical approaches could be used as the response and pathology is the same, other methods may cause for example unwanted and uncontrolled clots elsewhere, leading to unpredictable adverse effects and more variability (and so more animals). It was also pointed out that there will be control

	animals undergoing the same surgery without inducing stroke so that the effect of surgery can be established. Mortality rates were discussed, and there were some concerns over the percentage stated. It was acknowledged that this is a severe model associated with increased risk of mortality due to the nature of the procedure. It was however noted that the majority of mortalities will occur whilst under anaesthesia. It was raised that this was a new model to BMSU, but reassurances were provided in that the applicant has extensive experience of performing the procedure elsewhere, there is previous experience amongst the Named Persons in the care required for these models, and the IMPROVE guidelines also provide advice on the most refined approaches to support the welfare of these animals. During the harm-benefit discussion, the committee felt that the applicant had explained the benefits of the research, however this was not well described in the application itself. The applicant was asked to expand the information in the application so as to better demonstrate that the potential benefits outweigh the harms caused due to the severity of the model. **Decision: Committee agreed that further discussions are needed between the NVS, BMSU, NACWO and PI prior to being recirculated electronically for approval. It will then be sent to ASRU.**
22/10-07-2	*b) PPL Amendment: Mechanisms controlling anti-tumour responses in primary and metastatic disease* Summary: The stated aim of this licence is to determine how different cellular interactions control the anti-tumour immune response in primary and metastatic disease and how targeting certain mechanisms, termed immune checkpoints, alters this. • In the last 10 years, there have been enormous advances in exploiting immune responses to kill cancers. Successes include targeting immune checkpoints, which have revealed that even with late-stage diagnosis, common cancers such as melanoma can be cured in some patients. • This project will investigate how different immune cells interact to support the anti-tumour response in both primary cancer and in metastatic disease. • The focus will be on T cells as it is known these are the cells best equipped to kill cancer cells and which are able to respond to therapies such as immune checkpoint blockade. The amendments include: • New protocol for the development of dual liver and flank tumours. • The PI will utilise expertise in specifically labelling subcutaneous tumours (to track the entry and subsequent changes of newly recruited cells) to determine exactly how and why the response in a peripheral tumour is impacted by the additional presence of liver cancer • Under this protocol tumour cells will be injected directly under the liver capsule, following exposure of a lobe via (limited) laparotomy. Multiple research groups were consulted on the most effective means of establishing intrahepatic tumours and the approach of surgically exposing the tissue and directly injecting was recommended. • Liver tumour growth will be tracked using IVIS in conjunction with luciferase-expressing cell lines. This will ensure accurate assessment of tumour growth and that the tumour burden of the mouse remains well below the 10% bodyweight limit. • Mice with a single liver tumour will then be additionally given a subcutaneous tumour and treated with antibodies that target immune checkpoints to complete the model of the clinical challenge being investigated. • Controls with only one type of tumour (subcutaneous or liver) will need to be included. • Training in the surgical exposure of the liver and injection is available from experienced collaborators in the UK The Committee raised the following points: It was queried whether this is a model of liver metastasis or whether it is a primary liver tumour model. It was explained that whilst the two tumours are independently introduced rather than one metastasising from the other, it had been shown by others that the two tumours subsequently interact in a way that models metastasis.

	It was explained that the issue is that following liver metastasis, the original tumour ceases to be responsive to therapy, and it is not understood why. When this is modelled using two tumours implanted subcutaneously, this doesn't impact checkpoint blockade, and there is very little cell movement between the tumours. This suggests that there is something specific about liver metastases hence the need to implant the tumour cells into the liver itself. The same cell line will be introduced to both sites, because if difference cell lines are introduced there is no interaction between the sites. It was confirmed that colorectal cell lines will be used as it is known that these tumours metastasise to the liver. **Decision: Committee agreed that further discussions are needed between the NVS, BMSU, NACWO and PI prior to the application being sent to ASRU.**

