Pressure's on: is it time to move ahead with nonhuman primates?

As the father of a child who succumbed to globoid cell leukodystrophy (Krabbe disease), Dr. Leon Martel was passionate about his research to find a cure for this autosomal recessive neurological disorder, for which there is no satisfactory treatment. Martel's initial gene therapy research at Great Eastern University used mice for modeling the disease, and he found increased longevity, improvement of clinical signs, and no adverse side effects attributed to the therapy. He then progressed to treating affected dogs. Bone marrow transplantation, combined with or without gene replacement therapy, showed similar early indications of success, although some signs of mild liver and neural toxicity were found postmortem in two treated normal control animals.

Martel's work was published and presented at meetings, which eventually led to a phone call from his U.S. senator, who served on the Health, Education, Labor and Pensions Committee. The senator urged Martel and the college dean to push ahead with testing on rhesus monkeys as these nonhuman primates were previously used for Krabbe disease research. The senator's altruistic goal was to have Martel accumulate enough data for the school to apply for accelerated approval of the procedure from the Food and Drug Administration and then begin clinical trials with afflicted human children. Nevertheless, after initial talks between Martel, the dean, and the chair of the IACUC, it became obvious that Martel and the IACUC chair were hesitant to move forward with nonhuman primate studies until more work was done to elucidate the cause of the mild toxicity seen in the dog studies.The dean, under continuing pressure from the senator, argued that the mouse studies showed no toxicity at all and that the mild toxicity in dogs had no overt clinical impact and was found in only two of the twelve control animals. The discussion led to a key question: If affected and nonaffected monkeys were to be studied, what clinical signs would be used to determine if there was either improvement or toxicity to the animals? Clinical signs in affected monkeys were known[1], but clinical signs in normal monkeys subjected to Martel's gene therapy technique were unknown. Martel feared that given the infrequent and mild aberrant findings in dogs and the long life span of rhesus monkeys, there may no simple way for him to determine a clear and meaningful study endpoint.

If you were Martel, how would you deal with the pressure from the dean? Would you submit a protocol amendment to add monkeys to the study? Is there any federal regulation or policy that prohibits the senator from pressuring the dean, Martel, or the IACUC? ❐

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Animal welfare is the primary concern

This scenario illustrates one of the more difficult situations encountered by an IACUC: the balance between animal welfare and scientific progress. Martel developed a hopeful treatment for a rare but very serious disorder that affected his own child. After a promising study in mice he moved on to testing his treatment in dogs. Although successful, two of the control animals showed signs of mild liver and neural toxicity on necropsy. Martel was contacted by his U.S. Senator, who urged him to move to a rhesus monkey model so that the treatment could progress to human trials[1,2].

Martel and the IACUC chair were hesitant because of the issues found on the dog necropsies and a concern over whether they would be able to identify a good study endpoint in a long-lived animal, such as a macaque. The senator urged Great Eastern's dean to encourage the nonhuman primate (NHP) project and the dean is now pressuring Martel and the IACUC chair to move forward.

We agree with the PI and the IACUC chair in this case that caution is indicated. The liver and neural toxicity in canine subjects is concerning because it was found in treated members of the control group, not affected animals. It warrants further testing to isolate the cause before moving to the (NHP) model. The Animal Welfare Act (§2143,b,1) charges the IACUC with representing "society's concerns regarding the welfare of animal subjects used" at the institution. Animal welfare must be the primary concern of any IACUC. Further, PHS Policy IV.C.8 states: "Applications and proposals that have been approved by the IACUC may be subject to further appropriate review and approval by officials of the institution. However, those officials may not approve an activity involving the care and use of animals if it has not been approved by the IACUC." The authority to approve this work resides only with the IACUC. While both the dean and the senator may have the best intentions, their attempts to pressure the PI and the IACUC chair to begin work that neither is comfortable with should not be allowed. Martel and the IACUC chair should enlist support from the campus veterinarian and the Institutional Officer if needed to ensure the IACUC is able to do its job without any outside pressure. ❐

