**IACUC Training Exercise #3 - 2017**

The following exercise may be useful in stimulating discussion regarding compliance with PHS Policy and VA Handbook 1200.07. To facilitate discussion, page 1 of the exercise may be distributed to the IACUC members prior to a meeting. After a few minutes of discussion about the exercise during the meeting, the remainder of the exercise may be distributed to provide ideas for the committee’s consideration.

Local attorney, Sperry Blackburn, was known for always being prepared and for being a quick study. Sperry was good friend of Dr. Diaz, the Attending Veterinarian. Dr. Diaz had asked if he would be willing to serve on the VA-IACUC; when he received an email from the Hometown Medical Central Director appointing him to serve as a nonscientific member, he agreed. This afternoon’s IACUC meeting would be his third; as he became more familiar with the process, he began to have more questions. He was particularly concerned about a protocol that used a mouse model of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a heritable cardiomyopathy. In the protocol, the IACUC was reviewing today, the investigator had simply said he planned to use heterozygous Dsp-deficient mice because they were the best model of human ARVC/D and his previous work was performed using these mice. Sperry had learned as an attorney to accept very few things at face value so he did an on-line literature search for animal models of heritable cardiomyopathy. He discovered not only were there more mouse models (i.e. six) than the Dsp-deficient mouse model but the investigator could have also considered using a zebrafish, transgenic rabbit, or spontaneous dog model. A little more searching led to Sperry discovering an investigator’s research that used fruit flies, *Drosophila melanogaster,* to study specific genetic errors associated with heart disease. Sperry realized he was not a scientist but he also knew he wasn’t satisfied the investigator had presented a sound argument for using heterozygous Dsp-deficient mice in his study as opposed to the other mammalian models or even the zebrafish or fruit fly models. Sperry made some notes on his findings and was ready to discuss his concerns when the IACUC Chair called for questions about the ARVC/D protocol.

Do you think Sperry’s concerns about the investigator not adequately justifying his model selection are reasonable?

An overview of the ARVC/D protocol was presented by the two assigned reviewers and then the IACUC Chair called for discussion. Sperry presented his findings to the other IACUC members and voiced his concern that a strong justification for the use of the heterozygous Dsp-deficient mice model had not been provided by the investigator. Several other committee members expressed similar views; Dr. Rossi, the IACUC Chair, interjected that all animal models are not equal and the investigator may have had a valid reason for his model selection. After a bit more discussion, the committee voted unanimously that a revised animal/species justification clearly detailing the rationale for the selected model be a modification required to secure approval. The IACUC Office notified the investigator that modification of the animal/species justification was required to obtain protocol approval; the investigator promptly provided the following response.

*Preliminary studies were performed in vitro using cardiac myocytes isolated from human ARVC/D biopsy samples but a whole animal is now needed to appropriately model the physiology and pathology of this disease. Heterozygous* Dsp*-deficient mice exhibit excess adipocytes and fibrosis, increased apoptosis, defective cardiac contractility and ventricular arrhythmias, which mirror human ARVC/D. I considered using other mouse models such as the Jup+/- mice but the literature indicates that these mice only partially mimic the clinical ARVC/D phenotype. The mouse and zebrafish morpholino studies have limitations because they are usually restricted to the embryonic stage and knockdown models may be less representative of the pathophysiology of the human disease. Zebrafish and fruit fly hearts are very different from the human heart, which makes these models less desirable. The spontaneous canine boxer model of ARVC/D features exercise-induced ventricular tachycardia, which may be associated with a mutation in the ryanodine receptor type 2 gene (RYR2) as a cause of ARVC/D; however, dogs are a more sentient animal and it would be difficult to obtain a sufficient number of these canines. The transgenic rabbit model is a mutation of R403Q in the β-myosin heavy chain and was ruled out for reasons similar to those listed for the canine model. In light of the above, I have chosen the heterozygous* Dsp*-deficient mouse model because these mice closely model human ARVC/D, my previous studies were conducted with these mice, mice are a lower sentient animal, and are readily available.*

When animal rights groups request protocols through the Freedom of Information Act (FIOA), a prime target is the justification for the use of animals (i.e. ACORP items D and W). When investigators provide a clear rationale for why the use of animals is necessary and why a particular animal model was chosen, they earn the public’s trust and make their research less vulnerable to criticism.

**Sources:**

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