CHRISTIAN LEGAL SOCIETY

Seeking Justice with the Love of God

September 6, 2016

Submitted Electronically

Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: 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

Dear Sir or Madam:

On behalf of the Christian Legal Society and the Center for Law and Religious Freedom, we submit the following comments on the proposal by the National Institutes of Health ("NIH") to authorize federally funded human/animal chimera research, published at 81 Fed. Reg. 51921 (Aug. 5, 2016) ("August 5 Notice").

Interest of Christian Legal Society and the Center for Law and Religious Freedom

The Christian Legal Society ("CLS") is a nationwide fellowship of Christian lawyers, professors, and law students, committed to acting justly, loving mercy, and walking humbly with their God. (Micah 6:8). The Center for Law and Religious Freedom is the legal advocacy arm of the Society. Founded in 1961, CLS affirms the inherent dignity of human beings and defends all Americans' inalienable right to freedom of religious conscience before the courts, Congress and state legislatures, and the executive branch. Through its Christian Legal Aid ministry, CLS serves those most in need in our society.

For several decades, CLS has been concerned with the ethical treatment of human beings throughout all their stages of life. CLS attorneys have served as expert resources to legislatures considering bioethical issues. CLS attorneys have also published on the subject. *See, e.g.*, Samuel B. Casey and Nathan A. Adams, IV, *Specially Respecting the Living Human Embryo by Adhering to Standard Human Subject Experimentation Rules*, 2 Yale J. Health Pol'y, Law & Ethics 111 (2001).

General Comments

The NIH August 5 Notice seeking comments on proposed modifications to NIH Human Stem Cell Guidance and on the scope of review by a steering committee on chimera research is devoid of explanation or reference to the ethical review which NIH specifically had committed to when, on September 23, 2015, it announced a moratorium on funding such research ("September

2015 Notice").[1] Neither does the August 5 Notice suggest that such a review will occur or be within the mandate or expertise of the announced steering committee, or that any other process has occurred or will occur that will take into account the profound ethical issues raised by this research. Nor does the August 5 Notice articulate or link any such ethical review or conclusions to a rationale for the proposed modifications of the guidelines and proposed scope of review.

The proposed modifications themselves are legally problematic and, absent a clearly articulated ethical framework, carry significant potential for arbitrary and abusive application. The Dickey-Wicker Amendment prohibits amending the NIH Guidelines for Human Stem Cell Research as proposed. Furthermore, history establishes that a generally accepted ethical framework is essential to guide the scientific research -- or abuses most certainly will follow. Although proposing a steering committee to guide human-animal chimeric research, *the proposed changes to the NIH Guidelines for Human Stem Cell Research are silent about the ethical constraints that will guide the steering committee.* The foremost concern of NIH after evaluating the legality of the proposed amendment should be to pursue a consensual ethical framework for any human-animal chimeric research as the first step toward any amendment in research protocols and/or change in law necessary to regulate Federally-funded and non-Federally funded research in this area.[2] NIH itself recognized the importance of developing such an ethical framework when it announced its funding moratorium on September 23, 2015, calling for "a deliberative process to evaluate the state of the science in this area, *the ethical issues that should be considered*, and the relevant animal welfare concerns associated with these types of studies." September 2015 Notice at 1 (emphasis added).

The inherently ambiguous character of the human-animal chimera makes identifying the proper ethical framework challenging. Human subject experimentation rules will surely not apply for lack of any possible compliance with the prerequisites. Animal subject experimentation rules fail adequately to account for the human content of the chimera and, in any event, are also not met. Ironically, the proposed prohibition on human-primate chimeric research indicates that the unelaborated ethical framework that NIH has in mind for the steering committee is more concerned with primates than the human stem cells involved in the research. For these reasons, as explored in more detail below, we oppose any relaxation of the prohibition on human-animal chimeric research.

Procedural Concerns

The NIH August 5 Notice seeking these comments rightly recognized that human-animal chimera research involves disruptive moral and ethical issues: "These experimental designs raise

[1] "NIH Research Involving Introduction of Human Pluripotent Cells into Non-Human Vertebrate Animal Pre-Gastrulation Embryos." September 23, 2015, ("September 2015 Notice"), http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-158.html .

[2] See Antonio Regalado, *Human-Animal Chimeras Are Gestating on U.S. Research Farms*, MIT Technology Rev. (Jan. 6, 2016).

