Alternative Thinking about Animals in Research

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Animals have been used as scientific research subjects since at least the 4th century BCE (Guerrini, 2003). Since then, there has been both support for and objections to that use. Some similarity between nonhuman animals and humans powers the arguments of both research advocates (who see animals as relevant models for human disease) and animal protectionists (who see animals as victimized, nonconsenting individuals). Taking into account both science and health care concerns, as well as to human and animal welfare, the authors of this commentary encourage the biomedical research community to ask at least three questions about the use of animals in research:

- Has animal-based research helped advance the understanding of basic physiological and pathophysiological processes, reliably identified toxic substances, and advanced human and animal health care?
- Has unchallenged reliance on animal-based research diverted resources from developing what might have and could become other methods of scientific investigation (nonanimal methods or new approach methods [alternatives]) that predict positive or negative health care outcomes with equal or greater effectiveness?
- Lastly, who or what groups of people can most effectively champion the utility of nonanimal methods and their potential to replace or significantly reduce animal use after a controversy lasting more than two millenia?

This commentary focuses on the third question.

History of Guidelines on the Use of Animals in Research

To understand how we have arrived at this present discussion in 2022, we will briefly focus the retrospectoscope on 1959. That year, William M. S. Russell and Rex L. Burch published their Humane Principles of Animal Research, which formally laid out a humane philosophy for conducting investigations using animal research subjects (Russell and Burch, 1959). Specifically, their principles—the "3Rs"—are the *reduction* of the number of animals used in experiments (with regard to statistical adequacy), *refinement* of experimental methods using animals for their comfort (coincidentally, this may deliver more reliable scientific outcomes, but this topic is outside the scope of this manuscript), and *replacement* of animals with either phylogenetically lower species or with nonanimal substitutes (Smith, 2020). Internationally, regulators adopted the 3Rs and sensibly formulated them for inclusion in the new research "law" each developed, which scientists were then required to obey. Over time, funders and institutions voted in support of these guidelines by incorporating a necessity for an animal use statement in submitted applications to conduct research using animal subjects. It should also be noted that the *vox populi* in the U.S. and Western Europe had a striking influence on legislation regarding animal use in laboratories.

The imperative to consider alternatives to animal use is included in the U.S.'s federal Animal Welfare Act, which subtextually recommends consideration of the 3Rs (USDA, 2022).

Sixty years after the publication of Russell and Burch's seminal text, American bioethicists David DeGrazia and Thomas L. Beauchamp (2019) observed that "Animal research currently lacks but needs a guiding ethical framework that can meet 3 demands," which they characterized as being "*ethically defensible*, which requires being able to withstand well-informed scrutiny from specialists in ethics, investigators in science. . . . *[P]olitically reasonable* in offering a realistic chance of acceptance by persons interested in the advancement of animal research, persons interested in rigorous protection for animals involved in research, and the interested public" and "must be *practically instructive* by offering sound ethical guidance—even if only at a general level—to practitioners in the animal research enterprise" (emphasis added). These authors noted "six developments," or principles that informed the establishment of their suggested ethical framework of general moral principles: "(1) growing public concerns about animal welfare; (2) advances in the scientific study of animals; (3) the development of animal ethics as a scholarly discipline; (4) significant gaps in the content of the 3Rs conception of animal research ethics; (5) growing concerns among scientists about the reliabil-

ity of nonhuman animals as models for humans; and (6) a persistent but unconstructive perception that fundamentally different moral perspectives on the ethics of animal research are irreconcilable."

Current and Future Directions

In the authors' experience, the deliberations of Institutional Animal Care and Use Committees (IACUCs) have mostly focused on reduction and refinement of animal-based methods due to comparatively limited exposure to replacement technologies (Marx et al., 2020). Indeed, current efforts by the National Academies of Science, Engineering and Medicine seek to engage diverse stakeholders around new ideas in animal research, including non-human primates (see NASEM, 2022a;b). As IACUC members learn more, they and the broader scientific community may derive value not only from animal-based investigations but also from the potentially more human-relevant alternative methodologies. An additional benefit to the latter is the reduced carbon footprint due to a reduction in husbandry and body disposal requirements attached to animal research.

In 2022, the scientific community is not only intellectually armed with guidance from both the 3Rs and the six moral principles enumerated by DeGrazia and Beauchamp, but with decades of experience in the United States, European Union, and United Kingdom for creating, developing, and validating the use of nonanimal methods. Further, some recent events point to the importance, if not urgency, of considering these alternatives.

