

Jerald Silverman, DVM, Column Coordinator

## Miscommunication involving ‘standard care’

Dr. Herb Birnbaum, working for a small biotechnology company, was studying the expression of the gene *Brcal* in mice that had malignant ovarian tumors, mammary tumors or both tumors implanted subcutaneously. The goal of the study was to maintain the animals in good health as long as possible and to determine whether *Brcal* was overexpressed in animals that had both tumors, as compared with animals that had only one or the other. Birnbaum contracted with Great Eastern University for animal housing, care and procedural space. Birnbaum’s own technicians carried out the experimental procedures. His protocol had been reviewed and approved by the Great Eastern IACUC.

About halfway through Birnbaum’s study, Dr. John Brown, the Attending Veterinarian at the university, was approached by a new investigator and asked about the appropriate dosage of cisplatin (a chemotherapeutic drug) for

rats. Brown was aware of other rat studies that had used cisplatin, and he quickly provided the investigator with the dose that had been used on those studies. He also reminded the investigator to have the drug’s use approved by the IACUC and the Chemical Safety Committee before using it in any ongoing study. The investigator was surprised that he had to do this because Herb Birnbaum was using the drug in his *Brcal* study with only the approval of his own company’s Safety Committee. Brown was shocked to hear this, but Birnbaum soon confirmed that it was true. Birnbaum did not think he had done anything wrong. In fact, as he pointed out, he clearly wrote in his protocol that his mice would be given standard care for their tumors. To Birnbaum, ‘standard care’ meant the use of cisplatin, which is often used in human patients with ovarian cancer. To Brown and the Great Eastern IACUC, ‘standard care’ meant observing the tumors for

ulcerations, placing food on the cage floor if necessary and other similar non-medical interventions. To complicate matters, Birnbaum reminded Brown that he had sat through an hour-long lecture on rules and regulations, in which Brown often commented on the importance of ‘performance standards’ that provide flexibility based on the needs of the animal and the study, rather than more rigid engineering standards. Brown had also spoken of ‘practice standards’, which included the use of procedures considered by professional judgment to benefit the animal. Birnbaum claimed that cisplatin was used to help the animals in his study to remain healthy.

There was an obvious breakdown of communication between Birnbaum and the IACUC. What immediate steps should the IACUC take in this case, and what should the IACUC do to prevent problems such as this one from recurring?

### RESPONSE

#### Revise protocol form

Sonia Doss, MEd, RLATG, CPIA

The Great Eastern University IACUC should request that Birnbaum immediately stop administering cisplatin to mice used in his study and submit an amendment to the IACUC to include the use of cisplatin. Brown and the IACUC chair should meet with Birnbaum to discuss the incident and to develop procedures to prevent this situation from recurring.

Although Birnbaum is employed at another institution, as an investigator at Great Eastern, he should follow all of Great Eastern’s applicable policies and procedures unless an exemption is granted by the IACUC. During its initial review of the protocol, the Great Eastern IACUC

should have requested a copy of the approved protocol from Birnbaum’s home institution, which should have clearly stated the proposed use of cisplatin. The IACUC could then have requested more information regarding cisplatin use during its review process.

Great Eastern’s IACUC protocol submission form should be revised to include a section specifying the use of any hazardous agents as well as a section listing all substances that might be administered to the animals during the course of the study. Use of hazardous agents is generally flagged for review and approval by the institution’s safety office before the protocol can be approved. The *Guide for the Care and Use of Laboratory Animals* (the *Guide*) clearly addresses the establishment of formal safety programs to assess hazards and all procedures related to those hazards<sup>1</sup>. The *Guide* also indicates

that the use of hazardous materials should be included in the IACUC review. All agents that might be administered to animals should be listed in the protocol, along with their doses, frequencies, routes and proposed durations of administration. Any deviations should be requested and approved by the IACUC.

