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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee's Consideration of Certain Human-Animal Chimera Research.

**SUMMARY:** The National Institutes of Health (NIH) is requesting public comment on a proposal to amend Section IV and Section V of the NIH Guidelines for Human Stem Cell Research and on the proposed scope of certain human-animal chimera research that will be considered internally by an NIH steering committee to provide programmatic input to the director of the relevant NIH Institute(s) or Center(s) or equivalent NIH officials responsible for funding decisions.

**DATES:** Written comments must be received by the NIH on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER] in order to be considered.

**ADDRESSES:** Public comments may be entered at:

<http://grants.nih.gov/grants/rfi/rfi.cfm?ID=57>. Comments may also be mailed to: Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, 301-496-9838. Comments will be made publicly available.

Comments received, including any personal information, will be posted without change to [http://grants.nih.gov/grants/rfi/responses\\_57.cfm](http://grants.nih.gov/grants/rfi/responses_57.cfm).

**SUPPLEMENTARY INFORMATION:** On July 7, 2009, the NIH issued the NIH Guidelines for Human Stem Cell Research (“Guidelines”) 74 FR 32170 (July 7, 2009) to implement Executive Order 13505 (March 9, 2009), as it pertains to NIH-funded stem cell research, to establish policy and procedures under which the NIH will fund such research, and help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law.

Since the Guidelines were issued in 2009, growing knowledge and advancement of stem cell biology has created new research opportunities. Some scientists are exploring strategies for growing human tissue and organs in animals through the introduction of human pluripotent cells into early stage embryos of non-human vertebrate animals. These experimental designs raise questions regarding where the human cells might go in the developing animal and how they might function, such as whether the human cells might contribute to the central nervous system and affect the cognition of the animal.

While considering these issues, on September 23, 2015, the NIH issued a funding moratorium (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-158.html>) on “NIH Research Involving Introduction of Human Pluripotent Cells into Non-Human Vertebrate Animal Pre-Gastrulation Embryos.” The NIH subsequently held a workshop with experts on November 6, 2015, to review the state of the science and discuss animal welfare issues.

The workshop illustrated that while there are significant challenges to creating chimeric models, there is clear interest and potential in producing animal models with human tissues or organs for studying human development, disease pathology, and eventually organ transplantation. In the interest of moving the field forward while preserving the NIH's opportunity to provide continuing assessment and oversight of this emerging area of research, the NIH has decided to establish a steering committee to provide programmatic input to the director of the relevant NIH Institute(s) or Center(s) (or equivalent NIH official responsible for funding decisions) on certain human-animal chimera research proposals. The committee will be composed of federal employees. The committee is expected to consider and offer the director of the relevant NIH Institute(s) or Center(s) (or equivalent NIH official responsible for funding decisions) programmatic input on factors, such as, (1) the characteristics of the human cells to be introduced (including potency and any modifications of those cells); (2) characteristics of the recipient animal (e.g., species, stage of development, and any modifications that affect location or function of human cells); (3) other data relevant to the likely effects on the animal (e.g., changes in cognition, behavior, or physical appearance); (4) planned monitoring (including animal welfare assessments); and (5) any staging of proposed research (e.g., assessing the outcome of a particular experiment before conducting a further experiment). This internal programmatic work will be conducted independent of, and in addition to, the usual peer review procedures for research at the NIH. The relevant IC director(s) will consider the input from the steering committee, in addition to other NIH programmatic input, as well as the funding recommendations and evaluations of the initial Scientific Review Group and the relevant Institute or Center's Advisory Council or

Board. The committee will also monitor trends in this general field of research and the use of new technologies, and may provide such analysis and advice to the NIH leadership.

The NIH also proposes to revise the Guidelines to expand the existing prohibition on introducing human pluripotent stem cells into blastocyst stage nonhuman primate embryos to include pre-blastocyst stage nonhuman primate embryos; and to expand the prohibition on research involving the breeding of animals where the introduction of hESCs or human induced pluripotent stem cells may contribute to the germ line to include any human cells that may result in the formation of human gametes.

Therefore, NIH is requesting public comment on:

- 1) The following proposed changes to the Guidelines.

Sections IV and V of the Guidelines currently state:

**IV. Research Using hESCs and/or Human Induced Pluripotent Stem Cells That, Although the Cells May Come from Eligible Sources, is Nevertheless Ineligible for NIH Funding**

This section governs research using hESCs and human induced pluripotent stem cells, i.e., human cells that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although the cells may come from eligible sources, the following uses of these cells are nevertheless ineligible for NIH funding, as follows:

- A. Research in which hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells are introduced into non-human primate blastocysts.
- B. Research involving the breeding of animals where the introduction of hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells may contribute to the germ line.

**V. Other Research Not Eligible for NIH Funding**

- A. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding

of human embryo research (Section 509, Omnibus Appropriations Act, 2009, Pub. L. 111-8, 3/11/09), otherwise known as the Dickey Amendment.

B. Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.

The NIH is proposing to amend the Guidelines as follows:

IV. Research Not Eligible for NIH Funding:

A. Research in which human pluripotent stem cells are introduced into non-human primate embryos up through the end of the blastocyst stage, is not eligible for funding.

B. Research involving the breeding of animals where the introduction of human cells may contribute to the germ line, is not eligible for funding.

C. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations limitations on the funding of human embryo research (see e.g. Section 508, Omnibus Appropriations Act, 2016, Pub. L. 114-113, 12/18/15), otherwise known as the Dickey Amendment.

D. Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.

2) The NIH is also requesting public comment on the proposed scope of research (e.g., grant applications, contract proposals, intramural research protocols, etc.) to be considered by an NIH steering committee to provide programmatic input to the director

of the relevant Institute or Center (or equivalent NIH official responsible for funding decisions). The NIH proposes the scope of research include research in which:

- a. human pluripotent cells are introduced into non-human vertebrate embryos, up through the end of the gastrulation stage, or
- b. human cells are introduced into post-gastrulation non-human mammals (excluding rodents), such that there could be either a substantial contribution or a substantial functional modification to the animal brain by the human cells.

While the NIH seeks public comment on the proposed changes to the Guidelines, and on the proposed scope for an NIH steering committee's consideration of certain research, NOT-OD-15-158 will remain in effect.

Dated: July 28, 2016

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Lawrence A. Tabak, D.D.S., Ph.D.

Deputy Director

National Institutes of Health

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