



Animal Welfare Considerations with Neural Chimeras and Organoids

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Agenda Topics

- Discussion on the potential of increase responsibility to meet animal welfare requirements
- Not a discussion on “loss of dignity” to people, rather obligation to manipulated animals
- Quick review of laws/policies
- Review of Harm/Benefit Analysis and the 3Rs and Principles of Animal Research Ethics
 - I believe the above continue to be applicable, even as technology advances
 - will be important to show the thoughtfulness these can prompt
 - Should not be limited to IACUC discussions

Start with definition – from the AVMA

- “Animal welfare means how an animal is coping with the conditions in which it lives.”
- “Ensuring animal welfare is a human responsibility that includes consideration for all aspects of animal well-being, including proper housing, management, nutrition, disease prevention and treatment, responsible care, humane handling, and, when necessary, humane euthanasia.”

Public Health Service Policy on Humane Care and Use of Laboratory Animals

- U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training
 - II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
 - IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

AWA reference

- C. Animal Welfare Act – Public Law 89-544, 1966, as amended (P.L. 91-579, P.L. 94-279, and P.L. 99-198), 7 U.S.C. 2131 et seq. Implementing regulations are published in the Code of Federal Regulations (CFR), Title 9, Chapter 1, Subchapter A, Parts 1, 2, and 3, and are administered by the U.S. Department of Agriculture.

Harm/Benefit Analysis and the 3Rs

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- “HBA is the process of assessing the likely harms that the animals will experience and the likely **benefits** to be delivered and then determining whether the likely harms to animals are justified by the **benefits** likely to accrue.”
 - Harm is determined
 - 3Rs discussed/applied to mitigate harm
 - No comparable principles, like the 3Rs, to apply to benefits

Bioethical, Reproducibility and Translational Challenges of Animal Models

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- A major impediment to the HBA determination is not in the weighing of harms, but in difficulty of assessing benefit beyond what is stated in the protocol submission.
 - Prompts to ethical discussion are often limited to details concerning harm-benefit analysis (HBA) and the role of the 3Rs in study design
 - Challenge is when discussing benefit how is the animal aspect (harm) of the benefit captured

3Rs definition - changing

	Standard	Contemporary
Replacement	Methods which avoid or replace the use of animals	Accelerating the development and use of models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals
Reduction	Methods which minimise the number of animals used per experiment	Appropriately designed and analyzed animal experiments that are robust and reproducible, and truly add to the knowledge base
Refinement	Methods which minimise animal suffering and improve welfare	Advancing animal welfare by exploiting the latest <i>in vivo</i> technologies and by <u>improving understanding of the impact of welfare on scientific outcomes</u>

Consideration and Checkboxes: Incorporating Ethics and Science into the 3Rs

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- Moral considerability, or moral status for an entity, means that the entity has the right for its interests to be taken into account when a decision is made that will affect that entity.
 - Having moral standing or moral considerability can be thought of as a minimal threshold that, when reached, ensures that the entity's interests will at least be given some weight in moral deliberation.
 - Most agree that we have some obligation to refrain from treating animals badly, but the precise nature of those obligations and to which species they apply is often debated heatedly.

PRINCIPLES of SOCIAL BENEFIT

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- 1) The Principle of No Alternative Method
 - In a classic Three-Rs conversation, replacement discussions are driven by welfare questions. The “no alternative method” is not based on animal welfare (or science); rather, it asks us to declare that predicted benefits can be feasibly sought only in animal trials.
 - 2) The Principle of Expected Net Benefit
 - shift requires a shift away from our present thoughts on harm–benefit analysis and move to risk–benefit analysis, which involves the predicted risks and benefits for humans.
 - 3) The Principle of Sufficient Value to Justify Harm
 - While shadowing the well-established harm–benefit analysis, this principle asks more of us.
 - By accepting the moral status of animals, even on a sliding scale, we have an obligation to debate whether the study is of sufficient value to justify the harm of the study.

All three of the principles under consideration (in the framework of six principles) must be fulfilled to satisfy the requirements of moral justification under the principles of animal welfare

PRINCIPLES of ANIMAL WELFARE

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- 1) The Principle of No Unnecessary Harm
 - prohibits harm to or compromise of animal welfare, except where it is necessary for the research.
 - It is important to consider “harm” beyond what is required by the study design.
 - 2) The Principle of Basic Needs
 - include, but are not limited to, species-specific housing, food, appropriate handling, and veterinary care
 - there are institutions that comply with the law, but this does not always mean the basic needs of a specific species are being met.
 - 3) The Principle of Upper Limits to Harm
 - there is a point at which a study should not be approved due to the predicted harm, even if the study exhibits considerable potential for social benefit. Referring to the acceptance of moral status, I agree unambiguously that there should be an upper limit to harm.

All three of the principles under consideration (in the framework of six principles) must be fulfilled to satisfy the requirements of moral justification under the principles of animal welfare

Final Thoughts on Animal Welfare in neural chimeric and organoid models

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- Assess animal pain and distress during creation of the models
 - Assess if species specific behaviors are changed after recovery
 - Are animals demonstrating:
 - More aggression
 - More fear
 - Less movement
 - Less reaction to normative events
 - Recognize moral status of the animal
 - Moral status is neither enhanced or diminished by a study design but it must be considered

Final Thoughts on Animal Welfare in neural chimeric and organoid models

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In addition to traditional harm/benefit analysis and application of the 3Rs, consider the following:

Principles of Social Benefit

- 1) The Principle of No Alternative Method
- 2) The Principle of Expected Net Benefit
- 3) The Principle of Sufficient Value to Justify Harm

Principles of Animal Welfare

- 1) The Principle of No Unnecessary Harm
- 2) The Principle of Basic Needs
- 3) The Principle of Upper Limits to Harm