22/10-08	Matters relating to the 3Rs
	
	• The Regional Programme Manager (Midlands) gave a talk about NC3Rs resources and funding opportunities to the Institute of Cancer and Genomic Sciences earlier in the week, This talk has also been offered to other institutes.
	• The NC3Rs is now inviting applications from talented senior researchers to join the NC3Rs Grant, Skills and Knowledge Transfer, PhD Studentship and Technologies to Tools Assessment Panels from January 2023. More information is available on the NC3Rs website or via the Regional Programme Manager (Midlands).
	• Two CRACK IT challenges are open: T-Alert (a two-phase challenge, deadline midday 27 October 2022) and Thyroid Tox (a single-phase challenge, deadline midday 3 November, 2022). More information is available on the NC3Rs website or via the Regional Programme Manager (Midlands). The NC3Rs is running a workshop 'Recognition, prevention and alleviation of pain and distress in laboratory animals'. 21-25 November 2022. Based on the in-person workshops held previously in Newcastle, UK and is aimed at animal technicians, veterinarians, research workers and others who want to improve their understanding of this topic. Registration £300.
	
	• The university 3Rs Strategy Document had been circulated to all AWERB members for comment. Whilst some items have been removed due to completion, the majority have remained as they are activities that ought to be completed at least annually. The NC3Rs Regional Programme Manager will be seeking assistance over the coming weeks as many of the activities require input from various sources, for example in scoping 3Rs advances for replacement. The intention is to further increase 3Rs training and events, and to consider topic-specific workshops (e.g. an experimental design workshop). There have been discussions at focus groups regarding researchers publishing negative and null data for which there are data repositories and links on Open Research:
	  • There was an Open Research Forum at the end of 2021 (Open Research (birmingham.ac.uk)) which is now available as a course on Canvas (Open Research Forum Event Series Resources June 21 (bham.ac.uk)).
	  • Various data repositories are recommended:
	  ○ Deposit data — UK Data Service
	  ○ Home | re3data.org
	
	• The BMSU Director, Assistant Director and Deputy NVS attended the LASA/UFAW 3Rs event at GSK. The Deputy NVS gave a talk on surgical refinements that was well received. The presentation focussed on small but impactful changes that are widely applicable and easily implemented.
	• Two papers have been accepted for publication with three of the Named People listed as authors. One focusses on refinements to certain animal models, and the other on the practicalities of applying experimental design techniques in an animal facility.

22/10-09	Condition 18 Reports There have been four Condition 18 Reports since the last meeting. It was stated that these cases are not linked, and they were not due to lack of monitoring by BMSU staff.
22/10-10	Retrospective Reviews

	These formal non-technical reviews are for severe protocol licences: *PPL: PDCE16CB0 – Understanding mechanisms of inherited heart disease (cardiomyopathy) and exploring treatment options.* *PPL: P64E3B1FD – Targeted therapied to modulate inflammation on alcohol-induced injury* **Decision: Both reviews were agreed by AWERB and will be sent to ASRU.**
22/10-11	Any Other Business. Following the recent AWERB UK event, there was a discussion regarding whether there is a need for formal training for AWERB members. It was queried whether the members would benefit from some experimental training for non-scientists. It was stated that marked-up exemplar applications would also be beneficial so that members know what to look for in an application and have examples of areas of concern.
22/10-12	Date of Next Meeting The date of the next meeting – 1st December 2022 via Zoom

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GLOSSARY

3Rs	Replacement, Reduction and Refinement
ASRU	Animals in Science Regulation Unit
AWERB	Animal Welfare and Ethical Review Body
BBSRC	Biotechnology and Biological Sciences Research Council
BMSU	Biomedical Services Unit
EDA	Experimental Design Assistant
Je-S	Joint Electronic Submissions
MRC	Medical Research Council
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NACWO	Named Animal Care and Welfare Officer
NORECOPA	Norway's National Consensus Platform for the Advancement of the 3Rs.
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PEL	Establishment licence
PI	Principal Investigator
PIL	Personal licence (Procedure Individual Licence)
PPLs	Project licence (Procedure Project Licence)
PREPARE	Planning Research and Experimental Procedures on Animals: Recommendations for Excellence
RSPCA	Royal Society for the Prevention of Cruelty to Animals
UoB	University of Birmingham