Compiled Public Comments on the Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

Guide Notice Number: NOT-OD-26-031

January 23, 2026 – April 24, 2026

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1. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Research Participant/Patient Advocate

Date Submitted: 01/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Why is the metric whether new hESC are submitted for approval or grants using them. Perhaps do a PubMed search using
(human embryonic stem cells[MeSH Terms])?

There is a slight decrease over the past few years but not one that suggests no one is using this material or would not be interested in new sources of cell lines.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
I think this is asking the wrong question. If it is truly innovative research, we won't know until it is explored whether hESC's would be required to answer the question. And if we knew what questions people in the future were going to ask, they would have been asked already. That is how scientific research works.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

2. Kendra Westervelt

I am responding: On behalf of myself

Name: Kendra Westervelt

Name of Organization: Kendra Westervelt

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 01/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Date: January 27, 2026
To: Office of Science Policy, National Institutes of Health
Re: NOT-OD-26-031 – Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

I am writing to provide feedback on the NIH's proposal to pause the review of new human embryonic stem cell (hESC) lines. As a concerned citizen and former employee of the NIH, I would like to focus on the critical role hESCs play in the current biomedical landscape and urge that the NIH be allowed to continue reviewing and using new hESCs.

Specific reasons to continue the review of new hESC lines,

1. Research Areas where hESCs are the "Gold Standard"**:** hESCs remain the essential benchmark for pluripotency. While induced pluripotent stem cells (iPSCs) are valuable, hESCs are vital for validating the safety and efficacy of these newer models.

2. Regenerative Medicine Impact: Current clinical trials for Parkinson's disease, Type 1 diabetes, and macular degeneration rely on the stable genetic profile of hESCs. Restricting new lines could stifle the development of next-generation therapies for these incurable conditions.

3. Drug Safety and Toxicity**:** The use of hESCs in early-stage toxicity screening provides a human-relevant model that reduces reliance on animal testing and prevents potential birth defects in human trials.

Additionally, the sudden pause on new registry entries may lead to:

1. Scientific Stagnation**:** Limiting the registry to the current 503 lines may exclude newer, more genetically diverse lines that are more representative of the global population.

2. Global Competitiveness**:** A reduction in federal support may drive leading researchers and biotech investments to other nations with more permissive research frameworks, something we are already seeing due to the number of other damaging changes implemented within our nation's scientific institutions.

While I support the development of alternative technologies like organoids and iPSCs, they are not yet a complete replacement for hESCs. I urge the NIH to maintain a robust

registry to ensure that American patients benefit from the highest standard of regenerative medicine.

Thank you for the opportunity to respond.
Kendra Westervelt

3. Hans-Willem Snoeck

I am responding: On behalf of myself

Name: Hans-Willem Snoeck

Name of Organization: Columbia University

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 01/28/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The NIH registry of approved hESC lines now contains 503 lines. The fact that no new lines were recently submitted is not an argument for phasing out hESC research or halt submission of new lines, but indicates that a sufficient number of approved lines are currently available.

However, hESC lines will acquire mutations and epigenetic changes over time as they are passaged. We will therefore still need a regular supply of new lines in the future.

Furthermore, in addition to hECSs, cell lines may be generated from discarded IVF embryos that represent even earlier stages of embryonic development than hESCs (so-called totipotent cells). Such cells may have a broader developmental potential and may facilitate research into the earliest stages of human development, with repercussions on our understanding of infertility, of fetal demise and of environmental effects on early embryonic development, or may prove to be superior to hESCs or hiPSCs in clinical applications in the future. Such novel lines, if and when available, will also need to be submitted to and vetted by the NIH registry.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs are still the gold standard in all pluripotent stem cell research. All hiPSCs are benchmarked against hESCs, which therefore serve as essential controls. hESCs and hiPSCs show consistent epigenetic and transcriptomic differences, including differences in X chromosome activation and inactivation. iPSCs have also been reported to possess 'epigenetic memory', which means that the tissue from which the iPSCs were generated affects their pluripotency state and determines their potential as stem cells. For clinical applications, it is still not known which cell type, hESCs or hiPSCs, will be the ultimate gold standard in terms of both safety and efficacy for regenerative medicine using derivatives of pluripotent stem cells. We therefore still need research, including clinical trials, using both types of pluripotent stem cells. I also note that 42% of current clinical trials use hESCs.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
There are currently no such areas. A major advantage of pluripotent stem cells is the fact that they can be expanded quasi indefinitely. Furthermore, because of their broad differentiation potential, they allow the generation of complex organoids that begin to reflect the cellular diversity and architectural

complexity of organs. This is not the case for most adult stem cells, although, for example, intestinal stem cells have been shown to possess very extensive expansion potential.

Furthermore, some adult tissues do not contain stem cells. Human adult neural stem cells are very rare, nearly impossible obtain, and have not been shown generate brain organoids. The spinal cord and heart are not endowed with endogenous stem cells. The only well-validated kidney organoids are derived from pluripotent stem cells. Certain types of lung stem cells as well as lung organoids can currently only be generated from pluripotent stem cells. As I mentioned before, all hiPSCs are benchmarked against hESCs, which therefore serve as essential controls. It would therefore be unwise at this moment to systematically replace hESCs with other types of stem cells even in select areas of research.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

The significance of the epigenetic and transcriptomic differences between hESC and hiPSCs should be studied more systematically and more in depth. This is challenging and costly as such an endeavor would require the parallel study of large number of lines for differentiation into multiple tissues with functional validation by, for example, transplantation into immune deficient animals. In the context of scaling down the use of hESCs, this would be a worthwhile concerted effort, however.

4. Deirdre Logsdon

I am responding: On behalf of myself

Name: Deirdre Logsdon

Name of Organization: University of Colorado at Boulder

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 01/28/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
This is objectively UNTRUE. It is a priority to expand research to expand to organoids and stem cell based methods to study critical disease priorities including autism spectrum disorder, Alzheimer's disease, type II diabetes to name a few. Human embryonic stem cells are the gold standard pluripotent stem cells to generate organoids necessary to study such diseases. As of now, there are no previously derived human embryonic stem cell lines that contain the genetics that may predispose an individual to these diseases. Culture conditions are also constantly improving, and thus new lines that capture unique genetic backgrounds in optimal culture conditions are needed to make significant progress in diseases that plague our country.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
I study early placental development. Since fetal tissue is restricted, and placenta formation is truly unique to humans, differentiation of placental cell types from pluripotent stem cells is NECESSARY. This can either be accomplished from 1) primed-state pluripotent stem cells which is more efficient from human embryonic stem cells or 2) from naive-state pluripotent stem cells which is also more efficient in human embryonic stem cells. The former requires BMP4 stimulation by which human embryonic stem cells are more susceptible than induced pluripotent stem cells. Only female pluripotent stem cell lines will reset to a naive pluripotent state which restricts studies for male babies specifically. This is a problem since male babies are variably susceptible to pregnancy complications. In summary, if human embryonic stem cell use is restricted in addition to the fetal tissue ban and animal model restriction, research in placental development will suffer greatly.

Differentiation of pancreatic cell types are more robust in human embryonic stem cells. My daughter has type 1 diabetes, and stem cell based research and therapies in this space is so close to finding cure. This is not possible without the use of human embryonic stem cells. Millions of children will not have the hope of transplantation technology later in their life if research in this area is stalled. As a mother, I beg that research with human embryonic stem cells be allowed to extend my child's life.

Neural differentiation protocols are less efficient owing to the reduced expression of genes specific to neuron development in induced pluripotent stem cells compared to human embryonic stem cells.

Research for cell types that have specific patterns of X-chromosome activation (primitive oocytes,

primordial germ cell like cells) are altered in induced pluripotent stem cells because female induced pluripotent stem cells have already inactivated a random X chromosome.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Induced pluripotent stem cells will never truly replace human embryonic stem cells. Yes, somatic cells can be reprogrammed to a pluripotent state. However, this pluripotent state is not equivalent to the "gold standard." In a direct comparison, "iPSCs retain residual regulation characteristic of the cells from which they were derived. These differences do not appear to appreciably alter cellular function in the pluripotent state but instead may surface during differentiation as cells invoke gene expression programs needed for development." Signaling pathways retain activation left over from the originating cell type which can alter how they are used to model disease.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Early placental development, pancreatic cell differentiation, cerebral organoids, primordial germ cell-like cells

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/iPSC_hESC_commentary.pdf

Description: A direct comparison between iPSC and hESC was done by the lab that derived the first hESC line. This is a commentary on their work and includes relevant references.

process also has to be proven indisputably safe for offspring.

