ISSCR
Chimera Research Guidelines

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Working Group 3 – Organoids and Chimeras

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General approach for Working Group 3

- Think about the next 5 years
- Start with categories of review
- Add language and clarification around chimera research
  - Neurological chimerism
  - Use of non-human primate hosts
  - Use of livestock animals
  - Chimeric embryo research

Categories of review

Category 1B (reportable, not typically reviewed by full committee):

- Research in which human stem cells are transferred into non-human embryos and cultured *in vitro* for the minimum time necessary to achieve the scientific objective.

Category 2 (reviewed):

- Research in which human pluripotent stem cells are transplanted into non-human embryos *in vitro* followed by transfer into a non-human uterus.

Category 3B (not allowed because illegal and/or no scientific rationale):

-Research in which animal chimeras incorporating human cells with the potential to form human gametes are bred to each other.

- Transfer of chimeric embryos mixing animal and human cells (whether predominantly animal or human) to the uterus of a human or ape host.

What the 2016 Guidelines say about other forms of chimera research:

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Human-Animal Chimera Studies That Warrant Specialized Review

Recommendation 2.1.5: Research that entails incorporating human totipotent or pluripotent cells into animal hosts to achieve chimerism of either the central nervous system or germ line requires specialized research oversight. Such oversight should utilize available baseline animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.

What the revised version says:

Human-Animal Chimera Studies That Warrant Specialized Review

Recommendation 2.1.5: Research that entails incorporating human totipotent or pluripotent cells into animal hosts to achieve chimerism of either the central nervous system or germ line requires specialized research oversight. Such oversight should utilize available baseline animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.

Research that entails incorporating human stem cells or their direct derivatives into animal hosts to achieve or that risks achieving chimerism of either the central nervous system or germline requires specialized research oversight. Such oversight should weigh the potential benefits of the research and should utilize available baseline non-human animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.

The 2007 ISSCR Chimera Research White Paper

Hyun *et al.*, *Cell Stem Cell* **1**

Cell Stem Cell

ISSCR: Committee Forum

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Ethical Standards for Human-to-Animal Chimera Experiments in Stem Cell Research

The purpose of this report is to offer investigators and members of SCRO and animal research committees well-grounded ethical standards for evaluating research involving the transfer of multipotent and pluripotent human stem cells and their direct derivatives into animal systems. This report is deliberately written in general terms so that its recommendations can apply to diverse institutions and international settings. Thus, investigators and reviewers should aspire to these proposed ethical standards while exercising appropriate judgment in individual situations.

The 2007 ISSCR Chimera Research White Paper

- Chimera protocols should undergo animal research review supplemented with stem cell or developmental biology expertise.
- Monitoring and data collection should be based upon a sound assessment of the developmental trajectories that are likely to be affected and take into account the epigenetic context of regulation in which the mixed genes or cells are going to be deployed.
- As with transgenic animals, investigators and institutions should consider requiring the use of pilot studies to produce initial data on chimeric animals subject to experimental interventions, employ ongoing monitoring of deviations from normal behaviors, and prescribe reporting to pertinent animal welfare committees.
- Research with the known, intended, or well-grounded significant potential to create humanized cognition, awareness, or other mental attributes, while not absolutely prohibited, should be subject to close scrutiny, taking the most careful steps to collect data pertinent to ethical protection of animal subjects, and an extraordinary degree of justification.

Add anything else to neurological chimerism guidelines? (We are looking at the next 5 years.)

New for 2020/2021…

- Researchers using large animal models such as livestock and non-human primates should follow international standards for animal and non-human primate research, which call for frequent monitoring of animals whenever there is the potential for unexpected outcomes and unanticipated phenotypes.
- For chimeric embryo work without transfer to a uterus – no mandatory review. *In vitro* chimeric embryos should be cultured for the minimum time necessary to achieve the scientific objective. (Category 1B)

New for 2020/2021…

- For chimeric embryo work that includes transfer into a non-human uterus - mandatory review. (Category 2)
  - All non-human primate species, except apes, may be allowed for scientifically meritorious studies of chimeric embryo formation.
  - The length of gestation in monkey and other animal surrogates must be scientifically well-justified and investigators should proceed step-by-step, stopping at incremental timepoints to assess the degree and scope of chimerism before going all the way to full gestation, if full gestation is among the well-justified goals of the research.

Any other restrictions on human-monkey chimeric embryo studies that involve implantation and gestation? For example, “targeted chimerism” only?

We welcome your input.

Thank you

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