Birnbaum’s proposed protocol indicated that mice in his study would be provided with standard care for their tumors. During the protocol review, the Great Eastern IACUC should have requested that Birnbaum expound on the ‘standard care’ that he proposed for the mice. The Great Eastern IACUC should develop a policy to cover tumor burden in rodents, outlining the standard of care for all rodents with tumors, and principal investigators should be required to follow this policy or to request an exemption in the protocol proposal.

**A word from OLAW**

Brown should refine his use of the terms ‘performance standards,’ ‘engineering standards’ and ‘practice standards’ in his lecture to minimize miscommunication in the future. Perhaps he should use these terms in regard to the animal facilities and the animal care program in general but stress that animal care and use protocols should include a clear and concise outline of the proposed procedures involving the use of animals<sup>1</sup>.

Finally, the Great Eastern IACUC should consider developing a post-approval monitoring program to assist the IACUC in ensuring protocol compliance. During post-approval monitoring, the monitor would have observed the procedures carried out by Birnbaum’s research technicians, likely including the administration of cisplatin. Thus, the noncompliance with the approved protocol would have been identified. Even if the monitor did not directly observe cisplatin administration, discussion between the research technician and the monitor may have revealed its unapproved use.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2010).

Doss is Compliance Liaison at Duke University, Durham, NC.

**RESPONSE**

**Specify all medications**

**Harry Rozmiarek, DVM, PhD, DACLAM & Denise C. Connolly, PhD**

The rationale behind the suggestion that *Brcal* might be overexpressed when animals have both ovarian and mammary tumors implanted is confusing, as the normal BRCA1 protein usually repairs double-stranded breaks in DNA and thus prevents the formation of these tumors. Consistent with the function of BRCA1 as a tumor suppressor, only women who carry a mutation in the gene *BRCA1* have a much higher risk of developing breast and ovarian cancer. The suggestion that implantation of ovarian or mammary tumors may result in overexpression of

*In response to the questions posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) offers the following clarification and guidance:*

This response assumes that the biotechnology company does not have an animal facility or IACUC and is relying solely on the university’s IACUC. Under these conditions, the use of the drug constitutes an unapproved significant change to the animal activity. It is a reportable incident to OLAW if the animal activities are supported by the Public Health Service (PHS)<sup>1,2</sup>.

Appropriate corrective actions include stopping the unapproved activity, placing the animals on a holding protocol and obtaining IACUC approval<sup>3</sup>. If this is a PHS-funded activity, the grant or contract cannot be charged for the unapproved activity. Other appropriate corrective actions commonly taken by IACUCs include counseling and retraining of investigators on relevant policies, increased laboratory oversight, enhanced communication between the IACUC and the investigator and intensified training of the research staff by the principal investigator so that they understand the content of the protocol<sup>3</sup>.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
2. Office of Laboratory Animal Welfare. *Guidance on Prompt Reporting to OLAW Under the PHS Policy on Humane Care and Use of Laboratory Animals*. Notice NOT OD-05-034. (National Institutes of Health, Washington, DC, 24 February 2005). <<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html>>
3. Wolff, A. Reporting noncompliant events to OLAW. OLAW Online Seminar, 5 March 2009. <<https://webmeeting.nih.gov/p31061868/>>

**Patricia Brown, VMD, MS, DACLAM**

*Director  
OLAW, OER, OD, NIH, HHS*

*Brcal* raises some scientific questions, which may not be relevant to the IACUC, as it is charged with focusing its review on animal welfare. Our comments will thus also focus on animal welfare.

We feel that the progression of events described in this scenario resulted from a misunderstanding on the part of the investigator, likely stemming from a lack of communication regarding what should be included in an animal care and use protocol. The information provided in the protocol about drugs and treatments used was clearly inadequate and should be corrected immediately. The IACUC should request an addendum or a revised protocol from the investigator specifying that mice experiencing tumor-related illness will be treated with cisplatin, a chemotherapeutic agent commonly used for the treatment of ovarian cancer. In the addendum, Birnbaum should describe specific conditions under which chemotherapy would be used, as well as the dose and frequency of administration. Issues related to potential risk of handling cages

and bedding of drug-treated mice and specific methods for disposal should also be included. Work on this protocol should be discontinued until the addendum can be reviewed and approved, and its review should be expedited so that the work is only minimally disrupted. This situation should be reported to the Institutional Official and documented in the record, but it may not be necessary to officially report it to OLAW or the granting agency. We believe that Great Eastern should contact OLAW by telephone to assure that all appropriate measures are being taken and should follow any advice offered by OLAW.