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." 81 Fed. Reg. 51922. For these and related reasons, we appreciated NIH's prior announcement, dated September 23, 2015, of a funding moratorium with respect to this research, in which NIH stated that it was "informing the research community that it will not fund research in which human pluripotent cells are introduced into non-human vertebrate animal pre-gastrulation stage embryos while the Agency considers a possible policy revision in this area." September 2015 Notice at 1. In its September 2015 Notice, NIH also recognized the "rapid expansion of potential research models employed beyond the scope" permitted by NIH guidelines in this arena, and we were therefore gratified with NIH's commitment to the research community and to the public that it would "undertake a deliberative process to evaluate the state of the science in this area, the ethical issues that should be considered, and the relevant animal welfare concerns associated with these types of studies." *Id.*

NIH's commitment to conduct this deliberative process to review the ethical issues was a welcome recognition of the concerns held by many in the research community and in the general public about the ethical implications of this research, the parameters for this research, and the need for the public to have confidence that NIH is taking into account not only the views of those who desire to pursue the research, but also the broader ethical interests of scientists and the public over whether, and the extent to which, such science is consistent with concerns for human life and human dignity. Of course, NIH recognition that research in this area was rapidly expanding beyond that permitted by the NIH guidelines was an acknowledgement that there was already significant interest in the scientific community in pursuing such research, which occasioned the need for the September 2015 Notice of a funding moratorium pending a deliberative review of the technical, animal welfare, *and ethical* issues implicated. This leadership by NIH was essential and welcome.

It was surprising, therefore, to review the August 5 Notice request for comment announcing that NIH was proposing modification to the guidelines and establishing a scope for proceeding with this research, since the Notice was devoid of any reference to the promised ethical review or conclusions developed as a result, or any mandate or plan for an ethical review going forward. Instead NIH reported only that it "subsequently held a workshop with experts on November 6, 2015, to review the state of the science and discuss animal welfare issues." 81 Fed. Reg. 51922. Notably missing from the workshop summary, when compared to NIH's commitment in the September 2015 Notice "to evaluate the state of the science in this area, the ethical issues that should be considered, and the relevant animal welfare concerns," was any reference to what had or would be done to address "the ethical issues that should be considered." September 2015 Notice at 1.

Further discussing the November workshop, the August 5 Notice states that it "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." 81 Fed. Reg. 51922. That is, the workshop illustrated that there are technical challenges to creating chimeric models, and that there is clear interest in pursuing the research in any case. These workshop outcomes were already known to NIH when it announced its September 23, 2015, funding moratorium only a few weeks earlier; and as noted above, NIH had specifically associated the need to call the moratorium and undertake the deliberative process, including an ethical issues review, *because* of the mounting level of scientific interest in pursuing the research. In short, nothing in the August 5 Notice, including the report on the workshop, addresses the NIH's call for review of the ethical issues at stake on September 23, 2015.

Neither does the August 5 Notice suggest that a deliberative review of ethical considerations will be part of the process going forward. The August 5 Notice announced that NIH has established a steering committee composed of federal employees to provide "programmatic input" to the director of relevant NIH or Centers. The Notice identifies that the mandate of the steering committee is to provide "programmatic input" on factors such as the technical characteristics of the human cells to be introduced, the type of recipient animal, "other data relevant to the likely effects on the animal," planned monitoring (including animal welfare assessments), and any staging of the proposed research. *Id.* The steering committee provides this "internal programmatic input" independent of, and in addition to, "the usual peer review procedures for research at NIH" -- although it is not clear whether the steering committee members will be employees of NIH or of the specific institutes and centers that have an interest in pursuing the research.

While this role may generally be understandable for such a steering committee, it demonstrates that the responsibilities of the steering committee, presumably matched by the capabilities and experience of steering committee members who will be drawn from the institutes and agencies that would pursue the research, will be largely scientific, technical, and procedural – *i.e.*, they do not have a mandate for identifying, establishing, resolving, or ensuring compliance with as-yet-unidentified ethical parameters. Moreover, the August 5 Notice neither asserts nor suggests that the steering committee will have the expertise or mandate to determine whether novel applications of the research – and at this stage, as discussed elsewhere in this letter and in the NIH September 2015 Notice, almost all of this research presents novel scientific and profound ethical questions – comply with these yet unarticulated ethical boundaries. Nor does the August 5 Notice explain or suggest how and from what source the steering committee will receive guidance about the ethical parameters that should be applied. The August 5 Notice similarly does not state any criteria which suggests that the steering committee members will be prepared by experience or background to raise and address these complex and novel ethical issues. The steering committee thus is either put in a position where it cannot credibly identify, resolve, articulate, and apply these ethical issues, or perhaps more likely, is not expected to engage in any adequate ethical review.

This is not to suggest that the steering committee members are themselves unethical in any sense of the word. Rather, the point is that a steering committee of federal employees, likely working for NIH directors of institutes and centers that may have a strong desire to pursue the research, are not positioned, and not proffered by NIH as being prepared by experience or training, to conduct, address, or resolve the ethical issues NIH itself identified as critical in announcing its moratorium less than a year ago. Neither has NIH identified any process or mechanism by which it will identify, resolve, articulate, and apply the necessary ethical basis for modifying the guidelines or establishing the particular scope of research.