In conclusion, although the results of Ben-Nun *et al.*[6] are intriguing, the practical obstacles we mention here indicate that iPSCs are no quick fix. There will need to be decades of basic research investment before it is possible to reap the dividends of viable offspring production. Obstacles notwithstanding, it is an unambiguous fact that there is great value in cryobanking biomaterials from every valuable rare individual, which will permit continued pursuit of novel methods, including iPSC generation, for preserving rare species.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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The proteomes of native and induced pluripotent stem cells

Martin F Pera

A comparison of embryonic stem cells and induced pluripotent stem cells on the proteome level reveals subtle distinctions between these cell types that might explain differences in their ability to differentiate into specific lineages.

Like embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) can be expanded indefinitely *in vitro* and have the potential to develop into any type of cell in the body. Unlike ESCs, however, iPSCs can be generated from easily accessed tissues from individuals such as skin or blood. Thus, iPSC technology avoids the ethically problematic requirement of destroying embryos and enables the facile development of cell lines from individuals with genetic predisposition to disease or from donors representing a diversity of major histocompatiblity complex haplotypes. These features are the important advantages of iPSCs over ESCs in research and for tissue matching in cell therapy. However, from the first reports of the derivation of iPSCs[1], researchers have questioned whether they are truly biologically equivalent to pluripotent cell lines from embryos. In this issue of *Nature Methods*, Phanstiel *et al.*[2] report the first proteomic comparison of ESCs and iPSCs (**Fig. 1**). Their conclusion is that although it is actually quite difficult to distinguish the two cell types even with very refined analysis, there are small but reproducible differences in their proteomes and phosphoproteomes that might account for variations in their ability to undergo differentiation into specific lineages.

A plethora of studies have compared ESCs and iPSCs with respect to their genetic stability, and the status of their transcriptomes and epigenomes[3]. Although these reports have almost invariably uncovered differences between these closely related cell types, it remains to be seen how generalizable these differences are between experimental studies, whether the differences between ESCs and iPSCs are in fact any greater than those observed between ESC lines, and finally what the biological importance of the molecular differences is. It is, of course, possible that the critical features that distinguish the two cell types might lie in the regulation of gene expression at the post-transcriptional or post-translational levels. Phanstiel *et al.*[2] apply powerful and innovative proteomics technology to address this important question.

Phanstiel *et al.*[2] studied a total of eight cell lines, including four ESC lines and four iPSC lines, in biological triplicate. They used state-of-the-art mass spectrometry technology that enables enhanced coverage of the proteome and phosphoproteome, and isobaric tagging to facilitate the comparison of multiple samples and cell lines in a single experiment. Six weeks of data acquisition resulted in the identification of nearly 7,000 proteins and over 19,000 phosphorylation sites in the lines. But the amounts of approximately just 300 proteins and phosphoproteins differed between ESCs and iPSCs (mostly with a less than twofold difference). These relatively small differences would not have been detectable without multi-sample comparisons, as Phanstiel *et al.*[2] show. They also found that for the most part, the differences in the amount of a given protein in a cell line did not correlate with differences in the amount of its RNA transcript, and the subset of proteins showing differences in phosphorylation did not overlap with that of proteins showing differences in expression.

Notably, gene ontology analysis of the data showed that differences between ESCs and iPSCs could be detected at the transcriptome, proteome and phosphoproteome levels. They detected major variances in gene networks associated with muscle-system processes, muscle contraction and wound healing. The authors point out that these categories reflect functions of cells of mesodermal origin, and indeed, as anticipated, they found that the activity of the same networks discriminated fibroblasts from ESCs.

Their findings echo previous comparative transcriptome and epigenome studies that adduced evidence for a memory of somatic tissue origin effect in iPSCs: genes specific to the lineage of the parent somatic cell are only partially extinguished in iPSCs[4,5]. Such residual molecular memory is thought to impact the differentiation capacity of the iPSC line, which, as some observations suggest, may be biased toward the lineage of the somatic cell of origin and compromised for other lineages. However, the analysis of Phanstiel *et al.*[2] did not include differentiation studies to examine this hypothesis, and they did not explicitly address whether memory of tissue of origin as manifested in their study might be erased during long-term iPSC culture, as observed by others[5]. These important questions still remain to be investigated.

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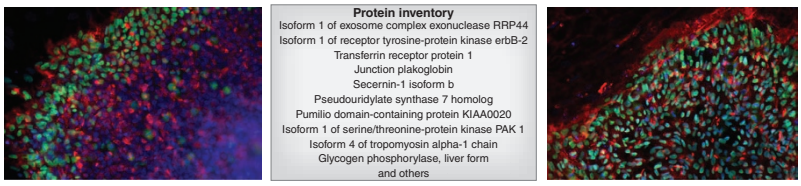


Figure 1 | A proteomic comparison of human ESCs and iPSCs. Images of iPSCs (left) and ESCs (right) are shown stained for Tra-1-60 (red), Oct-4 (green) and with 4′,6-diamidino-2-phenylindole (DAPI). Though the proteome inventories of iPSCs and ESCs are similar, subtle yet substantial differences in protein expression and phosphorylation were found for a number of proteins. Images courtesy of Jordan Pomeroy, Pera laboratory.

Finally, Phanstiel *et al.*[2] incorporated their data into a new, open-access database encompassing transcriptomic, proteomic and post-translational modification data for pluripotent cells, called the Stem Cell Omics Repository or SCOR. They also entered datasets from previously published reports into SCOR and analyzed them, though the authors do not indicate whether their conclusions about memory of somatic cell of origin are corroborated by the earlier work. As this study illustrates, robust examination of hypotheses concerning differences and similarities in ESC and iPSC lines will require meta-analysis on a scale that cannot be accomplished in a single laboratory. The availability of databases such as SCOR will help enable such analyses. Though welcome, the proliferation of databases on gene expression in pluripotent cells suggest that there will soon be a need for international harmonization on the platforms and analytical approaches used to perform large-scale comparisons of ESCs and iPSCs.

In a sense one can regard the study of Phanstiel *et al.*[2] as the latest in a series of tests of the hypothesis[6] that gene expression patterns are predictive of pluripotency. An emerging theory highlighted by this study, and from other recent work, is that although gene and protein expression patterns in ESCs and iPSCs maintained in the pluripotent state may be very similar, somatic cell memory of origin might strongly influence the cell's ability to undergo differentiation. A corollary of this concept is that the expression of pluripotency genes alone may not be predictive of a cell's developmental capacity.

There are multiple examples from the mouse and human stem-cell literature demonstrating that the ability of a cell to undergo self renewal and maintain an embryonic phenotype may be dissociated in either very subtle or very dramatic ways from its ability to undergo differentiation into derivatives of the three embryonic germ cell layers (for a review of the early literature, see ref. 7). In other words, it is likely that maintenance of the pluripotency network at the molecular level[8] is necessary but not sufficient to confer biological pluripotency. The data of Phanstiel *et al.*[2] indicate that very large scale studies will be required to address this question, and the problem is also confounded by uncertainty in the human pluripotent stem cell field over what biological assay best defines pluripotency (for example, ref. 9).

The study also points to the urgent need to develop robust biological assays to help decipher the relationship between the molecular phenotype of pluripotent cells and their differentiation capacity.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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Cells see the light to bring signaling under control

Jason M Haugh

The combination of optogenetics with feedback control counteracts variability in cellular signaling responses to promote a deeper understanding of the biochemical mechanisms involved.

