Transparency and the 3Rs

Introduction

In *The Principles of Humane Experimental Technique* (1959), Russell and Burch proposed an applied framework to improve the treatment of laboratory animals while advancing the quality of science. They introduced and defined the terms *replacement*, *reduction*, and *refinement* as the 3Rs, for conducting humane animal-based research. Replacement refers to the use of non-animal methods (absolute replacement) or utilizing alternative models or less sentient species (relative replacement), whenever possible. Reduction refers to using the lowest number of animals necessary to achieve reliable scientific results. Refinement refers to using methods that alleviate or minimize potential pain or distress or enhanced animal well-being. One of workshop at the 5th Basel Declaration Conference in San Francisco (February 14/15, 2018) was dedicated to the 3Rs and this position paper summarizes the discussions.

Position Statement

Over the past 45+ years, the 3Rs have evolved to become universally accepted and expanded principles by those engaged in research using animals and animal models. We accept the fact that research conducted using animals is necessary and has led to countless advances in scientific understanding and the development of appropriate treatments and cures for both human and animal diseases. Fields such as systems and computational biology, and methods such as microphysiologic systems, organs-on-a-chip and in silico modeling have led to improved scientific modeling, but there are only a few absolute replacements available because as of yet, nothing can mimic the complexities of human and animal physiology.

While the 3Rs framework should not be used in lieu of addressing the moral questions associated with the use of animals in research, it is a tool that, when complemented by the added principles of scientific rigor, reproducibility and responsibility, greatly improves many practical issues around the care, use and welfare of laboratory animals. Therefore, in communications with the public, more transparency regarding their use and role in biomedical research would provide a realistic understanding that while refinements in methods of research and animal care are implemented whenever possible, methods that lead to reduction and replacement are not as advanced and take more resources to develop and implement. This transparency should include how the scientific community is looking for ways to improve both science and animal welfare.

Background

There are several global efforts dedicated to the implementation of the 3Rs. The demand for 3Rs methods is high, but as there are limited resources to develop them, we must be creative and share a worldwide collective approach to maximize their impact. Given a commitment to excellence by the global scientific community, a strategy that prioritizes the 3Rs for optimal impact requires engaging and connecting professionals from differing scientific backgrounds and skill sets. This implies a need for improved coordination and collaboration between the various groups dedicated to the 3Rs. It further speaks to a demand for identifying the latest relevant scientific data, encouraging optimal use of statistical analysis, experimental design and scientific peer review, and supporting the use of new approaches and technologies for the creation of improved animal models in the context of the 3R.

The implementation of the 3Rs is supported by science-based investigative efforts, funding by governments and funding agencies; industry and NGOs; grants and awards by professional societies and organizations; research conducted by academic programs and welfare centers; external consortia, consortia-led committees and working groups.

San Francisco, February 15, 2018

Common challenges include

- Lack of resources and institutional commitment
- Identifying, engaging and/or inspiring the scientific stakeholders and experts who could be leading the development of 3Rs technologies in their respective fields
- Identification of redundancies and unmet needs in research which would support 3Rs implementation and animal welfare
- Acknowledging and overcoming cultural differences in interpretation of the 3Rs and developing common operational definitions
- Lack of dissemination and sharing of relevant information among the scientific community and the absence of a centralized repository, or centralized 3Rs organization
- Identification of common data streams that inform 3Rs relevant for welfare
- Appropriately framing the 3Rs (when communicating) – specifically, differentiating between the application of absolute vs. relative replacement, presenting a clear message that while 3Rs do exist, we are most focused on optimizing science for impact
- Prioritization of initiatives leading to the greatest impact when the scope of the 3Rs is so broad
- Assurance of appropriate study design and model selection
- Including appropriate relevant information in publications (despite the ARRIVE guidelines) as well as absence of publishing negative results or insignificant findings, potentially leading to unnecessary duplication of efforts
- Prevention of knowledge sharing and dissemination when working with proprietary information
- Implementation of the 3Rs in the Low to Middle Income Countries

Future needs and directions

To maximize the impact of 3Rs implementation, we must be creative, embrace a collaborative approach, and set an aligned 3Rs vision and strategy to addressing the common challenges.

References/resources

AWA [Animal Welfare Act]. 1990. Animal Welfare Act. PL (Public Law) 89-544. Available at www.nal.usda.gov/awic/legislat/awa.htm; accessed January 14, 2010

Directive 2010/63/EU on the protection of animals used for scientific purposes

The Guide for the Care and Use of Laboratory Animals, 8th Ed. NRC, 2011

Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd ed. CCAC [Canadian Council on Animal Care], 1993

Health Research Extension Act of 1985, Public Law 99-158, "Animals in Research" (November 20, 1985)

International Guiding Principles for Biomedical Research Involving Animals. CIOMS-ICLAS, 2012

"International Laws, Regulations, and Guidelines for Animal research" ILAR Journal, V 57, N 3, 2016

"The 3R's Issue" Journal of the American Association for Laboratory Animal Science. Vol 54, No 2 March 2015

Tannenbaum, J, Bennett, BT. 2015. Russell and Burch's 3Rs Then and Now: The Need for Clarity in Definition and Purpose. *Journal of the Am Association of Laboratory Animal Science*, 54:2, 120-32

"Terrestrial Animal Health Code" OIE World Organization for Animal Health, 2012

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training. 1985, the Interagency Research Animal Committee

San Francisco, February 15, 2018