In the wake of the September 2015 Notice, the research community and the public would reasonably have expected that, prior to announcing a proposed specific modification to its guidelines and a draft scope of research, NIH would have engaged in the promised and essential robust process of deliberative ethics, that the results of such process would have been articulated and transparent, and that this would inform and offer justification for any proposed modification of the guidelines or scope of research. Further, given NIH's recognition of the importance and complexity of the novel potential ethical boundaries in this arena, it would be reasonable to assume that, subsequent to this articulation of an ethical rationale for any proposed guideline changes and scope, the research community, ethicists, and the public would be given an adequate opportunity – certainly, more than 30 days -- to digest and comment on such novel, complex, and morally profound issues, and how NIH proposes to modify the guidelines to integrate its ethical conclusions.

Legal Constraints

The Dickey-Wicker Amendment states:

> SEC. 508. (a) None of the funds made available in this Act may be used for—
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> (1) the creation of a human embryo or embryos for research purposes; or
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> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
>
> (b) For purposes of this section, the term ''human embryo or embryos'' includes any *organism*, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is *derived by* fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or *human diploid cells*.

Section 508, Omnibus Appropriations Act, 2016, Pub. L. 114-113, Dec. 18, 2015.

The animal-chimera research that NIH proposes to fund will violate the Dickey-Wicker Amendment by funding research in which "a human embryo or embryos" are created and destroyed. These are defined for purposes of the Dickey-Wicker Amendment as any organism derived from human diploid cells, *i.e.*, cells containing two copies of each chromosome. Human stem cells are commonly diploid cells.[3] Human-animal chimera are organisms, unprotected under 45 C.F.R. § 46 (*i.e.*, human subject experimentation rules), that will be derived in part from human stem cells by combining the animal embryo with human diploid cells. Embryos for new creatures not belonging to any prior species will be created, not merely modified, only to be destroyed when the endpoint of the research is reached. As such, the Dickey-Wicker Amendment unambiguously forbids the amendment to the research protocol that NIH proposes. Approving the amendment will expose NIH to lawsuit.

Ethical Constraints

Many Americans believe that the human embryo inclusive of stem cells should not be destroyed or conjoined with animals due to the distinctive imprint of God on humankind. Regardless of whether NIH agrees with this belief, federal advisory boards have generally agreed with several legal scholars that the human embryo inclusive of stem cells at least deserves "special respect."[4] The failure to specify how this interest will be vindicated as part of the NIH proposal also undermines the amendment. The Notice refers to human stem cells as "pluripotent" instead of "totipotent," but the scientific record contradicts that presumption and indicates the possibility that human stem cells also can form trophoblast cells or, in other words, give rise to a born person.[5] Even if simply pluripotent, applying merely animal research rules to them falls far short of treating human stem cells with special respect. Additionally, since a human has intrinsic value distinct from any other species, research protocols applicable to human research in this matter should reflect an elevated respect superior to research protocols applicable to animal research.

The ambiguous and novel character of an organism both human and animal makes application of existing experimentation rules inapt, and determining what moral obligations are due the resulting organism uncertain. The Human Subjects Policy requires (1) legally effective informed consent of the subject or the subject's legally authorized representative; (2) minimization of risks; (3) risks to subjects reasonable in relation to anticipated benefits; and (4) additional safeguards to protect the rights and welfare of subjects when some or all of them are

[3] See Fan Y, Li R, Huang J., Yu Y, Quao J., *Diploid, But Not Haploid, Human Embryonic Stem Cells Can Be Derived from Microsurgically Repaired Tripronuclear Human Zygotes*, CELL CYCLE (Jan. 15, 2013).

[4] See John A. Robertson, *In the Beginning: The Legal Status of Early Embryos*, 76 VA. L. REV. 437, 446-47 (1990); National Institutes of Health, *Report of the Human Embryo Research Panel* 2 (Sept. 1994); National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research*, vol. I, p. ii (Sept. 1999).

[5] Mice studies prove that mice embryonic stem cells when implanted in the female give rise to a born mouse with the genetic make-up of the embryonic stem cells. See András Nagy et al., *Derivation of Completely Cell Culture-Derived Mice from Early-Passage Embryonic Stem Cells*, 90 PROC. NAT'L ACAD. SCI. 8424 (1993).

likely to be vulnerable to coercion or undue influence.[6] The proposed research potentially violates all of these prerequisites. No fiduciary can provide legally effective informed consent to un-make his or her own species. There can be no minimization of risks when the purpose of the research is merely to harvest organs. The human stem cells will be fundamentally altered as chimera. The potential benefits of the research are entirely speculative. No safeguards at all are proposed as part of the research amendment, and as noted above, NIH's announcement is devoid of any discussion, or reference to any discussion, on its view of how these profound ethical questions apply to its proposed modifications of the guidelines and scope of research.

