HARVARD UNIVERSITY
Embryonic Stem Cell Research Oversight ("ESCRO") Committee

Ethical Issues Related to the Creation of Synthetic Human Embryos

---

I. Introduction

The Harvard Embryonic Stem Cell Research Oversight (the "ESCRO") is an ethical oversight committee at Harvard University, charged with reviewing research protocols involving human embryos, human embryonic stem cells, and certain activities with non-embryonic human pluripotent stem cells. Like many institutional ESCROs, its mandate and scope of review derive largely from the National Academies of Sciences Guidelines for Human Embryonic Stem Cell Research (the "NAS Guidelines"), which first called for the establishment of ESCROs in 2005.

The ethical principles outlined in the NAS Guidelines guide the Harvard ESCRO's deliberations. However, the NAS Guidelines are somewhat limited in their capacity to anticipate and keep pace with evolving research technologies. The last update to the Guidelines was in 2010, prior to many of the recent developments in iPSC research, the emergence of technologies that would facilitate the genetic modification of embryos, the increasing sophistication of synthetic biology technologies and the attendant ethical issues these advances raise. As a result, the Harvard ESCRO occasionally receives inquiries to deliberate upon the ethical implications of emerging research technologies where there is no existing or established guidance to rely upon. In these instances, the Harvard ESCRO generally consults with its peer oversight bodies, reviews data from the scientific and bioethical literature and from scientists and ethicists in the field and, from time to time, convenes symposia to broaden the discussion around such emerging technologies.

At its December 2015 meeting, the Harvard ESCRO received such a request, prompting it to reflect on research regarding the creation of certain types of seemingly organized cellular structures that neither arise from embryogenesis nor derive from human embryos. In particular, the inquiry centered on whether the appearance of formations that resemble the primitive streak in non-embryo structures are subject to ESCRO review and oversight. In the case before the Harvard ESCRO, the formation arose, not from normal embryogenesis, but from the use of micro-patterning techniques to control the size and geometry of hiPSC colonies.

Pursuant to the Harvard ESCRO Policy and the NAS Guidelines on which it is based, the in vitro culture of any ***intact embryo*** for longer than 14 days or until formation of the primitive streak is prohibited. What was presented to the ESCRO Committee was not an intact embryo, or even an embryo at all, but rather, a self-organizing colony of iPS cells. Neither the NAS Guidelines nor the Harvard ESCRO Policy reference, or even contemplate, the ethical implications of the research case that was brought to ESCRO. Despite the early stage of this type of research, the inquiry raised broader questions, about the limitations of the NAS Guidelines and the 14 Day Rule, and the developmental potential of synthetic human embryos.

After internal deliberation, and some initial outreach to leaders in this field, the Harvard ESCRO convened a symposium on November 7th and 8th of 2016 to explore issues related to the responsible conduct of research with synthetic human embryos, with scientific, ethical and legal experts, as well as experts from other disciplines, such as Science, Technology and Society ("STS"), from the U.S. and the U.K., as well as members of the public. The symposium featured wide-ranging discussions into the nature of these entities, the scope and rationales for research involving such entities, the ethical implications of such research, the role of ethical oversight committees such as the Harvard ESCRO, and the limitations of existing guidance for emerging technologies such as this.

This document presents the Harvard ESCRO's views and findings reflecting insights gleaned from the deliberations of this convened group of scholars and members of the public, with recommendations for academic institutions and ESCRO Committees about how research involving synthetic human embryos could responsibly move forward, and what principles should guide ESCRO oversight and review, as well as potential restrictions on such research. The discussion proceeds through the following three-part analysis:

- What are synthetic human embryos?
- What ethical concerns are relevant to the creation of synthetic human embryos?
- Should synthetic human embryos be subject to ethical review?

II. What are synthetic human embryos[1]?

In addition to being synthetic and composed of human cells, a synthetic human embryo is self-organizing, patterned, and/or integrated in ways that may raise ethical concerns separate and distinct from concerns raised by research conducted with simple cell cultures. Synthetic human embryos are morphologically indistinguishable from an early stage embryo and can recreate early embryonic morphogenesis. An additional important characteristic of these structures is that they may arise or may be created without passing through earlier developmental stages or normal processes found in embryogenesis.

Not all human self-organizing cellular structures raise similar concerns. There are few concerns regarding self-organizing liver cells in a dish, for example, or self-organizing muscle cells in a dish. However, synthetic human embryos that are integrated and complex in a way that might manifest human organismal potential may raise ethical concerns ripe for an ethical review body. These are the focus of our discussion below.

[1] The term "synthetic human embryo" to describe these entities was arrived at after considerable deliberation, sensitive to the issues of nomenclature in emerging areas of science such as this, and with an eye to towards avoiding being overly broad.