Living cells must respond in prescribed ways to external cues. The underlying biochemistry of such responses is a jungle of interactions among intracellular signaling proteins, with multiple layers of regulation. Getting a handle on this complexity will be of paramount importance if our understanding of how signaling networks are controlled and of how they are corrupted in cancer and other disease states is to advance. Signaling phenomena that vary temporally and spatially are best characterized through direct observation of individual cells, usually in conjunction with fluorescent fusion proteins or protein biosensors, but such studies are often hampered by the intrinsic heterogeneity among cells and the variability of the cells' surroundings[1,2]. In this issue, Toettcher *et al.*[3] report an innovative approach to the problem that combines something new from chemical biology (optogenetics) with something borrowed from engineering (feedback control; **Fig. 1**).

Optogenetics (this journal's Method of the Year for 2010) refers to the introduction into a cell or organism of genetically encoded proteins that may be controlled with light to affect when and where a certain biological process is activated. Interest in this approach from the cell biology community has been heightened since the demonstrations that small GTPases of the Rho family and other signaling proteins can be activated locally and reversibly, through the clever use of light-responsive protein domains derived from plants[4–6].

Toettcher *et al.*[3] applied the light-gated interaction between a phytochrome (Phy) and a phytochrome interacting factor (PIF) to direct reversible protein translocation to the plasma membrane[5], a common strategy for activating signal transduction, and they merged this approach with one that is time-honored in engineering: feedback control. In this method, the measured variable (here protein translocation monitored by total internal

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5. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 01/28/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
There are no research areas that are ever sufficiently addressed by any experimental models. Science is an ongoing pursuit of truth that seeks to perpetually advance our knowledge of the universe, without ever attaining absolute, unimpeachable truths. Thus, there is no scientific rationale or line of research in which new hESC lines should be prohibited, particularly since the embryonic or fetal sources of hESCs would be otherwise discarded. Specific examples of when new hESC lines would be needed include research areas for which 1) existing hESC lines do not have ideal genetic backgrounds or differentiation potential, and 2) existing hESC lines are too limited in number to analyze how genetic background, sex, ethnicity, or other variables affect cellular or disease phenotypes.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs are the only existing source of cells that represent the naive, pre-implantation, pluripotent stem cell state. hiPSCs generally cannot mimic this state, and thus any research areas that require this state (such as early human development or developmental disorders) will require hESCs. In addition, the "naive" state of hESCs is a better model system for studying X chromosome inactivation, which underlies many severe diseases, such as Fragile X Syndrome, Rett Syndrome, Duchenne Muscular Dystrophy, and others. Finally, hESCs do not suffer from epigenetic memory of the tissues from which they were derived, unlike hiPSCs. hiPSCs are not able to differentiate into the different cell and tissue lineages as consistently as hESCs, and thus are not always suitable for stem cell based studies more generally. Finally, hiPSCs result from reprogramming single somatic cell clones, which are not representative of the patient they were derived from, due to vast genetic and epigenetic differences between the trillions of cells in the human body. hESCs, on the other hand, come from a much smaller number of ESCs that eventually give rise to an adult human.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
There may be areas of research in which hiPSCs or adult stem cells can effectively replace hESCs at some point, but this is a hypothetical that cannot be predicted. Thus, there is no rationale for prohibiting new hESC lines from being made.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
It's not clear to me why replacing hESCs should be a goal, given their inherent advantages over hiPSCs (naive, non-reprogrammed pluripotent cell state) and adult stem cells (ultimate source of adult stem cells that are infinitely renewing and easy to genetically modify), and the lack of alternative uses (embryonic or fetal sources of hESCs are simply thrown in the trash if not harvested for hESC isolation). While hiPSCs are a critical complement to hESCs, particularly due to their ability to be reprogrammed from virtually any human healthy control or disease patient somatic cells, scientific and medical progress will suffer any time specific model systems are eliminated or restricted.

6. Meaghan Courvan

I am responding: On behalf of myself

Name: Meaghan Courvan

Name of Organization: University of Colorado Boulder

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 01/28/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
A lot of developmental research requires hESCs, because they have the ability to differentiate into more different types of tissue than iPSCs or adult stem cells. They are the only ethical way to study fetal development, the placenta, and the molecular biology of pregnancy. The loss of hESC research would also be the loss of interest in the health and wellness of fetal development and expectant mothers.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

7. Paula Amato, MD

I am responding: On behalf of myself

Name: Paula Amato, MD

Name of Organization: Oregon Health & Science University

Type of Organization: Academic Institution

Role: Clinician

Date Submitted: 01/29/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Shifting away from hESC research is short-sighted in my view. We have published several papers showing the superiority of hESCs compared to IPSCs including this one:

https://pubmed.ncbi.nlm.nih.gov/25008523/

Science policy should be evidence-based and not ideologically based.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs show great promise for "therapeutic cloning" i.e. genetically matched cell-based therapies derived via SCNT, for conditions such age-related chronic degenerative disease (Alzheimer's, CVD, diabetes, etc.). The advantage of hESCs is that they are more genetically stable compared to iPSCs due to the fact that long culture times are not required. Furthermore, the mitochondria are from young oocytes whereas with iPSCs cells they are usually from older somatic cells which have acquired genetic mutations. We believe that mitochondrial transfer is one of the mechanisms by which SCNT-derived ESCs can be used to treat age-related diseases.

Also, shifting away from hESCS risks falling behind other countries such as China in biotech innovation which could have national security implications as many reproductive technologies have potential dual uses.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
iPSCs have some advantages over hESCs in that they do not require donor oocytes and are less ethically controversial. However, the therapeutic efficacy would be expected to be much less.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Stem cell models or organoids are somewhat useful to study early reproductive/embryonic development because they are less ethically controversial than using in-vitro human embryos.

8. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Other

Type of Organization - Other: N/A

Role: Member of the Public

Date Submitted: 01/29/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Research should not be further incumbered by adding restrictions. Sientific advance and betterment of the human condition requires options and research tools. To further restrict works against that goal. Further, our global competitors should not be handed advantages by our regulators and beurocrats. Support research. Keep tools available.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Research should not be further incumbered by adding restrictions. Sientific advance and betterment of the human condition requires options and research tools. To further restrict works against that goal. Further, our global competitors should not be handed advantages by our regulators and beurocrats. Support research. Keep tools available.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Research should not be further incumbered by adding restrictions. Sientific advance and betterment of the human condition requires options and research tools. To further restrict works against that goal. Further, our global competitors should not be handed advantages by our regulators and beurocrats. Support research. Keep tools available.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Research should not be further incumbered by adding restrictions. Sientific advance and betterment of the human condition requires options and research tools. To further restrict works against that goal. Further, our global competitors should not be handed advantages by our regulators and beurocrats. Support research. Keep tools available.

9. Sarah Hernandez, PhD

I am responding: On behalf of myself

Name: Sarah Hernandez, PhD

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Research Participant/Patient Advocate

Date Submitted: 01/30/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Huntington's disease and other devastating hereditary brain diseases that have a clear, urgent unmet medical need. hESCs are advancing future treatments for these diseases the decimate families generation after generation.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

10. Patrick Redmond

I am responding: On behalf of myself

Name: Patrick Redmond

Name of Organization: N/A

Type of Organization: Other

Type of Organization - Other: Citizen

Role: Member of the Public

Date Submitted: 02/02/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC can be solicited from adult volunteers, organ donors, even animals, without using Embryonic tissues from aborted children

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Cell lines grown from aborted childrens cells could be substituted by cells taken from adult volunteers, ond/or organ donors.Researc

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Research hospitals, Universities,and colleges, can obtain stem cells for their research from many sources other than aborted children or fertilized eggs stored in freezers.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
The medical and disease research should use cell lines obtained from volunteers. They could even use skin cells from the scientists themselves.