During a June 2021 National Institutes of Health (NIH) meeting of the Advisory Committee to the Director (ACD) Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research, the group recommended that NIH should "charter a high-level working group on 'non-animal modeling systems in biomedical research,'" to

1. address how to meet critical needs when no animal model exists;
2. develop a framework and a process for assessing the human relevance of nonanimal models and their value in complementing or replacing existing animal models;
3. maximize innovation potential; and
4. convene and nurture this highly interdisciplinary emerging area (NIH, 2021).

The United States is not alone in having proponents of nonanimal methods in national levels of leadership. On September 15, 2021, the European Parliament counted a 667–4 vote in favor of a resolution to replace animals in regulatory testing, research, and education (Naujokaitytė, 2021). This was not a reduction or refinement vote but a vote for the full replacement of animals in these investigative and educational areas. The European Commission responded that it would not proceed with the development of an action plan toward fulfilling these ends, since it viewed the existing EU Directive for laboratory animal protection (2010/63/EU) as already sufficient for the purpose (it requires use of nonanimal methods, when possible) (EU, 2010).

Given these and other efforts, enough information has been exchanged and discussed to propose a logical next step. The authors of this commentary believe it is time to shift the focus of the biomedical research enterprise to the pinnacle of the 3Rs strategy—replacement—and return our attention to question three: "Who or what groups of people can most effectively champion the utility of these newer developments and their potential to replace or significantly reduce animal use?"

Cultivating Champions to Advance the Use of Alternatives to Animal Methods

In the authors' estimation, there are eight stakeholder groups that are most closely related to safety testing and biomedical research using both animals and nonaminal methods and therefore should be prioritized for participation in conversations and as champions for eventual policy changes:

- scientists
- industry
- federal regulators
- government funders
- venture capitalists
- venture philanthropists
- animal research advocates
- animal protectionists

The authors submit that meaningful conversations among these stakeholder groups would do much to resolve present misunderstandings and acknowledge shared problems. Further, they would serve to construct a common vocabulary for use in the initial and continuing dialogue aimed at advancing science, health care, and animal protection. Clearly, each group has its primary language and would need to exercise patience with others while learning theirs. It is an effort worth making because synthesizing the contributions from these broad-based stakeholder groups is a much better way to answer the question posed by the authors than by continuing to rely upon the comparatively narrow published opinions of past and mostly siloed activities. Additional stakeholder groups will ultimately benefit from the progress of these initial conversations, as well, including patients and their families, clinicians, and bioethicists.

A dialogue regarding this potential for alternatives and advances in animal research is a great and urgent undertaking, which requires a new type of open-mindedness,

multidisciplinary input, and philosophical commitment. To that end, the first Burroughs Wellcome Fund Microphysiological Systems Roundtable (March 15–16, 2022) seated key thought leaders from each stakeholder group in one place for this important conversation about the creation, development, reliability, translatability, and cost of nonanimal methods in safety testing and biomedical research (see also NASEM, 2021). This first in a roundtable series populated with the noted multi-stakeholder body served as an initial survey into these areas.

In terms of importance, the first roundtable addressed four immediate and specific aims:

1. identify support structures optimal for developing these new technologies and recognize any limiting factors to doing so;
2. determine how to realize the identified support structures and to mitigate potentially limiting factors;
3. recognize that whatever realistic timeline is estimated for regulatory approval and implementation of these nonanimal methods (as either partial or full replacement methods), the dynamics associated with acquiring new information may require revision of that timeline; and
4. establish a system of metrics for evaluating progress on that approximated continuum.

This conversation, along with the second (June 7-8, 2022), which focused on action items beneficial to advancing the field, and future roundtables, represents a novel cooperative of these relevant stakeholder groups that offers great promise to produce the joint recommendations for best exploring the existing safety testing and biomedical research landscape (EUSAAT Conference, 2022). If we draw inspiration from an oft-quoted African proverb—if you want to go fast, go alone; if you want to go far, go together—our multi-demographic constituency would travel farther along this exploratory route by going together than would any single group in going quickly. In the context of identifying best scientific practices and responsible resource use (finances, time, animal life), the importance of this collaboration cannot be underestimated. One tangible outcome from these initial discussions is the recognized need for ongoing convening of stakeholders internationally by a dedicated center or other infrastructure whose focus is on animal alternative innovation and best practices with the potential to provide catalytic investment for research support. In an age calling for optimized health care outcomes, reduced reliance on animal methods, and promotion of animal interests, isn't this what we all want?

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