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Never do anything against conscience, even if the state demands it

Academic research is a high stress environment, with pressure to meet deadlines, manage lab activity and personnel, and maintain regulatory compliance. As Dr. Martel, I would be very uncomfortable with actions of the dean and the external political demand placed on my research

If the dean is receptive, I would first voice my moral and ethical conflicts with moving to the nonhuman primate (NHP) model; however, if this argument fails, I would attempt to outline the additional risks and costs associated with NHP research (i.e., costs to renovate facilities and train care staff; costs of maintaining animals as well as rehoming or retirement costs for NHPs; and possible attention from activist groups). The dean should be aware that the IACUC will likely identify these same ethical and regulatory concerns and the final decision to approve the NHP research lies with the IACUC. Per the U.S. Animal Welfare Regulations[1], institutional officials "may not approve an activity involving the care and use of animals if it has not been approved by the IACUC."

If this approach failed, my next step would be to contact my department head, institutional official, institutional legal office, faculty senate representative, or other relevant office to voice my concerns and to determine if the dean may have a conflict of interest. I would document all interactions so that if the dean's actions violate any laws, including the Animal Welfare Act and Regulations, I would have records to report the violations. Fortunately, in case of attempted retaliation, I would be protected by the Animal Welfare Regulations[2], which states, "no facility employee, Committee member, or laboratory personnel shall be discriminated against or be subject to any reprisal for reporting."

As Martel, I would not submit an amendment to add NHPs to the study. This would be a significant change according to OLAW and must be reviewed by the IACUC. While no federal regulations prevent me from submitting an amendment, I have spoken with the IACUC chair, and we are hesitant to move forward until I am ready to conduct the NHP research. I don't feel comfortable with assuring that the rhesus is an appropriate species, something I know the Animal Welfare Regulations requires me to include in my proposal. In

A WORD FROM OLAW AND APHIS

In this scenario, a researcher who developed a promising new treatment in mice and dogs for a genetically transmitted, fatal disease in humans is pressured by a U.S. senator to quickly conduct similar studies in rhesus monkeys. The researcher and the Institutional Animal Care and Use Committee (IACUC) must decide a course of action when faced with continuing pressure from the university dean and the senator amid concerns over mild toxicity seen in the dog study.

In response to the issues posed in this scenario, the National Institutes of Health – Office of Laboratory Animal Welfare (NIH-OLAW) and the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS) provides the following clarification:

A Word from NIH-OLAW

The PHS Policy states that activities approved by the IACUC may be subject to further appropriate review and approval by officials of the institution. However, those officials may not approve an activity involving the care and use of animals if it has not been approved by the IACUC[1]. To address the current situation, the IACUC chair and the researcher should consider educating the dean and the senator about the necessary legal safeguards that require a thorough review of the potential harms of the research balanced with the potential benefits. This is critical considering the unknown cause of the toxicity found in normal control dogs. In addition, the PHS Policy and the *Guide for the Care and Use of Laboratory Animals* require research personnel to have sufficient training or experience to conduct procedures on the species used[1,2]. It is not clear if Martel or his staff have the requisite qualifications and expertise to work with monkeys. Lastly, for NIH-funded research, substitution of one animal model for another from what was identified in the approved project is a change in scope that requires prior approval from the NIH awarding Institute or Center[3]. If the researcher decides to begin work with monkeys and the change in scope is approved, conducting an IACUC-approved pilot study may delineate clinical signs useful for humane and scientific endpoints before proceeding with a full study.