11. Melissa Kemp

I am responding: On behalf of myself

Name: Melissa Kemp

Name of Organization: Georgia Institute of Technology

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/03/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
My lab studies neural rosette formation using human ESCs. This is an example where iPSCs are not appropriate for substituting the properties of ESCs when asking questions regarding human embryonic development. Our research minimizes the use of fetal tissue and is an excellent NAM for studying organizational properties during early loss of pluripotency.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

12. Kristin moore

I am responding: On behalf of myself

Name: Kristin moore

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 02/04/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Research is ever changing and evolving and the procedures that were used in the past to cultivate and store cells may not be appropriate for future applications. It is short-sighted to assume that currently developed lines will be sufficient to meet the needs of future research.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
The is only one type of tissue that has the innate ability to develop into any tissue type of the human body and those are embryonic stem cells. While less viable alternatives exist some research can only be done using these specific types of cells specifically in areas of developmental reseach

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
iPSCs are undoubtedly a valuable tool for researchers, but they will never be the same biologically as a cell that has not previously been differentiated. iPSC cannot replace the truly pluripotent nature of hESCs.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
hESCs are the gold standard to compare against. As stated above research is ever changing and new models developed to replace hESCs will need to be validated against them requiring the continued use of hESCs

13. Mollie Meffert

I am responding: On behalf of myself

Name: Mollie Meffert

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/06/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
New hESC lines are urgently needed for many diseases of the nervous system. Even when iPSC lines are available, issues of iPSC lines retaining gene signatures from their cell of origin and inability to differentiate into all cells, means that hEPSC lines are exceptionally valuable and neccessary for conducting reliable and robust science.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human embryonic stem (hES) are the gold standard for robust and reliable derivation of many human cell and tissue types for biomedical research related to human disease. hEScapacity for sustained self-renewal and the ability to differentiate into all cell types in the body makes hES a critical foundational platform enabling research into human development, disease mechanisms, the development of new regenerative medicines, and screening tools for the discovery of new disease therapies.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Even when iPSC lines are available, issues of iPSC lines retaining gene signatures from their cell of origin and inability for distinct lines to differentiate into all cell types means that hEPSC lines are exceptionally valuable for conducting reliable and robust science.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Federal support and funding for hES cell research is essential. Statements in the congressional letter reflect misinformation or misunderstanding about the present science of stem cell research. Eliminating federal support for hES cell research would not save any embryos from destruction as these lines were already created from discarded embryos. Eliminating federal support for hES cell research would delay and/or prevent the discovery of therapies for human patients with serious medical conditions. Responsible, innovative treatment strategies to save and improve the lives of citizens in this nation will be best developed by not tying the hands of scientists in this nation.

14. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/06/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Currently existing hESC lines are sufficient:
1. Research areas where new methods are to be developed to produce different tissue or cell types in vitro and confirm the function in vivo.
2. Investigating how the human stem cell pluripoteny are regulated and differentiation pathways are regulated.

Research areas where new hESC are needed:
1. Establishment of genomic stability in human pluripotent stem cell states.
2. Derivation of genetically unique stem cell lines, such as a large deletion or whole arms or whole chromosomes are absent.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Bona fide hESCs are needed to determine the whole genome-wise epigenetic states and 3D genome structures.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Establishment of methods to differentiate pluripotent stem cells into specific tissue of interest or use.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Investment or funding opportunity for testing the in vivo function of hESC-derivatives is needed.

15. George Chen

I am responding: On behalf of myself

Name: George Chen

Name of Organization: UCLA

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/06/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Human embryonic stem cells have the potential to make any cell type in the body in unlimited quantities. Research in this area is producing innovative new approaches to treat diseases that represent major public health problems, and cells derived from human embryonic stem cells are now being tested in clinical trials as treatments for diabetes, spinal cord injury, heart failure, macular degeneration and Stargardt's macular dystrophy.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Fetal tissue research has been critical for scientific and medical advances that have saved the lives of millions of people, including the development of vaccines against polio, rubella, measles, chickenpox, adenovirus, rabies, as well as treatments for debilitating diseases such as rheumatoid arthritis, cystic fibrosis, and hemophilia.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
I support all forms of stem cell research, performed under rigorous and transparent oversight, and advocates that embryonic, adult, and reprogrammed stem cell research must move forward in parallel to best understand disease and identify treatment.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Recent advances in stem cell research, gene therapy, genomics, and cancer biology have created unprecedented opportunities to create new treatments for human disease. However, decreased funding investments and budget cuts could slow the development of new cures and cause long-term damage to the international research infrastructure and to public health efforts around the world.

16. Shigeki Iwase

I am responding: On behalf of myself

Name: Shigeki Iwase

Name of Organization: University of Michigan

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/06/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Already generated hESC lines for human genetic disorders are a very important resource. Generating new human disease models in hESCs is still very important.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Modeling human genetic disorders and drug screening with the hESCs.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Human induced pluripotent stem cells (hiPSCs) has limitation in that they have remaining epigenetic marks of original cell types, such as fibroblast and blood cells. These artifacts limit the accurate modeling of human genetic disorders.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Understand and manipulate the difference between human ESCs and iPSCs such that iPSCs become a true replacement of hESCs. Investing in animal models is also important.

17. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/07/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Many established differentiation protocols (pancreatic beta cells, heaptocytes, neurons, myeloid cells etc) were established on Wisconsin cells, such as H1, H9, Harvard cells (HUES), and other cells such as WIBR cells. If stop hESC completely, it will be very challenging, and impossible to benchmark additional human stem cells including iPS cells.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

18. Justin Brumbaugh

I am responding: On behalf of myself

Name: Justin Brumbaugh

Name of Organization: University of Colorado

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/09/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The federal registry provides a list of validated human embryonic stem (ES) cell lines that are used for a broad range of applications, both related to basic science and the direct development of therapeutics. These lines remain a mainstay of the field and are well-suited to study many aspects of post-implantation development, to characterize differentiation processes, and to perform assay development. That said, human ES cells remain a relatively new technology and both the derivation of ES cells and their maintenance are challenging because these cells are delicate and difficult to stably culture. Optimizing media and culture conditions is an iterative process and both continue to improve, which greatly extends the utility of the cells. For example, the field continues to work on conditions that permit stable passage of the "naïve state," which models pre-implantation cells and enables the study of key developmental transitions that simply were not possible only a few years ago. A crucial point is that culturing cells in media designed to capture ES cells in later developmental stages (as is the case for many lines of the federal registry) can change their epigenetic profile, rendering them unusable for other applications, particularly studies of pre-implantation developmental stages. Moreover, many of the cells currently on the federal registry were derived in undefined culture conditions and, in some cases, in the presence of mouse feeder cells. As a result, some lines may not meet the regulatory standards for GMP designations and clinical use. Finally, genetic background has a strong influence on normal physiology and disease states. Our current lines reflect only a small fraction of the population and are therefore insufficient to represent the complexity of human biology. For these reasons, halting the addition of new human ES cell lines to the federal registry would restrict the availability of lines derived under optimized, defined conditions and severely limit both basic science and medicine moving forward.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human ES cells remain the gold standard comparator for novel and innovative techniques to model development. They have widespread applications in drug testing, disease modeling, and developmental studies. Specifically, they are key for benchmarking and validating induced pluripotent stem cell reprogramming strategies and serve as a reference standard for pluripotency. The field has a deep understanding of the molecular features associated with human ES cells and hundreds of directed differentiation protocols have been developed using human ES cell lines. Moreover, complex tools like reporter lines, knockout lines, knock-in lines, and degron lines are currently more broadly available and far better characterized in embryonic stem cell lines. Experimental workflows in academic labs, clinical labs, and the pharmaceutical industry were developed and standardized using human ES cells and are

supported by established regulatory frameworks. It would take many years and millions of dollars to re-establish the same tools and breadth of knowledge for alternatives like induced pluripotent stem (iPS) cells. Finally, as the field continues to work toward models that recapitulate the earliest developmental events, it is unclear whether iPS cells, which have already experienced later developmental conditions, can contribute in the same way as human ES cells. In any case, human ES cells will be necessary to demonstrate that models developed from iPS cells are a faithful representation of early cell fates.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

Human iPS cells are a valuable, complementary tool to ES cells, but they are not a replacement. A crucial point is that the quality and developmental status of iPS cells are dependent on reprogramming method, culture conditions, and even passage number. As a result, substantial variability exists between iPS cell lines that limit their broad utility. For example, some iPS cell lines don't differentiate as efficiently as ES cells into neural lineages (PMCID: PMC2840097). It should also be noted that the reprogramming process itself causes cellular stress that may increase mutation burden, which may, in turn, influence applications in basic science and is an important consideration for any clinical application. Moreover, c-Myc, an oncogene, is often used to reprogram cells to an induced pluripotent state and even if non-integrating methods are used for reprogramming, the long-term effects of c-Myc expression and potential to contribute to an oncogenic state are unclear. A final important point is that the discovery and validation of iPS cells were made possible by foundational research on ES cells and efforts to improve reprogramming still rely on ES cells to benchmark their developmental state. Adult stem cells are a valuable tool in their own right, but they are naturally limited to modeling certain cell fate transitions and cannot recapitulate early developmental events.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

For reasons described above, additional investments should continue to focus on developing technologies to complement, not replace human ES cells. With that in mind, it will be fundamentally important to standardize iPS cell line derivation to ensure cell quality, genomic stability, and differentiation capacity. It will likewise be important to establish reference lines for use across the field. Investment is also needed to incorporate iPS cells into parallel workflows with human ES cells, enabling rigorous benchmarking and validation of iPS cells in applications already developed for human ES cells. Finally, understanding how culture conditions and reprogramming methods impact iPS cell developmental status and stability continues to be an important area moving forward.

