

All in the barn: who oversees agricultural research animals?

Very few researchers require llamas for their studies, but Dr. Helen Zymansky had such a need. Zymansky, a professor at Great Eastern University's College of Agriculture, used small llama-derived antibodies (nanobodies) as part of her investigations on bovine immunodeficiency virus (BIV), a lentivirus with an uncertain impact on animal health, that is found in cattle from the U.S. and other countries. The research was funded by federal government grants and focused on determining if BIV affected the reproductive efficiency of dairy cows. The IACUC was aware of Zymansky's work because the llamas were housed in the same barn with animals used for studies overseen by the IACUC. However, because Zymansky's animals were being used to study the effect of BIV on reproductive efficiency of dairy cows, the research committee of the College of Agriculture, not the IACUC, approved and monitored Zymansky's work.

During an AAALAC site visit for the colleges of medicine and veterinary medicine, the visitation team went to the

barn that housed Zymansky's animals and those under the jurisdiction of the IACUC. The visitors saw a llama with a generalized skin infection that was rubbing itself against the side of its stall. There was no record of any veterinary examination of the animal and no indication that the infection was being treated. The barn manager said that he had not noticed the problem. At the site visit exit briefing the visitors questioned the lack of an IACUC protocol for Zymansky's work and stated that the untreated infection will lead to a recommendation that AAALAC issue a mandatory notice indicating a need for more thorough animal monitoring and veterinary oversight. The schools replied that research on and for the benefit of agricultural animals did not fall under the jurisdiction of the IACUC and therefore no IACUC protocol was required, but they would inform the College of Agriculture research committee that the animal required medical care and the veterinarians would immediately contact Dr. Zymansky. The site visitors said they agreed with the immediate action to be taken. They then cited the

*Guide for the Care and Use of Laboratory Animals*¹, which states that "Regardless of the category of research [i.e., agricultural or biomedical], institutions are expected to provide oversight of all research animals and ensure that pain and distress are minimized."

Did the schools of medicine and veterinary medicine respond appropriately in this situation? Do you think that the BIV study was biomedical or agricultural? Did the site visitors overstep their authority by recommending a mandatory item for correction when the IACUC claimed that it had no jurisdiction over the study? □

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Published online: 22 January 2019

<https://doi.org/10.1038/s41684-018-0221-6>

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Who's responsible for the llama drama?

This scenario addresses IACUC oversight and responsibilities as they pertain to agricultural animal research. After a llama is noted to have an untreated generalized skin infection during the AAALAC site visit of the schools of medicine and veterinary medicine at Great Eastern University (GEU), the site visitors recommended the schools receive a mandatory notice "indicating the need for more thorough animal monitoring and veterinary oversight." The IACUC responded that since the llamas are part of a research study aimed at improving the reproductive efficiency of dairy cows, this research would not fall under its purview but that they would inform the College of Agriculture, whose research committee approved the work, and the PI of the need for veterinary care. Despite their assertion that research on and for the benefit of agricultural animals does not fall under the jurisdiction of the IACUC, their response

to AAALAC's mandatory notice could have been more robust.

Assuming that GEU holds a PHS Assurance, OLAW encourages institutions to perform program oversight institution-wide using uniform and consistent standards for animal care and use regardless of funding source¹. PHS Policy requires adherence to the *Guide for the Care and Use of Laboratory Animals (Guide)* which "... applies to agricultural animals...including those maintained in typical farm settings²." The *Guide* affirms that the species involved in research does not affect the fundamental roles and responsibilities of the institutional entities charged with regulatory oversight and gives IACUCs flexibility to categorize "research uses of agricultural animals and define standards for their care and use... based on both the researcher's goals and concerns for animal well-being³." As such, GEU's IACUC has jurisdiction over these animals despite this being agricultural

research. In this case, the IACUC could ensure appropriate oversight by requesting that Dr. Zymansky provide documentation to the IACUC administrator and the Attending Veterinarian (AV) detailing the study goals, procedures (e.g. frequency of blood collection), and the qualified personnel providing the daily husbandry and veterinary care. Ideally, this information can be captured in a protocol and the IACUC can decide whether the protocol will adhere to the standards outlined in the *Guide* or the *Guide for the Care and Use of Agricultural Animals in Research and Teaching (Ag Guide)*. In either case, veterinary care of these animals should be specifically outlined in their AAALAC Program Description. If the decision is made to adhere to the performance standards of the *Ag Guide*, then the IACUC will need to ensure that it is properly constituted and may need to add a member with agricultural animal experience.