III. What Ethical Concerns are relevant to the creation of synthetic human embryos?

As indicated above, a broad range of entities may qualify as embryo-like, but only a subset of these may raise ethical concerns ripe for oversight and review. Taking a cue from the 2016 updates to the ISSCR Guidelines, an appropriate distinguishing factor may be synthetic human embryos that exhibit human organismal potential vs. those that do not. The 2016 ISSCR guidelines recommend that ethical oversight bodies review research involving the generation of embryo-like structures ***that might manifest human organismal potential***. However, the guidelines fail to define ***human organismal potential.*** We determined that we might contribute to this dialogue by outlining what it may mean to manifest human organismal potential. Some of the ethical concerns raised during the 2016 symposium proved particularly useful in beginning the process of outlining the contours of human synthetic embryos that might manifest human organismal potential, and thus warrant oversight, review, and potential restrictions.

A. Human Form: Does the synthetic human embryo have the physical appearance of the human form? The human form has had great symbolic, cultural, and religious significance throughout history. Somewhat distinctive from the ethical concerns highlighted below, this concern may not be dispositive of the question of whether a synthetic embryo manifests human organismal potential. However, entities that approximate the human form might warrant caution, consideration of these concerns, and analysis of whether oversight, review, and/or restrictions are warranted.

B. Human Reproduction: Another ethical concern is the relationship of the research on synthetic human embryos to assisted or artificial reproduction, an issue that has become entangled with views about the nature and moral status of prenatal life. In this rapidly evolving field, some techniques are currently widely permitted (for example, IVF and PGD), whereas others are generally deemed impermissible (human cloning or implanting a genetically modified embryo into a woman's uterus). The intended or unintended contributions of synthetic human embryos to asexual human reproduction will raise similar ethical issues and concerns.

C. Self-Consciousness: The possibility of creating a synthetic human embryo with the property of self-consciousness is a major ethical concern. While the definition of consciousness is itself a perennial question in philosophy and the sciences, often self-consciousness is considered to involve awareness of oneself versus others and the environment. Concern about the creation of entities that are self-conscious is not unique to synthetic biology; this has been a longstanding issue in the field of artificial intelligence.

D. Sentience: A related concern is the possibility of creating a synthetic human embryo with the level of awareness involved in what we might term "experiences of pain." Several distinctions are important with regard to this concern. While even single-celled organisms

like amoebae may demonstrate behaviors of aversion and attraction to certain stimuli, these are not considered to be synonymous with pain and pleasure. Pain is not merely the physiological response to a noxious stimulus; pain is the *experience* that is evoked by this physiological response. As such, we generally assume that only complex life forms are capable of experiencing pain. Suffering is an even more complex phenomenon and results from the cognitive and emotional responses we have to physical or psychological pain.

These relevant ethical concerns are not intended to be exhaustive, and additional concerns may arise as the research progresses. Of note, participants in the Symposium did discuss whether the so-called 14-day rule, which prohibits the culturing of human embryos beyond 14 days in a laboratory setting, was relevant to the research question before the ESCRO in particular and to human synthetic embryos generally. In the ESCRO Committee's view, the 14-day rule does not adequately contemplate or address the questions raised with respect to synthetic embryos. Application of the rule could result in under- or over-regulation and restriction. In coming to this conclusion, the Committee found the analysis explicated in an article authored by John Aach and the Church lab following the symposium particularly persuasive.[2] The article, *Addressing the ethical issues raised by synthetic human entities with embryo-like features (SHEEFs),* highlights the fact that the 14 day rule simply establishes a bright line limit for the development of embryos in a dish, based upon what it terms "canonical embryological stages" of development. But, as the authors elaborate, synthetic entities do not necessarily develop through these canonical stages of embryogenesis upon which the 14 Day Rule is premised[3]. In fact, advances in synthetic biology-based tissue and cell engineering make it possible for such entities to bypass stages such as the formation of the primitive streak, a stage specifically referenced in the NAS and ISSCR Guidelines' formulation of the 14-day rule. Thus, it is important to understand the rationales behind bright line rules such as the 14-day rule, to answer the *why* rather than focusing solely on the *what* in establishing guidelines for review. The Aach article posits "basing research limits … directly on the moral status signifying features," a proposal the Harvard ESCRO wholly endorses with respect to synthetic human embryos. Thus, the ESCRO Committee's decision to focus on the ethical concerns outlined above relevant to human synthetic embryos rather than milestones along the continuum of normal embryogenesis.

Additionally, the relevant ethical concerns are not intended to be conjunctive. In fact, the emergence of some may far pre-date the emergence of others. For instance, sentience and self-consciousness generally emerge at much later stages of human development than embryogenesis. Each ethical concern raises an independent basis for analysis of whether further ethical review and oversight is required and whether restrictions are appropriate. Thus, the emergence of one may be enough to counsel in favor of caution far in advance of the emergence of others. However, the

[2] Aach J, Lunshof J, Iyer E, and Church GM. Addressing the ethical issues raised by synthetic human entities with embryo-like features. eLife 2017;6:e20674. DOI: 10.7554/elife.20674.