19. Louis Dang

I am responding: On behalf of myself

Name: Louis Dang

Name of Organization: University of Michigan

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 02/09/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Currently available hESC lines and their derivatives (e.g. knock-out and knock-in lines) have been valuable resources for studying genetic diseases. To stop using these lines would deprive the stem cell research community of numerous resources that are currently available to study biology and diseases. This would waste the resources that were previously used to make the hESCs and their derivatives.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
While human iPSCs can likely replace hESCs in many areas (for example to study human neurological diseases with hPSC-derived neural cultures), deriving new iPSC lines, particularly those with specific knock-out or knock-in genetic variants would be costly when there are already established hESCs for use.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

20. Cherie Stewart

I am responding: On behalf of myself

Name: Cherie Stewart

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 02/11/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

21. Diane Krause

I am responding: On behalf of myself

Name: Diane Krause

Name of Organization: Yale University

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 03/04/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
It is absolutely essential that existing approved hES lines continue to be used in NIH proposals. These cells are the gold standard for pluripotent cells and tools have been created using these lines that would take years of work to reproduce in other systems. With the NIH steering investigators away from the use of animal models, these human cell line models. You are intentionally limiting what scientists can do for no reason.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Any research for which lines have already been optimized and modified for the work to continue. If a laboratory has worked with hES already then this work needs to continue with the same tools. This includes work in multiple systems including lung, hematopoiesis, endocrine organ function (we have created reporter lines at a significant cost of time and reagents thab would take years and more than $200,000 to reproduce), as well as studies of niche and fibrosis.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
None. Unless the work has not started and iPSC are considered adequate.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Not sure - there are already a lot of lines. But what's the difference to the NIH since making such lines is already outside of NIH funding? Why bother creating rules that affect the use of newly made lines if the are going to exist anyway? There is no logic to these NIH funding limitations. Just creating more pain for researchers who already have limited funding and a crippled NIH due to nonstrategic across the board layoffs.

22. San Diego Regenerative Medicine Institute

I am responding: On behalf of an organization

Name: Xuejun Parsons

Name of Organization: San Diego Regenerative Medicine Institute

Type of Organization: Non-profit Research Organization

Role: Organizational Official

Date Submitted: 03/16/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
All the NIH-approved human embryonic stem cell (hESC) lines currently on the NIH hESC Registry are research-grade for research purposes only, only suitable for preclinical research. The NIH hESC Registry has no clinical-grade hESC lines suitable for therapeutic purposes, clinical applications, human trials, or patient uses.

All the currently approved hESC lines on the NIH hESC Registry are research-grade exclusively for preclinical research only, but none of those hESC lines eligible for Federal finding are biologics-free, clinical-grade hESCs suitable for therapeutic purposes, clinical applications, human trials, or patient uses. Because all the NIH-approved hESC lines were initially derived and maintained on mouse feeder cells and proteins, therefore, such hESC lines have been contaminated with animal cells, biologics, and genetic materials, unsuitable for clinical applications to patients or not clinically compatible. Using mouse feeder cells and foreign biologics for derivation, maintenance, and differentiation of these hESC lines currently on the NIH hESC Registry has compromised their therapeutic potential because of the risk of transmitting xeno-biologics and xeno-pathogens, altering genetic background, and promoting the expression of immunogenic proteins.

Although the NIH hESC registry currently has approximately 486 approved hESC lines, only a few, about 4-6 hESC lines, are commercially available for research purposes only, all from the Wicell Research Institute. Due to early improper handlings during passaging, most of the hESC lines currently on the NIH hESC registry are in extremely low quality or already dead, and therefore, could not be used for research anymore. For example, some of these NIH-approved hESC lines could not even be thawed alive from cryo-freezers. Even though some of these hESC lines could be grown back from cryo-freezers, they were found no longer at the pluripotent stage (e.g., no longer express pluripotent markers like Oct-4, SSEA-4), and therefore, no longer useful to get any hESC research going. All the NIH-approved hESC lines were initially derived and maintained using mouse supporting cells. Mouse cells grow much faster than human cells and survive harsh handlings during passaging much better than hESCs too. As a result, some of these NIH-approved hESC lines (e.g., Doug Melton's lines of Harvard) have apparently been contaminated or altered by mouse cells, because those cells actually express mouse cell markers (e.g., SSEA-1), but not hESC markers (e.g., SSEA-4), and behave more like mouse cells too. Therefore, it is essential for NIH to authenticate all the NIH-approved hESC lines and assess the quality of all the hESC lines currently on the NIH hESC Registry to ensure they are actually pluripotent hESC lines and in good

quality for hESC research.

High-quality, biologics-free, clinical-grade new hESC lines are needed for clinical translation of hESC research and therapeutic applications, such as developing hESC-based stem cell therapies for tissue and function restoration and bio-fabrication of human replacement tissues/organs. Breakthroughs and advances in the last 20 years of hESC research have established defined hESC culture platforms to provide biologics-free (e.g., feeder-free, xeno-free, conditioned-medium-free, serum-free), defined culture systems for well-controlled, efficient derivation, maintenance, and differentiation of clinical-grade, high quality, cGMP compatible, stable hESC lines [e.g., Parsons. 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. Gene and Cell Therapy: Therapeutic Mechanisms and Strategies, Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318; Parsons, et al. 2012, Defining conditions for sustaining epiblast pluripotence enables direct induction of clinically-suitable human myocardial grafts from biologics-free hESCs. J. Clinic. Exp. Cardiology 2012;S9-001]. Defined hESC culture platforms allow all poorly-characterized and unspecified biological components and substrates in the culture system, including those derived from animals, to be removed, substituted, and optimized with defined human alternatives for de novo derivation and long-term maintenance of cGMP-quality, xeno-free, stable hESC lines and their human cell therapy derivatives, which have never been contaminated with animal cells and proteins, thus suitable for therapeutic development and clinical applications. Such breakthroughs in hESC research have overcome some major obstacles in bringing hESC therapy to the clinic, enabling de novo derivation of clinical-grade, cGMP compatible, stable hESC lines from human blastocysts that have never been contaminated by animal cells and proteins, and direct conversion of such pluripotent hESCs into a large supply of clinical-grade, functional human neurons and cardiomyocytes to be translated to patients for mending the damaged CNS and heart.

In 2009, President Obama lifted Bush administration's restriction on NIH. As a result, the NIH registry has been expanded to include hundreds of hESC lines since. So far, those hESC lines on NIH registry are exclusively for research purposes only, but none of the hESC lines eligible for Federal funding are biologics-free, clinical-grade hESCs suitable for patient uses or clinical trials. hESC research has been surrounded by decades of social and legal controversy. The central ethical concern and controversy surrounding hESC research is the derivation of hESC lines, because it involves the destruction of human embryos to obtain stem cells, raising questions about the moral status of an early embryo and whether it constitutes a human life, with proponents arguing for the potential medical benefits of stem cell research while opponents believe it is morally wrong to destroy embryos for research purposes. So far, all the hESC lines on the NIH registry eligible for Federl funding were derived from surplus embryos with funding from private sector or the State (e.g., CIRM), that were in excess from IVF procedures and otherwise destined for destruction, and that were donated under IRB-approved guidelines that mandated informed consent, protection of the donor's identity, and strict ethical research practices. Despite some progresses, Federal funding remains barred from any activities associated with the derivation of hESC lines from IVF leftover embryos for research purposes by the Dickey-Wicker Amendment, a federal law that prohibits the use of federal funds to support research that destroys or harms human embryos, or prohibits the use of federal funds for the creation, destruction, or discarding of human embryos for research purposes, and also prohibits subjecting human embryos to a greater risk

of injury or death than is allowed for research on fetuses in utero. Basically, Federal funding could not be used to derive hESC lines from human embryos for research purposes only.