Ultimately, the site visitors did not overstep their authority by recommending a mandatory item for correction despite

the IACUC claim that it did not have jurisdiction over the study. The *Guide*, *Ag Guide*⁴, and ACLAM⁵ all state that a

facility shall provide adequate veterinary care, which includes timely and accurate methods for communication of any abnormalities or concerns about animal health to the attending veterinarian. Finally, AAALAC has had a long standing policy of following animal ownership as a mechanism for determining inclusion in the accredited animal care and use program. Since it is assumed that Dr. Zymansky's llamas are institutionally owned animals, according to AAALAC they would be included in the accredited animal care and use program. In addition, though the College of Agriculture may not be part of the currently "accredited unit", the llamas are housed within the accredited program and may impact the health and welfare of the institutionally owned animals and may be reviewed during the site visit⁶. □

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Published online: 22 January 2019
<https://doi.org/10.1038/s41684-018-0222-5>

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3. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. 8th edn, (National Academies Press, Washington, DC, 2011).
4. Federation of Animal Science Societies (FASS). *Guide for the Care and Use of Agricultural Animals in Research and Teaching*. 3rd edn. (Federation of Animal Science Societies, Champaign, IL, 2010).
5. American College of Laboratory Animal Medicine. Position Statement on Adequate Veterinary Care. <https://www.aclam.org/about/position-statements>
6. AAALAC International. Frequently Asked Questions. Animals Included in the AAALAC International Accredited "Unit". #1. Ownership. https://www.aaalac.org/accreditation/faq_landing.cfm#A1

A WORD FROM OLAW AND APHIS

In response to the issues posed in this scenario, the US Department of Agriculture-Animal and Plant Health Inspection Service (USDA-APHIS) and the National Institutes of Health-Office of Laboratory Animal Welfare (NIH-OLAW) provide the following clarifications:

In this scenario, a llama producing antibodies for federally funded research to study reproductive efficiency in dairy cows is found in need of veterinary care by AAALAC site visitors. In addition to a lack of veterinary care, the site visitors raise serious concerns about the lack of IACUC review of the research and the intensity of animal monitoring.

NIH-OLAW response

As noted by other reviewers, it is an institutional responsibility to provide care for all animals, not just those housed in areas listed on the Animal Welfare Assurance or supported by the Public Health Service (PHS) or National Science Foundation¹. The institution must also ensure that any standards that might not be consistent with PHS Policy do not affect or pose risks to PHS-supported activities². As the scenario fails to identify the source of the federal funds, the specific requirements of the granting agency for the conduct of research with animals are undetermined. However, the US Government Principles mandate that all federal agencies conducting or supporting research with animals ensure that veterinary care is provided³.

USDA-APHIS response

The Animal Welfare Act's (AWA) definition of "animal" excludes farm animals used

or intended for use as food or fiber, or intended for use for improving animal nutrition, breeding, management, or production efficiency⁴. The AWA regulations define "farm animals" to include llamas. Here, the institution is using the llamas to support research in dairy cows for the purposes of improving production efficiency. The use of the llamas for this purposes excludes them from the definition of "animal" and AWA regulatory requirements. Although there are no applicable AWA regulatory requirements, USDA supports the position that institutions using animals for research purposes should provide such animals with adequate veterinary care. □

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Published online: 22 January 2019
<https://doi.org/10.1038/s41684-018-0222-2>

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3. Office of Science and Technology Policy. Federal Register, May 20, 1985, Vol. 50, No. 97. [FR Doc. 85-12059]. U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. Found on line at: <https://olaw.nih.gov/policies-laws/gov-principles.htm>.
4. The Animal Welfare Act Section 2132g https://www.aphis.usda.gov/animal_welfare/downloads/AC_BlueBook_AWA_FINAL_2017_508comp.pdf

Oversight should be uniform and consistent

In its 'Rules of Accreditation,' AAALAC discusses the topic of 'contiguous facilities'¹. To paraphrase: when programs being evaluated by AAALAC have contiguous animal care and use facilities (e.g., same floor or building) which are assigned to other units not being evaluated, "(t)he extent to which contiguous facilities are evaluated is at AAALAC International's

discretion and depends mainly on whether facilities and practices within the contiguous facilities have an effect on the facilities and programs under primary AAALAC review." Thus, it appears that the site visitors encountered conditions within the 'llama barn' they felt could have an effect on the program being evaluated, and were within their authority to recommend a mandatory

item for correction based upon the organization's stated rules that are on record.