A Word from the USDA-APHIS

The Animal Welfare Act regulations (AWAR) define the roles and responsibilities of the IACUC, Principal Investigator (PI), and the Institutional Official (IO); and ensures a Federal funding agency receives information on the work it financially supports[4]. Under the AWAR, the IACUC is required to review and approve an animal activity or a significant change to an on-going activity before the work begins, but it is not permitted to describe methods or set standards for the design, performance, or conduct of actual experimentation conducted by a research facility[5,6]. As a result, the PI in this scenario is permitted to decide whether or not to add nonhuman primates to the study as long as the work is in compliance with the requirements as set forth in the regulations and approved by the IACUC[7,8]. The dean, who is serving as the IO, has the authority to conduct an additional review of an activity approved by the IACUC but no authority to request an activity that was not approved[9]. The senator in this scenario has no authority over the study because he is not a member of the IACUC or representing a funding Federal agency. In light of the requirements, it behooves all parties involved to work together within the context of the regulations to achieve optimal research findings. ❐

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9. Code of Federal Regulations, Title 9, Chapter 1, Subchapter A — Animal Welfare: Part 2 Regulations. §2.31(d)(8)

terms of relative replacement (described in *The Guide*[3]), I don't want to proceed with the NHP studies until I have learned all I can from my canine work. The next amendment I submit will be to add the additional animal numbers and tests I need to further elucidate the cause of the mild toxicity observed.

Lastly, the Animal Welfare Act[4] authorizes the Secretary of Agriculture of the United States or his representative to promulgate humane handling, care and treatment of animals at research facilities, but it does not authorize the Secretary to promulgate rules, regulations, or orders with regard to the design, outlines, or guidelines of actual research or experimentation by a research facility. Additionally, the U.S. Senate has a code of official conduct that the senator may have violated with his actions. The senator himself has no authority to determine the course of the research. ❐

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A Senator's altruistic overreach

We can appreciate that Martel is faced with a challenging ethical dilemma, having lost a child to globoid cell leukodystrophy (GCL, Krabbe disease). It is without question that Martel is eager to move his GCL gene therapy research forward at Great Eastern University. However, we agree that his concerns regarding the toxicity findings warrant a judicious approach to investigate these outcomes. He is justified in not moving forward with the macaque model until the canine studies have been thoroughly investigated, per the guidance outlined in the FDA's *Guidance for Industry – Preclinical Assessment of Investigational Cellular and Gene Therapy Products* and *Human Gene Therapy for Rare Diseases*.

While the traditional approaches to preclinical drug development are not necessarily applicable for gene therapy development, investigational studies require consideration of new types of safety issues, including: formulation; identification of potential vector or transgene toxicities and physiologic parameters helpful in the guidance of clinical monitoring; the persistence of vector and the expressed transgene; the potential for insertional mutagenesis or oncogenicity and the scope of tissue distribution, including gonadal tissues that may impact germline transmission[1,2].

In light of the liver and neural toxicities found in two of the control treated dogs, we feel that Martel not only has an obligation to explore these findings but could also increase the scientific merit of his study design to move forward with FDA preclinical nonhuman primate studies by investigating the potential causal factors for the toxicities noted. Moreover, if there is potential for germline transmission, Martel will need to consider expanding his study design towards a longer, multi-generational study to assess the potential impact to non-targeted genes and persistence of the expressed transgene in offspring. We feel that the canine model is advantageous to explore these potential safety considerations, as dogs produce greater numbers of offspring at each generation than primates, have shorter lifespans, which aid in studying longer term effects and typically allow for greater ease of clinical management and monitoring than do primates.

The U.S. Senator's seemingly altruistic interest in accelerating the timeline for Martel's studies is bringing significant attention and pressure to the dean at Great Eastern University, which is unfortunately trickling down to Martel. We are not aware of any regulation or policy that precludes governmental overreach by the senator in this situation. However, assuming that the dean is also the Institutional Official (IO), the IACUC's authority to perform duties must exist without undue interference from the IO[3,4]. We would advise Martel to stand behind his concerns and convey the potential safety considerations, inherent to gene therapy research that should be explored. This safety assessment is not only critical prior to moving into clinical trials, but it may help to refine the study design of the primate model which could potentially reduce the number of primates required on study. Results from assessing the potential safety risks of gene therapy in the canine model may also more quickly meet the criteria to support progression to early-phase clinical trials. With a scientifically sound study rationale and an understanding of the safety considerations for gene therapy products, the dean may want to seek the Senator's support to first expand the canine studies prior to moving into a preclinical primate model. ❐

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