

Section III: Bioethical Considerations

What should be considered when using transgenic and chimeric nonhuman primate models in neuroscience

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This presentation is based on my experience working in drug discovery and development, providing veterinary care for laboratory animals, serving as the Chief Veterinarian responsible for animal welfare, ethics, and animal research strategy at a large pharmaceutical company and, most recently, completion of formal education in bioethics. What follows are my thoughts and comments; mine alone.

Regulation/Policy synopsis

- **[The Animal Welfare Act - Public Law 89-544 Act of August 24, 1966](#)**
 - The complete amended act can be found in *United States Code*, Title 7, Sections 2131-2156.
- **[Public Law 99-198, Food Security Act of 1985, Subtitle F - Animal Welfare](#)**
 - Enacted December 23, 1985
 - It directs the Secretary of Agriculture to establish regulations to provide ... an adequate physical environment to promote the psychological well-being of nonhuman primates.
 - It specifies that pain and distress must be minimized in experimental procedures and that alternatives to such procedures be considered by the principle investigator.
- **[PHS Policy on Humane Care and Use of Laboratory Animals – revised 2015](#)**
- **[U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training](#)**
- Recombinant DNA, Biosafety policies and regulations

Primary points for consideration:

- Should we require ourselves to go beyond what the laws state?
- Is meeting regulations enough?
- With genetic modification of NHPs for experimental studies – is harm/benefit enough of an ethical principle/debate?

IACUC debate:

- With genetic modification of NHPs for experimental studies – is harm/benefit enough of an ethical principle/debate?
 - The 3Rs are about eliminating or reducing harm
 - Benefit is often stated and accepted by IACUC
 - E.g. by using genetically modified non-human primates a new treatment may be found and/or there will be increased understanding of “neurological disease X”
 - Any chance for improving benefit in addition to decreasing harm?
 - Would criteria help?

Independent of Criteria, prospective establishment of what are commitments made:

1. access to species appropriate food and water;
2. access to species specific housing, including appropriate temperature and humidity levels;
3. provision of humane care, and a programme of veterinary care through guidance of a veterinarian;
4. animal housing that minimizes the development of abnormal behaviours;
5. adherence to principles of replacement, refinement and reduction in the design of in vivo or ex vivo studies with processes to optimize animal use and to ensure effective population management;
6. supported by a relevant scientific justification/rationale, approved by an institutional ethical review process and subjected to independent scientific review;
7. commitment to minimizing pain and distress to the animal during in vivo and ex vivo studies;
8. work is performed by staff documented as trained and competent to conduct the procedures for which they are responsible.

Important to capture basic needs and our obligations

- access to species appropriate food and water;
 - Is there a change in which the animal can chew food, drink?
 - Has food digestion been changed?
 - How will this be observed, documented and acted upon – agree ahead as much as possible
- access to species specific housing, including appropriate temperature and humidity levels;
 - Does the new phenotype mean temperature and humidity need to be modified
 - Are there mobility, balancing problems? Tremors and vomiting? Is a new housing paradigm needed
 - Will the animal age and grow during the study? What gender?
- provision of humane care, and a program of veterinary care through guidance of a veterinarian;
 - Program must have veterinarians, behaviorists and technicians trained to work with non-normative monkeys
 - How far “from normal” is the model?
- animal housing that minimizes the development of abnormal behaviours;
 - Would present housing aggravate or potentiate the development of stereotypic behaviors that may be subclinical in with the new genotype

Important to capture basic needs and our obligations

- adherence to principles of replacement, refinement and reduction in the design of in vivo or ex vivo studies with processes to optimize animal use and to ensure effective population management;
 - Important to design studies to minimize any wastage (more common issue with rodent studies, but should be considered)
- supported by a relevant scientific justification/rationale, approved by an institutional ethical review process and subjected to independent scientific review;
 - “they’re primates, we’re primates, justification is obvious”
- commitment to minimizing pain and distress to the animal during in vivo and ex vivo studies;
 - Standard ways of working may be challenged with unknown phenotypes
- work is performed by staff documented as trained and competent to conduct the procedures for which they are responsible.
 - If the program does not have veterinarians and technicians trained and competent to work with non-normative monkeys; a training program must be instituted

Housing considerations and Performance Standards

(European versus US housing debate)

- NHP should be able to interact with compatible conspecifics
- NHP should exhibit appropriate coping behaviours
- NHP must have positive regular interactions with humans
- NHP should be able to hide, avoid conspecifics and have access to secure locations
- NHP should be able to engage in activities that are mentally stimulating and promote use of their senses
- NHP should be able to forage for food
- NHP should be able to exercise

Transport considerations – an example

(looking beyond the study itself)

- Time in transport should not exceed 48 hours for any mammalian species, from leaving a vendor/supplier site to receipt.
- Any shipments for which transit times are routinely greater than 48 hours must have an exemption granted by the local ethical review committee and the Risk Owner for Animals.
- If the time taken for delivery of a shipment is an exception to the expected transit time; reasons for the delay will be documented and notification sent to the IACUC and the Risk Owner. If needed, an after action review will be conducted to determine any learnings for future application.

They are still monkeys...
sentient, high cognitive abilities,
social animals, predators who
hide pain and distress, so they
do not become prey