PHS Policy mandates a similar policy in that U.S. institutions conducting PHS-supported activities "...must ensure that any standards that might not be consistent with PHS Policy do not affect or pose risks to PHS supported activities"². Thus, even though AAALAC uses the *Guide*³ as a

primary standard for evaluating animal use programs⁴, the site visitors would also have been familiar with PHS Policy and cognizant of potential risks posed by practices or conditions that were external to a program that the PHS-supported activities were being conducted under. Point being—oversight of the llama study was performed by the

College of Agriculture (Ag College), which was not a component of the animal use program being evaluated by AAALAC.

The university's current policy allows some farm animals to be exempt from IACUC review and oversight based upon definitions provided under the Animal Welfare Act Regulations (AWARs; §1.1, Animal)

and the AWA (§2132.g). This was the basis for why the IACUC thought the llama study was outside its purview. But this wasn't an appropriate response since this attitude could inadvertently lead to a "not my job" type of culture that would lead to other incidences of unnoticed animal health issues. Ideally, and to avoid appearances of differential treatment of animals cared for within its animal use program, the University should institute a uniform policy of IACUC oversight that covers all animals, regardless of how it's used in research, testing, or teaching.

The site visitors insisting that Dr. Zymansky's llama work come under IACUC review was understandable from the perspective of wanting to establish uniform oversight within the program being evaluated for accreditation, which in turn promotes the minimization of animal pain and distress. But other discoveries during the site visit could have precipitated this request. E.g., the visitors may have felt that the llama-antibody work was biomedical in nature, eliminating the exemption the Ag College may have been claiming per certain definitions given in the AWA and its regulations. Or maybe the visitors learned that the antibody work received PHS-support, since it was stated that the BIV study was funded by federal government grants (plural). The BIV study directly involving dairy cows could certainly be considered agricultural in nature. The use of the llamas to produce the antibodies that support the dairy cow research seems biomedical in nature. There should be a written institutional policy to address such nuances—e.g., if the end goal of the use of an animal is to benefit another species, that research should be categorized as biomedical. □

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Published online: 22 January 2019
<https://doi.org/10.1038/s41684-018-0223-4>

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3. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. (National Academies Press, Washington, DC, 2011).
4. AAALAC International. AAALAC International's Reference Resources. <https://www.aalac.org/accreditation/resources.cfm>

A WORD FROM AAALAC INTERNATIONAL

AAALAC International appreciates the opportunity to engage in this dialogue and to offer a response to this hypothetical scenario. As defined in our Mission Statement (<https://www.aalac.org/about/mission.cfm>), AAALAC International is a voluntary accrediting organization that enhances the quality of research, testing, and education by promoting humane and responsible research animal care and use through the provision of advice and independent assessments to participating institutions, and accreditation of those that meet or exceed applicable standards. Further, AAALAC works with institutions and researchers to serve as a bridge between scientific progress and animal well-being. This is done through AAALAC International's voluntary accreditation program in which institutions using animals in research, testing and education demonstrate that they meet the minimum standards required by law and are implementing global standards established by AAALAC to achieve excellence in animal care and use.

Each AAALAC International site visit is unique and may offer subtle variations in oversight, veterinary care, animal husbandry, occupational health and safety, etc., depending on the specific context of the animal care and use program. The written Program Description (<https://www.aalac.org/programdesc/index.cfm>) is designed to elicit responses that provide a comprehensive overview of the entire Program covered by the accreditation. AAALAC International encourages institutions to contact the AAALAC office with any questions regarding what Program components must be included in the accredited "unit" and consequently included in the Program Description. Fundamentally, AAALAC International uses institutional animal ownership to determine which animals are included in the application for, or renewal of, accreditation. All animals owned by the applicant or accredited unit must be

