ID 241189 FD-S

Home Office

PPL Standard Condition 18 Notification Form

Please use this form to notify the Animals in Science Regulation Unit (ASRU) of procedural-related adverse effects that have exceeded or are likely to exceed the severity limitations or controls described in the project licence. ASRU will use this information to determine whether any further action is required.

Do not use to report:

- adverse effects that are due to non-procedural issues;
- potential non-compliance (report by other means);
- issues without adverse welfare consequences.

If you are in doubt whether or not you need to fill in this form, please contact your assigned Inspector.

Please clearly title your document: **'ASRU_establishment name_PPL number_PPLh surname_date_sc18'** and send to your Inspector (e.g. using cjsm) with the subject heading 'PPL SC 18 Notification PPL [Number] – **Check Home Office's Updated Bridging Ways of Working for updated advice on email addresses and subject headings. Cjsm no longer necessary.**

Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Brian Huntly
PPL number	PP3042348
Protocol no	9
Protocol title	Study of the genetic and therapeutic vulnerabilities of pre-leukaemia and leukaemia (Mice)
Severity classification	Moderate
1. Date of incident	16/6/24

2. Species	Mouse
3. Brief details of study and how the limits or constraints have been breached	We have identified that the combination of inhibitors of CREBBP and Venetoclax synergise in the treatment of B cell acute lymphoblastic leukaemia (B-ALL). Our previous work has demonstrated the efficacy of daily oral combination treatment in NSG mice engrafted with B-ALL cell lines. This work has been reviewed at Nature Cancer, and all the reviewers have requested in vivo confirmation of these findings in primary human PDX models. We have therefore transplanted NSG mice with a B-ALL PDX with the aim of confirming treatment efficacy. On the 6th day post sublethal irradiation and iv injection of PDX cells a mouse was found dead on morning checks. At this early stage post-transplant no other procedures had been performed on the mouse (i.e. no blood sampling, imaging or drug dosing). The mouse had been checked daily by us during the week and the animal technicians over the weekend. Weight was stable on Friday 14th June (-0.8%). All other mice in the cohort were checked at the time by the technicians and were stable.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	Yes – discussed with NVS

5. Cause of Problem, if known	The mice had undergone sublethal irradiation and tail vein injection from a batch of PDX material that has been successfully engrafted into multiple mice before. No other procedure had been performed, in particular drug dosing. There was no evidence of splenomegaly on autopsy to indicate leukaemia as the cause of death. Furthermore, in terms of leukaemia kinetics, our previous experiments with this PDX have shown low level engraftment being first detectable by BLI imaging at approximately 4 weeks and untreated mice from a previous cohort survived for over 8 weeks until being culled for tissues. It is therefore highly unlikely to relate to B-ALL at this early timepoint. The most likely cause is therefore an infection in the context of myelosuppression post transplantation.
6. Action that has been or will be taken *(For example, formulation of drug changed, supportive treatment given, study design modified). If no action needed, indicate why (for example, none required as study has been terminated and will not be repeated)*	The incident happened on a Sunday morning. We checked the mice later that day and weighed the cohort, identifying a further mouse from the cohort that they culled for clinical signs of ill health. This mouse was in a separate cage and from a different litter from the first mouse. Again, there were no abnormal signs on autopsy. All remaining mice remained well on Monday 17th and Tuesday 19thJune. We have contacted the named vet to agree a plan. Tissues from this mouse will be sent to look for histological evidence of infection. We will continue to monitor all animals twice daily for any abnormal signs and communicate any concerns with the named Vet in the first instance. If any further mice become unwell we will check a peripheral blood for blood count and if a high WCC for NGS mice is noted we will also flow looking for evidence of B-ALL engraftment. We will also discuss with the vet regarding taking fresh peripheral blood or tissues for culture.
7. Reported by (name)	Simon Richardson

8. Date	18/6/24

******************************For official use**

Inspector's comments and recommendations:

Comments and recommendations	Thank you for submitting this notification and thereby complying with standard condition 18 of your project licence. The content of this SC18 report has been reviewed and this matter is now CLOSED.
Inspector name	Karen Mason
Date	27/06/2024