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Animals on ‘hold’

The Transgenic Mouse Production Facility (TMPF) at Great Eastern University was a specialized unit for producing genetically engineered mice. It had a comprehensive IACUC-approved protocol to produce animals for faculty researchers. The protocol focused on the technical aspects of the procedures to be done for investigators (surgery, aftercare, genotyping and all other appropriate information). Typically, an investigator with an approved IACUC protocol would provide the TMPF with the required genetic and other necessary materials, along with information about the background strain of the mice to be produced. The TMPF would take over from that point, develop the genetically modified founder animals, genotype them, allow those with the appropriate genotypes to undergo one breeding cycle and then transfer the mice to the investigator.

The investigator would breed and subsequently use the animals under his or her own IACUC protocols.

There was one potential flaw in the system that did not reveal itself until Dr. Richard Peskin had the TMPF develop a transgenic mouse for his research. The technical process went fine. However, Peskin forgot to submit breeding and research protocols to the IACUC. When he went to the TMPF to get his animals, the TMPF staff asked him for his IACUC approval number so that they could inform the animal facility that an animal transfer was being made. Recognizing his oversight but wanting to have his animals, he quickly wrote an IACUC protocol which stated that the animals were to be housed only and that no research or breeding would be done. Eventually, he stated in the protocol, the mice would be transferred to IACUC-

approved breeding and research protocols. Peskin’s ‘holding’ protocol was approved by the designated member review process, the business at the TMPF continued as usual, and Peskin soon submitted breeding and research protocols to the IACUC.

The TMPF director was a member of the IACUC and related the story to the IACUC chairman. The chairman was not particularly concerned, because everything worked out well. But is everything well? Was this just a one-time error on the part of an investigator, or are there deeper problems? Even though the TMPF works under its own IACUC-approved protocol, should it be allowed to produce mice for an investigator before the IACUC approves that investigator’s breeding or experimental protocols? What are the potential consequences—if any—of the actions that occurred in this scenario?

RESPONSE

Experimental protocols are essential

Peter Flanagan, DVM

This scenario presents an apparent dilemma. On one hand, the TMPF protocol seems to provide adequate oversight of the production of transgenic animals. On the other hand, in the absence of an experimental protocol, several essential IACUC concerns are overlooked: scientific merit, animal health, biosafety and animal reduction.

Pragmatically, most investigators would be reluctant to request TMPF services if the transgenic animals were not usable. In this scenario, however, the IACUC lacks a mechanism for evaluating the scientific justification for these animals because there is no review by a funding agency, peer group or IACUC. If no credible review of the scientific merits of a study

occurs, then a rogue investigator could conceivably ask the TMPF to produce a ‘frivolous’ transgenic animal; and neither the TMPF nor the IACUC would be aware of its uselessness until the TMPF tried to transfer the animal to a nonexistent experimental protocol.

Furthermore, the transgenic animal could potentially pose a serious biosafety risk. Although the TMPF protocol addresses the technical aspects of transgenic animal production, the biosafety concerns are ignored. Normally, an IACUC protocol entailing genetic manipulation would trigger an Institutional Biosafety Committee (IBC) review. As long as the blanket protocol appears to be adequate, it is unlikely that the TMPF would submit an amendment for each new construct. Once again, without an experimental protocol in place to address the details of each construct, the IACUC would not be able to alert the IBC of a potential biosafety issue.

Similarly, as a generalized description of procedures, the TMPF protocol does not

detail the various phenotypes and health issues resulting from the production of specific constructs. Normally, investigators inform the IACUC of the likely health issues arising from various manipulations. The IACUC then evaluates these concerns during the review process and offers appropriate remedies. Clearly, an adequate evaluation is impossible if the IACUC does not have the information. Consequently, an ill-considered transgenic model could lead to an unacceptable level of health problems that should have been anticipated during the IACUC review.

The TMPF is in the business of providing transgenic animals. Its ultimate goal is similar to that of standard breeding programs. The TMPF usually starts with a predictable number of animals to reach the production target of founder animals. In this case, perhaps 80 animals were used to produce 10 live animals, which would remain on the TMPF protocol until they could be transferred to the experimental protocol. If no experimental