included in the Program Description for assessment by the AAALAC International site visit team. Animals that are not owned by the accredited unit, but are housed in the accredited program and may impact the health or welfare of the institutionally owned animals or the occupational health and safety of personnel, may be reviewed during the site visit. The scope of animal ownership may include animals housed in multiple sites or remotely (e.g., contract research organization, satellite facility, temporary housing). The concept of animal ownership is highlighted in an AAALAC "Frequently Asked Question" (https://www.aalac.org/accreditation/faq_landing.cfm#A1) and further communicated in an in-depth article on this particular subject (page 6), available for downloading from the AAALAC International Web site (https://www.aalac.org/publications/Connection/Spring_2003.pdf).

In the hypothetical example, the llama was under the purview and ownership of the College of Agriculture, and was not part of the accredited program (Colleges of Medicine and Veterinary Medicine). There was no indication the llama was in proximity to the animals that were part of the accredited program, which potentially would have had a negative impact on their welfare. The site visitors provided the barn manager with information that would allow subsequent follow-up with the veterinary staff to ensure the llama was appropriately examined/treated. This observation by the site visitors and communication with the barn manager is an example of the professional, collegial nature of AAALAC site visits that is intended to promote both animal welfare and high quality science. □

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Published online: 22 January 2019
<https://doi.org/10.1038/s41684-018-0226-1>

Fair ball-in the park

This reviewers' reading of the scenario assumes: (1) the "Research Committee of the College of Agriculture" (COA) is not a separate IACUC committee, and (2) that exemption of IACUC oversight of research "on and for the benefit of agricultural animals" maintained by the Schools of Medicine and Veterinary Medicine also reflects the position of the COA. If so, then the rationale for exclusion of oversight is likely based upon the definitions in the *Animal Welfare Act* that "Federal facilities, elementary and secondary schools, and agricultural research institutions" are exempt, and that nanobody production is a use to "improve animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber."

Did the schools respond appropriately? No. The *Guide for the Care and Use of Agricultural Animals in Research and Teaching (Ag Guide)*¹ requires an IACUC; presumably, the COA's Research Committee is not such a committee. As a research university receiving public funding, adherence to the principals of the Ag Guide should be the minimal benchmarks. These are enumerated in its first paragraph: "Because a variety of management systems and physical accommodations may be used for agricultural animals, an understanding of the husbandry needs of each species and of the particular requirements of agricultural research and teaching is essential for an effective institutional

program of agricultural animal care and use. Critical components of such a program should include: 1) clearly established lines of authority and responsibility; 2) an active Institutional Animal Care and Use Committee (IACUC); 3) procedures for self monitoring of the IACUC through semi-annual review of programs and facility oversight by the institutional officer; 4) appropriately maintained facilities for proper management, housing, and support of animals; 5) an adequate program of veterinary care; and 6) training and occupational health programs for individuals who work with the animals."

Is this biomedical or agricultural research? Llamas are defined by the USDA as "farm animals" when used solely for work or pack purposes. Antibody production (nanobody) is neither food nor fiber research but could be interpreted as being used "for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber" as described for Dr. Zymansky's research scope. Absent more specific details of the research, I am conflicted to classify this as agricultural despite BIV being a disease of agricultural animals. I suspect the USDA would consider this to be nanobody production, not consider the ultimate use of the nanobodies, and classify the research as biomedical. Depending on the antigens and adjuvants used the final disposition of these animals

may also be regulatory restricted (i.e. exclusion from human food chain) with such oversight best assured by an IACUC supported by other institutional expertise such as a Biosafety Officer and Attending Veterinarian.

Did the site visitors overstep their authority? No. The cause of the skin condition was not known or documented and as such posed a potential threat to the other animals in the barn. The lack of awareness by the barn manager is a possible indicator of inadequate daily health assessment, caretaker training, or veterinary oversight. That the veterinarians contacted Dr. Zymansky does not ensure adequate veterinary care. The clinical veterinarian and attending veterinarian should have been contacted. Even if the llamas are "agricultural," there is a potential impact on biomedical animals and thus IACUC oversight is appropriate. Oversight of all animals must be provided regardless of whether they are biomedical or agricultural. □

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Published online: 22 January 2019
<https://doi.org/10.1038/s41684-018-0224-3>

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