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Rationale for new model development

Dr. Bruce Hampton, an orthopedic surgeon, was a high-energy researcher who always had a new project on the horizon. Hampton had been using rabbits as his animal model for nearly two decades. The cost of purchasing and housing rabbits was increasing every year, whereas his federal grant funding was moving in the opposite direction. To compensate for this discrepancy, Hampton decided to try to develop a rat model of the orthopedic condition he was studying. The process he proposed to the Great Eastern University IACUC was to use five rats in a pilot study to determine whether the surgical modifications he made on rabbit femurs

could be duplicated and remain effective in the smaller animal model. If the surgical procedures proved to be effective, he then would move ahead with the various treatment methods that he was studying.

At the next full committee meeting of the IACUC, Hampton's protocol was presented by Dr. Alex Burke. Burke pointed out some minor inconsistencies, but overall, he strongly supported Hampton's plan for developing a new, efficacious and much less expensive animal model. Only one IACUC member questioned the proposed new model, asking why five rats had to be subjected to a major survival surgical procedure when there

already was a perfectly acceptable model for Hampton to use. The response from Burke was that without the new model, Hampton might not have sufficient funds to continue his research, and that in any case, a new animal model is always a welcome addition to the research armamentarium.

What is your opinion? Should the IACUC consider the cost of using rabbits as a factor in its discussion of Hampton's protocol? Should the rationale for the development of the rat model be based on its possible need to sustain Hampton's research, or is the general concept of having a second model available a sufficient reason?

RESPONSE

Not so fast

Patricia A. Preisig, PhD &
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The task at hand for the Great Eastern University IACUC was to evaluate a pilot study. Although research cost and career sustainability are valid concerns for investigators, neither should be the sole or a major factor influencing the IACUC's discussion. Assuming that the rabbit model was both scientifically justified and appropriate for Hampton's studies during the preceding two decades, the IACUC's deliberation of the pilot study request seems to be incomplete.

Irrespective of Hampton's incentive for developing a new model, the IACUC must require him to present a logical rationale for doing so, even for a pilot study¹⁻³. Pilot studies are often discrete feasibility studies that are limited in animal number. Nevertheless, a proposed pilot study must be accompanied by a scientific rationale and a confirmation that it does not unnecessarily duplicate known work. Hampton's request should have included the intellectual basis for proposing that development of an alternative model is a logical approach to

advancing the project in the face of limited resources and an adequate justification for the number of animals proposed to be included in the pilot study. The rationale could include physiological, anatomical or mechanical features of rodents; advantages and disadvantages of a rodent model; or the homologous and analogous characteristics of the relevant tissues and systems in rodents compared with rabbits, but it must provide enough information for the IACUC to determine whether the pilot study is justified. If the focus of the discussion was on the factors of cost and research program sustainability, then the IACUC's deliberations were not in keeping with its responsibilities.

If the pilot study is approved and Hampton later submits another protocol proposing to use additional animals to advance the model, then that request should include additional justification based on the pilot study results, with some indication as to whether the surgical manipulation of the femur could be duplicated and remain effective in the smaller animal. Such justification could include the potential for the rodent model to meet some or all of the project goals, including species-specific requirements; a discussion of the impact of combining data from different species on the interpretation, validity and quality of the data; and a description of the model's value toward advancing scientific

knowledge and to society in the context of the principles of the 3Rs⁴.

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. Animal Welfare Act and Animal Welfare Regulations. Part 2, Subpart C, Research Facilities.
3. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).
4. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen, London, 1959).

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RESPONSE

The economy of research

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Laboratory animal regulations are thoroughly silent on the financial evaluation of research protocols. The Animal Welfare Act¹ nowhere

A word from OLAW

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

This column poses several questions: Should the IACUC consider the cost of using a particular species in its discussion of a protocol? Should the rationale for the development of a new model be based on fiscal factors? Is having a second model for a particular disease or condition a sufficient rationale?

Although financial considerations are a necessary step in the pursuit of a scientific inquiry, decisions involving costs of research are made by bodies other than the IACUC. The peer review of grant applications evaluates the proposed model; if it is found meritorious, an award is made. Department heads at research institutions often make decisions on support for research models funded locally. A separation between the fiscal decision-makers and the body that oversees animal welfare relieves the IACUC from this responsibility and focuses the committee's efforts on considering US Government Principle III and the appropriateness of the species to obtain valid results¹. OLAW has provided similar guidance on the choice of species in stating, "It is the IACUC's responsibility to review and confirm that a sound, objective and logical reason has been provided... prior to approving the use of animals for the research proposal"^{2,3}.

Although cost must not be the primary reason for proposing a new model, it certainly may influence the investigator's practical considerations, as does the availability or complexity of a given model. Likewise, alternative model development is fundamental to innovation and the creative scientific pursuit. Although the investigator neglected to include important scientific considerations in his proposal to justify his new model, a request for a modification addressing the committee's concerns should easily rectify the situation, as highlighted by the scenario reviewers.

1. Interagency Research Animal Committee. US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (US Department of Health and Human Services, Washington, DC, 1985).
2. Gipson, C., Holt, M.A. & Brown, P.A. A word from USDA, FDA and OLAW. Deciding which animals to use. *Lab Anim. (NY)* 37, 295 (2008).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals—Frequently Asked Questions*. Protocol Review, Question No. D7. (US Department of Health and Human Services, Washington, DC, 2006; revised 2013).

