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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