However, breakthroughs and advances in the last 20 years of hESC research have changed the premise of the Dickey-Wicker Amendment, the federal law that prohibits the use of federal funds to derive hESC lines from human embryos for RESEARCH PURPOSES only.

In August, 2001, when President Geroge W. Bush announced the restriction of Federal funding to hESC lines derived before his announcement, he basically provided a compromised solution to both pros and cons. To those who supported hESC research, he allowed hESC research continue with NIH funding in the hope that it would provide scientific evidence of medicinal uses of hESC for many diseases to warrant continued Federal funding and public support for hESC research in future. To those who were against hESC research, he also ended derivation of more hESC lines by destroying embryos. 25 years later, his policy to invest Federal funding in hESC research has paid off. Breakthroughs and advances in the last 20 years of hESC research have provided scientific evidence of medicinal uses of hESCs for many life-threatening and devastating diseases to warrant continued Federal funding and public support for hESC research. Those original hESC studies in the last 20 years have presented hESCs as a novel, advanced therapeutic strategy for a host of chronic diseases that destroy lives. The IVF techniques offer a small portion of the millions of excess embryos currently stored in the IVF clinics worldwide, which are otherwise destined for destruction, to be an unlimited source that could potentially deliver in future a whole range of therapeutic treatments or cures to patients with life-threatening and devastating diseases for tissue and function restoration. The breakthroughs and advances in the last 20 years of hESC research have laid the foundation for relaxing Federal policy to allow Federal funding to be used to derive biologics-free, clinical-grade hESC lines from human embryos for THERAPEUTIC PURPOSES, CLINICAL APPLICATIONS, PATIENT USES, OR HUMAN TRIALS. Such deregulation efforts will dramatically increase the overall turnover of investments in biomedical research, deliver urgently-needed treatments or cures for a host of incurable or hitherto untreatable disorders that destroy lives, speed hESC medical breakthroughs to patients, and drive real progress on ending the chronic disease epidemic.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

2.1. Human embryonic stem cells (hESCs) are the gold standard of regenerative medicine in restoring vital tissue and function for a wide range of incurable or hitherto untreatable chronic diseases. hESCs offer the only scalable health solution to address the unmet medical needs of many costly and devastating chronic diseases. Those life-threatening chronic diseases are major health problems, cost trillions in healthcare, affect millions of people, and could not be pursued or solved if hESCs were unavailable.

Chronic diseases are major causes of morbidity and mortality in US and leading drivers of health care costs. Many chronic diseases, including heart disease and failure, stroke, Parkinson's disease (PD), Alzheimer disease (AD), spinal cord injury (SCI), traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), Type 1 diabetes, liver diseases, lung diseases are caused by damage or loss of tissue that leads to impairment or loss of function. Those devastating and life-threatening diseases are leading causes of death or permanent disability and major health problems that cost trillions in healthcare annually and affect millions of people in the US, but there is no effective

treatment or drug that can restore the damaged or lost tissue and function. The limit capacity of cardiomyocytes (the mature contracting heart muscle cells) of the heart as well as neuron circuitries of the brain/spinal-cord for self-repair constitutes a significant challenge to traditional medicine for tissue and function restoration in seeking cures for those serious life-threatening diseases and injuries. To date, the need to restore vital tissue and function for a wide range of chronic diseases remains a daunting challenge to the conventional mode of drug development.

The successful derivation of hESC lines from the in vitro fertilization (IVF) leftover embryos is considered as one of the major breakthroughs of the 20th century life sciences. Pluripotent hESCs can maintain long-term, stable growth and differentiate into clinically-relevant lineages, providing an inexhaustible source of replacement cells for human tissue and function restoration. It is public consensus that hESC research holds huge promise for treating major human diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable chronic diseases. Millions of people are pinning their hopes on hESC research. Despite these devastating and life-threatening chronic diseases are leading causes of death or permanent disability, yet, there is no effective treatment or drug available. hESCs are genetically stable with unlimited expansion ability and unrestricted plasticity, proffering a pluripotent reservoir for in vitro derivation of a large supply of disease-targeted human somatic cells that are restricted to the lineage in need of repair. Therefore, they have been regarded as an ideal source to provide an unlimited supply of large-scale, well-characterized human specialized cell types for cell-based therapies to resolve some worldwide major health problems, such as neurodegenerative diseases, paralysis, diabetes, and heart diseases. So far, hESCs are the gold standard of regenerative medicine in restoring vital tissue and function for a wide range of incurable or hitherto untreatable chronic diseases. hESCs offer the only scalable health solution to address the unmet medical needs of many costly and devastating chronic diseases. Those life-threatening chronic diseases are major health problems, cost trillions in healthcare, affect millions of people, and could not be pursued or solved if hESCs were unavailable.

The rising prevalence of chronic diseases, coupled with increased healthcare costs, has fueled the exponential growth of the cell-based regenerative medicine market over the last 2 decades, to address the need to repair, replace, or regenerate the damaged or lost tissue or organ for many incurable or hitherto untreatable chronic diseases that have been challenging to traditional medicine. Although stem cell therapy represents a promising regenerative medicine approach closest to provide a cure for those diseases, demonstrating stem cell production at the scale and product purity adequate to heal the damaged or lost tissues that have naturally limited capacity for repair, such as the human heart and brain, has been a big challenge for traditional adult stem cell sources or products, including the prototypical heart/CNS tissue-derived epithelial-like Nestin+ human cardiac/neural stem cells (hCSC/hNSC), mesenchymal stem cells (MSC), bone marrow-derived stem cells (BMSC), and the so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Adult cell therapy products currently in clinical trials or on the market for heart and neurological indications, if any, have not demonstrated production at scale as well as any regenerative potential for heart muscle or neuron circuitry repair. So far, there is no evidence that any traditional adult stem cells are able to give rise to the contractile heart muscle cells (cardiomyocytes [CM]) or functional neurons following transplantation into the heart/CNS, thus achieving graft-dependent myocardium/CNS regeneration. Despite significant research efforts, the overwhelming majority of human trials with such traditional adult stem cells have failed to demonstrate clinical efficacy and benefit. Those clinical studies have revealed that most cell types are safe, but exert their therapeutic effects primarily through anti-inflammatory and protective actions to prolong the survival and function of existing cardiomyocytes/neurons, rather than mediate graft-dependent cardiomyocyte/neuron cell regeneration/replacement, suggesting that such therapeutic effects that primarily produce trophic or protective factors to rescue endogenous host cardiomyocytes/neurons or enhance endogenous cardiac/neural repair provide no substantial improvement in clinical end points and have no effect on overall survival. The over 2 decades of clinical studies have identified the urgent need for safe and effective therapeutic stem cell sources adequate to regenerate the damaged/lost myocardium/nerve tissues.

Technology breakthroughs and advances in hESC research over the last 2 decades have provided innovative, scalable, and reproducible platforms to ensure high degrees of efficacy and safety of the hESC-derived regenerative medicine advanced therapy (RMAT) products, thus robust clinical benefit leading to therapies, which not only constitutes clinically representative progresses in both human neuronal and cardiac therapeutic products for treating a wide range of incurable or hitherto untreatable neurological and cardiovascular diseases, but also offers manufacturing innovation for production scale-up and creation or bio-fabrication of replacement tissue/organ products, such as the human heart and brain [e.g., Parsons. 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. Gene and Cell Therapy: Therapeutic Mechanisms and Strategies, Chapter 31:795-818; Parsons XH. Direct conversion of pluripotent hESC under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318. DOI: 10.1007/7651_2014_69. PMID: 24500898].