The protocol form used by Great Eastern University should be reviewed and amended if necessary. The form and accompanying instructions should clearly require that all drugs, medications and treatments be included and described, along with dosing, frequency and route of administration as well as a description of any anticipated clinical signs or side effects. Nursing care and special provisions and observations provided for animals

in stress, discomfort or pain should be included. Clinical signs leading to severe pain and discomfort should be described, along with a clearly stated and described endpoint that would lead to euthanasia.

A review of all current protocols in use at Great Eastern University should be carried out to assure that the above requirements are being followed, and any which are deficient should be amended and corrected immediately. The training program conducted by Brown and his staff should also be reviewed and modified as necessary to assure that instructions on protocol writing are clear, complete and adequate to guide investigators who describe work with research animals. If major deficiencies in this training are discovered, retraining of all current investigators and staff members should be considered. This might be done using electronic training methods or any other means that reaches everyone with the required material.

*Rozmiarek is Professor Emeritus and Director of the Laboratory Animal Facility and Connolly is Assistant Professor of the Women's Cancer Program and Deputy Chair of the IACUC at Fox Chase Cancer Center, Philadelphia, PA.*

## RESPONSE

### Describe in detail

**Alan Ekstrand, BS, CPIA, LATg & Victor Lukas, DVM, Diplomate ACLAM**

In this case, the IACUC and Attending Veterinarian had one idea about the

meaning of 'standard of care' and 'performance standards' but the researcher had a very different idea. The first step taken by the IACUC should be to temporarily discontinue the use of the cisplatin, as it poses a potential hazard to the animal care staff and is not approved in the protocol. A hazardous chemical specialist should be consulted to advise Birnbaum, Brown and animal care staff on how to handle the current contaminated cages and exposed animals. An occupational health physician may also be consulted to help determine whether there have been any significant employee exposures. The animals should be examined to determine whether they are experiencing any adverse effects.

Birnbaum, in consultation with the campus safety professional, should then establish a procedure to safely work with cisplatin in the facility. Once this plan has been established, he should amend his animal care protocol to include cisplatin. Once all approvals have been granted, the work can resume.

We suggest two changes in protocol review procedures that may help to avoid these types of issues in the future.

First, the IACUC protocol form should be revised to state clearly that researchers must list all animal manipulations, and the form should include a section addressing potentially hazardous agents. The *Guide for the Care and Use of Laboratory Animals* indicates that animal care protocols should cover the use of hazardous materials and provisions for a safe working environment<sup>1</sup>. The IACUC should

work closely with the safety committee or with an environmental health and safety specialist to ensure that work involving hazardous agents in animals is appropriately designed and reviewed so that the animal care and research staff are protected. If the institution does not have a safety committee, then the IACUC should provide the necessary review.

Second, when reviewing protocols, the IACUC should avoid approving vague statements, such as "animals will be cared for using standard care for tumors," as these are of little use unless the IACUC has an approved standard operating procedure or policy for the care of animals with tumors. Birnbaum should have been asked to describe the care of animals with tumors in detail, including information such as dose, frequency and route of administration of any medications; routine monitoring; potential adverse effects; methods to minimize potential pain and distress; and humane endpoints.

In conclusion, it is important to have a well-designed protocol form that captures all of the needed information to ensure both animal and employee well-being. This, along with a thorough protocol review, will help to avoid the situation described above.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2010).

*Ekstrand is IACUC Administrator and Lukas is Attending Veterinarian at University of California Davis, Davis, CA.*