ENDOCRINE SOCIETY
Hormone Science to Health

Endocrine Society Comments
Re: NOT-OD-20-130
Request for Information (RFI): Enhancing Rigor, Transparency, and Translatability to Improve Biomedical Research Involving Animal Models

Submitted August 21, 2020.

Actions NIH can take to facilitate the translatability of animal research to human biology and disease.

We reiterate the importance of considering sex as a biological variable in animal research. The Endocrine Society maintains that a significant component of the rigor and completeness in research is the investigation of sex-specific effects and that consideration of sex as a biological variable is an important component of efforts to ensure that clinical trials are based on rigorous preclinical research in animal models.

The implementation of the 2015 policy mandating the consideration of biological sex in NIH-funded research was an important achievement, particularly for preclinical research that is meant to inform the development of therapies and interventions for humans. NIH should analyze the effect of this policy on research practices and determine whether additional guidance for reviewers or researchers is required, for example to encourage sex-disaggregated analysis for research studies. Where the policy has had effects on research culture, this could serve as a model for other efforts to improve rigor and translatability. NIH should also consider expansion of the NIH's Sex & Gender Administrative Supplement Program, to ensure that research programs are adequately funded to more fully explore SABV research.

How research culture drives the choice of animal models.

There are various drivers of research culture influencing decisions that impact rigor and reproducibility, including financial considerations and career pressures. While not all drivers are under the control of NIH, review panels have an enormous influence on research culture and practices. For grants that are oriented towards basic research and relatively removed from clinical application, an emphasis on translatability may not be appropriate. One consequence of an emphasis on translatability and significance in grant applications is that researchers utilizing model organisms that are not viewed as recapitulating human disease are disadvantaged, even though this same animal model might be more appropriate for the investigation of a fundamental biological question or pathway. Rather than focusing exclusively on translatability, in the

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vertebrate animals section of a research grant, investigators should be encouraged to describe why they chose that animal model and why that model is specifically useful to address their research question.

Researchers should also be encouraged to identify and use the correct experimental approach to address their research questions. Comparative endocrinology has a critical role in discovery-based research related to hormone biology and signaling. Comparative animal models for endocrine disorders, such as spontaneous genetic mutations in larger animals, are often more relevant to human disease than other more common or inexpensive animal model systems such as rodents.

How preregistration, the process of specifying the research plan in advance of the study and submitting it to a registry, would impact animal research including improving the quality of scientific research.

We do not support proposals aimed at mandating preregistration for animal studies. Animal research already is subject to laws and regulations with substantial administrative requirements; our members are concerned that preregistration would introduce additional administrative burdens for researchers and have unintended negative consequences on scientific discovery in general. Endocrine Society members have experienced challenges with preregistration in the context of clinical research using clnicaltrials.gov, and we are concerned that similar barriers would be encountered in preregistration for animal studies.

Preregistration may not be appropriate for exploratory or basic research where investigators should have the freedom and flexibility to explore unexpected/novel results. We recognize that for clinical trials, especially large trials, where secondary analyses of large datasets are common and important, there is a clear benefit to preregistration. We do not envision a similar benefit to preregistration for research using animal models.

We encourage NIH to clarify any potential approach to preregistration before advancing specific policies, which should then be further discussed with the biomedical research community via a separate solicitation. Specifically, NIH should explain:

- what the goal of preregistration would be and what information would be captured;
- the anticipated time commitment and detailed expectations for the practical aspects of preregistrations for researchers using a variety of animal models and experimental approaches;
- how NIH's approach to preregistration would differ or not be duplicative of those efforts already undertaken by institutional oversight bodies such as animal care and use committees (IACUCs).

While preregistration is often considered in the context of hypothesis-testing and confirmatory experiments, would it be useful at other stages of the research process, such as the exploratory and hypothesis generating.

We do not anticipate that preregistration would be useful at earlier stages of the research process, including exploratory and hypothesis-generating research. We are concerned that preregistration would prevent researchers from exploring unanticipated new results and lines of investigation that often emerge during basic research studies.

How all researchers, including trainees, are educated in research design, statistical considerations, transparent research practices that are fundamental to rigorous animal research, and the role of the NIH in this training.

The role of NIH in training is important and the issues of rigor, reproducibility, and translatability are not unique to animal research. Generalizable modules for training and baseline research standards should be developed, but it will be important for NIH to partner with specialty organizations and scientific societies for discipline-specific guidance.

As an overarching consideration, NIH should be careful not to create or enforce standards that would be prohibitively expensive for under-resourced institutions to implement or create barriers to international collaborations. Standards and guidance should also be flexible to allow for creativity and innovation in research methodology.

How to encourage researchers to select or develop animal models with high utility and design experiments that have external validity to the clinical populations.

Researchers and funding agencies should be encouraged to work with disease specific philanthropic organizations to create disease models that have validity to their specific clinical populations. These organizations provide one of the biggest drivers of the search for appropriate disease specific models in general.