Due to lack of a scalable human neuron source, the need to restore vital tissue and function for a wide range of neurological diseases and injuries remains a daunting challenge to conventional drug development. Technology breakthrough in hESC research enables direct conversion of non-functional, clinical-grade hESCs at the pluripotent stage by small molecule induction uniformly into a large supply of human neuronal progenitor cells and functional neurons [e.g., patent: USPTO# 8,716,017; Parsons. 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. Gene and Cell Therapy: Therapeutic Mechanisms and Strategies, Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318], providing the scalable manufacturing capability for large scale production of high quality clinical-grade human neuronal cells adequate for neuron circuitry repair and nerve tissue bio-fabrication to fill the capability gap in nerve tissue and neurological/motor function restoration for a wide range of incurable or hitherto untreatable neurological diseases. So far, hESCs offer the only scalable source of human neurons adequate for

neuron regeneration and neurological function restoration to treat serious, life threatening, progressive or fatal neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and injuries such as spinal cord injury (SCI), traumatic brain injury (TBI), and strokes. hESCs offer a novel, advanced therapeutic strategy for a wide range of incurable or hitherto untreatable neurological disorders that destroy lives, and those urgently needed cutting-edge stem cell therapy solutions could not be pursued if hESCs were unavailable.

Lack of a scalable human cardiac stem cell source with adequate heart muscle regeneration potential remains a major setback for heart replacement, and fabricating a human heart is still beyond reach. Technology breakthrough in hESC research enables direct conversion of non-functional clinical-grade hESCs at the pluripotent stage by small molecule induction uniformly into a large supply of human cardiac precursor cells and contractile cardiomyocytes [e.g., patent: USPTO# 9,428,731; Parsons. 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. Gene and Cell Therapy: Therapeutic Mechanisms and Strategies, Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318], providing the scalable manufacturing capability for large-scale production of high-quality clinical-grade human heart muscle cells adequate for heart muscle regeneration and bio-fabrication to fill the capability gap in myocardial tissue and contractile function restoration for heart disease and failure. So far, hESCs offer the only scalable source of human cardiomyocytes adequate for heart muscle regeneration and contractile function restoration to treat heart disease and failure. hESCs offer a novel, advanced therapeutic strategy for cardiovascular diseases (CVD), and those urgently needed cutting-edge stem cell therapy solutions could not be pursued if hESCs were unavailable.

Despite false claim that "the adult alternative iPSCs and hESCs are identical", iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells. hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.

Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal

benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.

Today, cutting-edge hESC technology platforms have been developed, some even commercialized, for defined media and culture systems to derive high quality, clinical-grade, stable hESC lines suitable for human trials and patient uses, for large-scale production of clinical-grade hESC-derived CNS/heart-related human stem/progenitor/precursor cells, accessory cells, and functional human CNS/heart cell/tissue/organ products to support clinical trials of regeneration or replacement therapies as well as tissue/organ biofabrication for those most-costly and devastating chronic diseases. Innovative hESC technology platforms and products have broad applications for a wide range of chronic diseases that destroy lives, thus providing high-impact therapeutic solutions across a wide spectrum of life-threatening chronic diseases, and ultimately, relieving the high burdens of diseases, and generating high-yield return for public investment.

Current state of hESC research has provided much-need therapeutic solutions for a wide range of incurable or hitherto untreatable chronic diseases, and has laid the foundation for CNS/heart tissue and function restoration as well as for bridging the key knowledge gaps in human CNS/heart development. Despite the social and legal controversies constantly surrounding hESC research, advances in the last 20 years of hESC research have presented hESCs as a novel, advanced therapeutic strategy for a host of chronic diseases that destroy lives, thus warranting continued public support and Federal investment. It is crucial for the Federal government to prioritize such frontiers of regenerative medicine to ensure that these reachable, urgently-needed, better treatments and new cures brought by the breakthrough medical innovations of hESC research for those costly and devastating chronic diseases are near, thus ensuring taxpayer money be used to pave a successful path in the war against diseases.

2.2. hESCs are the gold standard for understanding human embryonic development, providing much-needed human model systems to unlock the mysteries of human development and disorders, and facilitating rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

Traditional drug development usually starts with drug leads discovered in non-human simple model organisms, thus requires lengthy and costly both demonstration in animal model testing and establishment of proof-of-concept and safety in human trials. As a result, millions of drug leads have vanished before even reach clinical trials, and for few lucky ones, have encountered the very high drug failure rate in human trials. Among those very few drugs that eventually obtained their market approvals, there were not any cures, or even meaningfully effective treatments, for Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure, or a host of other chronic diseases that destroy lives. The difficulty of crossing the gulf between finding a promising new agent and demonstrating its safety and efficacy in humans in biomedical research has been referred as

"the valley of death".

The difficulty of crossing "the valley of death" in drug development is the pounding consequence of a vast amount of Federal and private investments only go to maintain the status quo of mainstream biomedical research in the non-human, lower organism models or systems that do not reflect the complexity of humans, thus have little implications for the prevention and treatment of human diseases. Without a readily accessible and effective human model system to unlock the mysteries of human development and disorders, the road of desperately seeking cures has become all but a dead end to real world remedy.

Due to the restrictions on human embryonic and fetal materials that significantly limit their availability for study, there is a fundamental gap in our knowledge regarding the molecular networks and pathways underlying human embryogenesis. Derivation of hESCs provides powerful in vitro model systems to remove limitations at the cellular or biological systems levels that stymie progress towards developing human-based tools and platforms that can apply to a broad range of human diseases. Development and utilization of hESC models of human embryonic development facilitate rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of human diseases. Technology breakthroughs in the last 20 years of hESC research enable neuronal or cardiac lineage-specific differentiation direct from the pluripotent state of hESCs with small molecule induction, which have provided much-needed in vitro model systems for bridging the key knowledge gaps in human CNS (central nervous system) and heart development [e.g., Parsons. 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. Gene and Cell Therapy: Therapeutic Mechanisms and Strategies, Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318]. It opens the door for further unveiling genetic and epigenetic programs embedded in the human CNS and heart formation during human embryogenesis using genome-wide high-throughput high resolution profiling approaches. Therefore, hESCs are gold standard for understanding human embryonic development, providing much-needed human model systems to unlock the mysteries of human development and disorders, and facilitating rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

2.3. hESCs are the gold standard for developing human-based risk testing systems for rapid and high-fidelity safety evaluation of health risks, particularly cumulative health risks, of developmental toxins with sensitivity equivalent to vulnerable children, infants, and fetuses, thus uncovering the root causes of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

In order for a drug to be approved in the US, the FDA typically requires preclinical toxicity tests and animal model studies on small and large animals to provide sufficient evidence of proof-of-concept for the prospect of safety and efficacy to justify an Investigational New Drug (IND) application for the proposed clinical investigation of a new drug. Companies use tens of thousands of animals for such tests each year. Yet more than nine in 10 drugs that enter human clinical trials fail because they are unsafe or

ineffective.

Thus far, testing potential therapeutic strategies has largely relied on animal models for evaluating the behavior, safety, and efficacy of therapeutic candidates and human cell therapy products. However, because of interspecies differences, conventional studies using animal models are often poor predictors of human efficacy and safety. Animal models are xeno-hosts for the transplantation of human cells, not ideal for testing the behavior, safety, and efficacy of therapeutic outcomes of human stem cells. Large primate models are very costly and often taken years to obtain results. In addition, the results of animal studies can be highly variable and difficult to reproduce, making them unreliable as benchmarks for decisions on humans in clinical trials. Preclinical data using animal models, even results of large animal models, do not necessarily provide the benchmarks or indicators for safety and efficacy in human trials.

Children are still in a sensitive developmental stage, uniquely vulnerable to environmental chemical exposures, including pesticides, microplastics, dioxins, flame retardants, BPA, PFSA, fluoride, EMR, Phthalates, Bisphenols, herbicides, and insecticides. Since President Clinton's executive order 13045 in 1997, childhood health has largely worsened, and the chemicals children are exposed to have grown. There is a growing concern about the link between environmental health risks, particularly cumulative health risks, and chronic diseases. The emerging crisis of overmedication and the growth of childhood vaccine schedule also compound the health risks, particularly cumulative health risks, of childhood environmental chemical exposures, drugs, and vaccines to vulnerable children who are still in a sensitive developmental stage. Such health risks, particularly cumulative health risks, could be the root causes of childhood chronic disease epidemic that warrant scientific investigations.