[3] Aach J, Lunshof J, Iyer E, and Church GM. Addressing the ethical issues raised by synthetic human entities with embryo-like features. eLife 2017;6:e20674. DOI: 10.7554/elife.20674.

presence of more than one ethical concern may serve to bolster the conclusion that ethical oversight, review and related restrictions may be required.

Finally, analyzing these ethical concerns as they might apply to synthetic human embryos necessitates consideration of the physiological structure and developmental potential of these entities. Such consideration may help to inform whether the ethical concern is relevant. For instance, vascularization of such entities emerged as a significant factor in determining the developmental potential of the same. Engineered tissues, such as synthetic human embryos, need a vascular network to supply the cells with nutrients and oxygen to grow and develop. Without the development of vascularization, there are technological limitations on the size and development of such synthetic structures in vitro. These are considerations that might inform the deliberative process of any oversight body in this area.

In the ESCRO Committee's discussions, researchers raised two additional issues that deserve mention here. Researchers were concerned that merely mentioning characteristics such as consciousness or sentience could give the impression that the entities currently being created may actually possess these characteristics. The Committee wishes to emphasize that current research is far from creating entities that have these characteristics. In articulating these areas of moral concern, we are stating that restrictions on this research will only become necessary if, and when, the emergence of these characteristics becomes a measurable scientific possibility.

A second issue raised by the researchers concerned the absence of any concrete bright-line guidance on what is permissible and what is not. Given the current development of research into synthetic human embryos, it would be premature to attempt to define bright-line limits, since the entities being developed are still far from raising the moral concerns described above. As the science develops, however, the principles outlined above may help us to discern where bright-line guidance may be helpful and necessary.

IV. Should synthetic human embryos be Subject to Ethical Review?

The short answer is yes.

Like many ESCRO Committees, the Harvard ESCRO Committee's current scope of review is confined to the NAS Guidelines. We thus commend the Church lab for recognizing the ethical implications of this work and for voluntarily raising this emerging issue for our review and consultation. The Committee determined that the precise question before it did not violate existing guidelines, nor did it raise the ethical concerns highlighted above. As these colonies of iPS cells were not intact embryos, the Committee determined it would be appropriate to move forward with additional studies to determine the physiological potential for these entities, which only appeared to exhibit formations similar to the primitive streak. However, the Committee instructed the lab to return to the committee if it obtained histological and/or gene expression analyses indicating the initial formation of a nervous system, displaying appropriate anterior-posterior regionalization (i.e., a

forebrain, midbrain, hindbrain, and spinal cord). Additionally, the Committee instructed that the lab report back if they observed the formation of discrete endodermal or mesodermal derived organs in an organized pattern that mimics that observed in developing human embryos. At either point, the Committee would further analyze whether such entities raise any of the ethical concerns outlined above.

This type of deliberative process reflects how the Harvard ESCRO has historically approached emerging technologies for which there exists no established guidelines. The Committee requests that labs share their findings with the Committee in a step-wise process as it explores the broader issues of how to address gray areas such as this under the NAS and ISSCR Guidelines. Further, the Committee engages external researchers, and peer ethical oversight committees who have straddled this gray area, as well as thought leaders in the area of bioethics and other disciplines, such as Science, Technology and Society ("STS"), who have professional knowledge of the evolution and implementation of norms in these areas. This is largely what prompted the Harvard ESCRO to partner with the Safra Center for Ethics, the Petrie-Flom Center for Health Law, Bioethics and Biotechnology, the Harvard Stem Cell Institute and the HMS Center for Bioethics to convene the November 2016 symposium which broadened the discussion to include scientific, bioethics, and other thought leaders from across the US and abroad. In recognition of the fact that hPSC technologies have progressed beyond the confines of the current NAS guidelines, the Committee is always interested in determining how it might inform its own ethical guidance to its researchers. This is particularly so, in instances such as this, where human iPS-derived cells may be cultured in such a way as to approximate synthetic human embryos which may recapitulate phases of normal human development.

V. Recommendations:

The Aach article referenced above called for the development of guidelines that address the ethics of synthetic entities. The Harvard ESCRO Committee endorses this recommendation for the subset of entities that meet the definition of human synthetic embryos as described in this document and offers as its preliminary proposal that the ethical concerns listed above, coupled with what is learned about the physiological potential of these entities, provide the foundation upon which guidelines for the responsible conduct of this research and for ESCRO review of the same are developed. We anticipate that the deliberative process described above will lead to the development of more specific informed guidance in the future, as our collective understanding of these emerging entities evolves.