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Eastern University to fund creation of the appropriate vivarium for rabbits? The dichotomy becomes exceptionally stark when one considers the use of expensive species (nonhuman primates, canines or ruminants) or animal modeling instrumentation such as advanced imaging or telemetry. Surely many IACUC protocols are approved with the often unspoken knowledge that the most scientifically accurate and strictly 3Rs-conformant animal model may not be the most economically practical, reasonable or even achievable. In a nod to the concept that money factors into decisions on animal welfare, the Office of Laboratory Animal Welfare³ has recently approved the use of non-pharmaceutical-grade pentobarbital, ruling, "Recent exorbitant cost increases of pentobarbital have placed it logistically into the unavailable category." Though perhaps not routinely recognized or consciously considered, the economy of research is a consistent underlying feature of animal use protocol management.

Despite the financial realities of research, the focus should shift from speculations on fiscal conservatism to the specific scientific and animal welfare benefits of the protocol at hand. In this scenario, we feel there is much sound scientific reasoning and valid animal welfare motivations to pursue the rat model: greater accuracy owing to increased bone density in the rat⁴; greater versatility for future genetic manipulation; reduced regulatory oversight and greater accessibility as the rat is not covered by the USDA; and greater amenability to advanced imaging techniques owing to smaller body size. Such justification is what the protocol reviewer, Burke, hints at when he asserts, "...a new animal model is always a welcome addition to the research armamentarium." Therefore, we suggest that although economics may be a factor in the decision to pursue the new animal model, it is not the sole focus. Because the endeavor has strong scientific merit and holds up well under scrutiny of animal welfare concerns, the IACUC should feel justified to approve the pilot study.

1. Animal Welfare Act.
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

addresses economic considerations, and the *Guide for the Care and Use of Laboratory Animals*² tackles the issue only tangentially: "cost savings alone is not an adequate reason for performing multiple major survival surgical procedures." It seems IACUCs are largely left to their own discretion in making decisions in this regard and, in general, have taken the position to avoid using financial considerations as the sole or a primary factor in approving protocols.

Nevertheless, IACUCs should appreciate that financial considerations are intimately intertwined and often inseparable from the protocol approval process. The truth of this is found in the realization that research time, equipment and husbandry costs are

economic parameters and play a large part in driving development of animal models. In fact, one could argue that the explosion in the use of rodent models over the last few decades is driven by the motivation to reduce costs: rodents require less space and less food and have shorter lifespans than some larger animals.

Let us suppose for a moment that Hampton is a new investigator on a limited budget and that his facility does not have the space, expertise or capability to properly house and care for rabbits. Assuming that a well-established rabbit model suitable for his research does exist, should the IACUC disapprove development of the new rat model and require Hampton or Great

3. Brown, P., Clarke, C. & Newcomer, C. Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals. OLAW Online Seminar (1 March 2012). <http://grants.nih.gov/grants/olaw/120301_seminar_transcript.pdf>
4. Bagi, C.M. *et al.* Comparative bone anatomy of commonly used laboratory animals: implications for drug discovery. *Comp. Med.* **61**, 76–85 (2012).

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RESPONSE

Questionable intentions

Brad Ahrens, DVM

Money is a funny thing that people can't always agree on. Some would say it makes the world go 'round, while others believe it's the root of all evil. My mom seems to think it doesn't grow on trees, and the idea that it can buy happiness has always been a matter of vigorous debate (though it certainly makes misery more comfortable). However, one thing I think we can all agree on is that it makes a lousy motive for justifying the loss of life.

Animal research is not something that is done for the sake of convenience; it's done out of necessity. Using a computer

model or cells in a test tube is certainly cheaper and more convenient than performing surgery on a living animal. In many applications, however, animal models are a far superior means to understand processes in the context of their interactions with other systems in a complex organism. The selection of an animal model should never be made on the basis of convenience or cost; it should be made based on extensive knowledge of the problem being studied and the biological and physiological responses necessary to create an effective experiment. In Hampton's case, developing a novel animal model because of the monetary need to sustain his research is reprehensible. Even the general concept of having a second model available is not a sufficient reason to do unnecessary harm. But in this instance, he may incidentally be doing a good thing for the wrong reason.

In his haste to find a bargain by developing a small rodent model of his orthopedic research, Hampton may be unwittingly employing the principles of the 3Rs that guide the responsible use of animals in research¹. Because they have thin, lightweight bones; saltatorial locomotion; and excessive musculature, rabbits may be more likely to develop complications when being used as orthopedic models compared with cursorial species such as rodents. Hence, the development of a rodent model for Hampton's research could be considered a refinement.

It is ultimately the responsibility of the IACUC to look out for the best interest of the animals, and in this case, replacing rabbits with rats is a good idea. Although money may be Hampton's primary motive, this should matter little to the IACUC, whose members should recognize the numerous potential benefits of this endeavor. I would imagine that some IACUCs might have even advocated such a substitution upon initial review. Development of a rat model could not only benefit Hampton by reducing expenses but could also benefit the institution by reducing the need to house and care for additional USDA-covered species. Hampton's pilot study might also offer a major benefit to the field of orthopedic research if he is successful in establishing a new, simpler, model for a condition previously thought to be best studied in rabbits.

Although Hampton's rationale for the development of a rat model may have been less than desirable, I think the outcome is a positive one. Regardless of intentions, "[t]he time is always right to do what is right" (in the words of Martin Luther King, Jr.), and the IACUC should move forward with this proposal.

1. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen, London, 1959).

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