The "three r's" of ethical animal use are no more availing on these facts with their focus on: (1) replacement -- referring to methods that avoid using animals (*i.e.*, computer programs); (2) refinement -- referring to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress; and (3) reduction -- involving strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals so that in the long run fewer animals are needed to acquire the same scientific information.[7] By virtue of suggesting this change in research protocol, replacement has been ruled out without any finding that using solely animal stem cells is sufficient for now to test the validity of underlying theories. Refinement is inapplicable to un-making a species or cultivating a species exclusively for utilitarian ends necessarily leading to termination. The proposed rule change does not address the use of appropriate species, quality, or number of animals. Nor does the proposed rule change address the experimental, much less humane, "endpoint" when the scientific aims and objectives of a study have been reached. Ordinarily, experiments terminate the chimeric embryo within weeks, but NIH has articulated no prohibition on birth of the chimera nor any limit on the contribution of human cells to the animal.

Neither the type of animals nor parts of animals affected are materially limited by the proposed amendment. Aside from excluding primates from study, the amendment does not further delimit the types of non-human vertebrate animals that could be impacted. Historically, animal research ethics have been concerned more about higher order animals than lower order animals, yet there is no limitation on the complexity of the animal as part of the proposed amendment, aside from the exclusion of primates. Morally and theologically, many traditions may be even more concerned about mixing human stem cells with lower animals. Yet the proposed changes affirmatively anticipate chimeric research using rats without even steering committee review.

In addition, NIH anticipates that the most complex of animal organs will be targeted for delivery of human stem cells, including those parts considered the most morally and theologically sensitive, such as the brains of the animals, notwithstanding that NIH has itself

[6] Protection of Human Subjects, *Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research*, 45 C.F.R. § 46.203(g) (2001).
[7] National Research Council, Guide for the Care and Use of Laboratory Animals 4-5 (8th Ed.).

publicly stated its concern that the animals' "cognitive state" could be altered.[8] The result would be a new species itself entitled to quasi-human respect, yet intended for chronic manipulation as a "model" or for the purpose of harvesting tissue certain to terminate the chimera. Not even human gametes are out of bounds.

Conclusion

The proposed changes to the NIH Guidelines for Human Stem Cell Research and the proposed scope of the NIH steering committee's consideration of certain human-animal chimera research are unlawful. Furthermore, the proposed changes to the guidelines and the steering committee's scope are entirely untethered to any consensual ethical research paradigm, leaving it entirely to the discretion of a rudderless steering committee to decide how best to proceed. The gravest ethical concerns involved in this type of research -- including infusing the lowest level species with human stem cells leading to cognitive development -- are not even addressed.

For the above reasons, NIH should:

a. Suspend the proposed modification of guidelines and proposed scope of review pending evaluation of the legality of the proposed amendment, and articulate its legal rationale in the event it decides to proceed further with the announced course of action.

b. Pursue a consensual ethical framework for any human-animal chimeric research as the first step toward, and prior to, any amendment in research protocols and/or change in law necessary to regulate Federally-funded and non-Federally funded research in this area. This action is consistent with NIH's commitment, in announcing the funding moratorium for research in this area, to consider deliberatively the profound ethical parameters that are involved and potentially could be implicated by this research. Nothing in the August 5 Notice refers to or suggests that the promised deliberative review of the ethical issues has occurred or will occur to inform NIH, the steering committee, the research community, or the public, or to justify the proposed guideline modifications and scope of research; and NIH has not articulated the result of such a review as justification for the proposed changes or removal of the funding moratorium.

c. NIH should either expand the mandate and membership of the steering committee to include non-federal employees who do not report to the directors of the respective research institutes and centers which may be involved in pursuing the research, who do not otherwise have a personal interest in pursuit of the subject research, and who credibly and independently are prepared by training and expertise to contribute on the critical *ethical* considerations implicated by this research; or if such considerations are beyond the scope of such a steering committee, or the steering committee is limited to federal employees with responsibilities as stated in the August 5 Notice, NIH should identify

[8] Regalado, *supra* note 2.

another appropriate body to fulfill NIH's commitment to ensure that the scope of research now and in the future complies with the ethical parameters developed as a result of the consensual ethical framework to be developed, and which clearly and transparently addresses not only the scientific state of affairs and animal welfare issues, but the broader ethical issues implicated by integrating human cells in animals.

Respectfully submitted,

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Christian Legal Society