However, scientific inquiry into the links between the health risks of childhood environmental chemical exposures, drugs, and vaccines to chronic diseases, has been hindered by the lack of a human-based risk testing system with sensitivity equivalent to that of vulnerable children, infants, and fetuses. In the US, federal regulations do not allow research that presents "greater risks than minimal" on children. In addition, federal restrictions on human embryonic and fetal materials significantly limit their availability for study. As a result, there are significant gaps in available data regarding the effects of developmental toxins that may play a crucial role in the rising prevalence of childhood chronic diseases.

The advances in pluripotent hESC research have provided the unique opportunity to develop human-based risk testing systems for rapid and high-fidelity safety evaluation of developmental toxins with sensitivity equivalent to that of vulnerable children, infants, and fetuses. Human embryo-originated hESC and their cell/tissue/organ products/models offer viable, adequate, timely, cost-effective, sensitive, and superior alternatives that meet higher quality and safety standards than current animal testing systems and other human adult cell/tissue/organ-based testing systems. hESCs are derived from human embryos, negating the species-species differences observed in animal testing. hESCs and their derivatives have a very low tolerance threshold and are highly sensitive to any toxic chemicals/drugs/products/vaccines, providing scalable, more timely, predictive, reliable alternative methods to current animal testing systems and other human adult cell/tissue/organ-based testing systems, ensuring higher quality and safety standards, and reducing the time and cost. hESC-based human cell/tissue/organ products or models offer rapid, cost-effective, and high-fidelity safety evaluation of developmental toxins with sensitivity equivalent to that of vulnerable children, infants, and

fetuses.

FDA Modernization Act 2.0 legitimizes alternatives to animal testing for advancing a drug or product to human trials. Enacting such a law for a drastic change in FDA regulation, passed by Congress and welcomed by animal welfare groups, was only made possible by advances in hESC research that have begun to offer increasingly viable alternatives to animal testing. However, many of the new approach methodologies (NAMs) proposed by the FDA in the "Roadmap to Reducing Animal Testing in Preclinical Safety Studies", such as adult-cell/tissue/organ-based organ-on-a-chip systems, computational modeling, and advanced in vitro assays, are unable to provide higher quality and safety standards than animal testing. For example, organ chips and organoids based on adult stem/cancer cells (e.g., iPSCs that are in fact adult cells reprogrammed with oncogenes or actually cancer cells) have proven to be inadequate as alternatives to animal toxicity testing because the tolerance threshold of adult/cancer cells/iPSCs to toxic chemicals/drugs is much higher than the tolerance threshold of normal human tissues or organs. Such as, the drugs screened by the liver chips of Emulate based on iPSCs either failed in clinical trials because they were toxic to the liver or were approved for market but then withdrawn or scaled back because of liver damage (see the New York Times report "Could the next blockbuster drug be lab-rat few?"). In addition, reprogrammed-adult-cell or iPSC-based organoids or organ-on-a-chip systems do not authentically replicate the in vivo human development or organ systems. Reprogrammed-adult-cell or iPSC-based brain organoids or organ-on-a-chip systems are insensitive to any toxic chemicals/drugs/vaccines/products, inadequate and unreliable to test the safety of chemicals/drugs/vaccines/products, thus unable to provide any meaningful knowledge to fill the gaps in available data regarding the effects of neurodevelopmental toxicants on children's brain development. Therefore, those iPSC-based NAMs (e.g., brain organoids) in FDA proposed Roadmap are inadequate and insufficient to uncover the root causes of childhood chronic diseases.

The hESC-based innovative platforms provide scale-up capability for the creation of human replacement CNS and heart, such as micro-brains, micro-spinal-cords, and micro-hearts, thereby increasing the biological complexity of human-based in vitro models and assays to mimic the in vivo structure, behavior, and function of the human CNS and heart. These hESC-based in vitro models and assays are controllable, reproducible, and scalable, and can be monitored and validated against responses on multiple hierarchical levels. Development and utilization of complex 3D multi-cellular models of human embryogenesis and organogenesis using hESCs provide a highly-sensitive, authentic, and reliable in vitro tool for rapid and high-fidelity safety evaluation of developmental toxins that may play a crucial role in the rising prevalence of childhood chronic diseases, thus uncovering the root causes that will lead to better prevention strategies and evidence-based therapeutic solutions to end the childhood chronic disease epidemic. Therefore, hESCs are the gold standard for developing human-based risk testing systems for rapid and high-fidelity safety evaluation of health risks, particularly cumulative health risks, of developmental toxins with sensitivity equivalent to vulnerable children, infants, and fetuses, thus uncovering the root causes of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

There is no research area in any emerging biotechnologies that can replace the use of hESCs.

Any efforts to replace the use of human embryonic stem cells (hESCs) would only result in additional waste of a staggering amount of taxpayer money on false promises and frauds, just like hundreds of billions of taxpayer money have been wasted on the fruitless efforts of iPSC fraud in the last 20 years.

hESC research holds the greatest benefit to humankind and has overwhelming public support. Prioritizing hESC research is vital to addressing childhood chronic diseases and ending the chronic disease epidemic. It is bad policy to ban hESC research or replace hESC research with adult stem cell scams and scientific frauds that would result in enormous waste of taxpayer money just like the massive fraud and waste iPSCs did in the last 20 years, stall any progress on life-saving solutions for many chronic diseases, deny access of millions of patients to life-saving treatments or cures brought by the breakthrough medical innovations of hESC research, cause public outrage, and push scientific research back to a dark era even worse than the Bush administration.

hESC research holds huge promises for treating major chronic diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable neurological and heart diseases, including Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure that cost trillions and affect millions. Millions of people are pinning their hopes on hESC research. Even President Bush didn't ban hESC research 25 years ago, but allowed hESC research continue with Federal Funding, so someday, we could find lifesaving treatments and cures for a host of chronic diseases that destroy lives. There is no alternative for hESC research. And the so-called adult alternative to hESCs --- induced pluripotent stem cells (iPSCs) of ISSCR endorsed by the Nobel Foundation with Nobel Prize --- are in fact cancer cells reprogrammed with oncogenes, a massive scientific fraud and adult stem cell scam that has wasted a lot of government research funding in staggering amounts of hundreds of billions of taxpayer dollars, but produced absolutely nothing hopeful for any diseases. Adult stem cells and iPSCs have not created any life-saving treatments for any diseases and conditions, and iPSCs have failed safety tests in clinical trials by causing serious spontaneous mutations and harming patients just like cancer cells would do. Please see sdrmi.org for more.

The so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Despite false claim that "the adult alternative iPSCs and hESCs are identical", iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact

reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells. hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.

Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.

In 2009, President Obama lifted Bush administration's restriction on NIH. As a result, the NIH registry has been expanded to include hundreds of hESC lines since. So far, those hESC lines on NIH registry are exclusively for research purpose only, but none of the hESC lines eligible for Federal funding are biologics-free, clinical-grade hESCs suitable for patient uses or clinical trials. hESC research has been surrounded by decades of social and legal controversy. The central ethical concern and controversy surrounding hESC research is the derivation of hESC lines, because it involves the destruction of human embryos to obtain stem cells, raising questions about the moral status of an early embryo and whether it constitutes a human life, with proponents arguing for the potential medical benefits of stem cell research while opponents believe it is morally wrong to destroy embryos for research purposes. So far, all hESC lines in NIH registry eligible for Federl funding were derived from surplus embryos with funding from private sector or the State (e.g., CIRM), that were in excess from IVF procedures and otherwise destined for destruction, and that were donated under IRB-approved guidelines that mandated informed consent, protection of the donor's identity, and strict ethical research practices. Despite some progresses, Federal funding remains barred from any activities associated with the derivation of hESC lines from IVF leftover embryos for research purposes by the Dickey-Wicker Amendment, a federal law that prohibits the use of federal funds to support research that destroys or harms human embryos, or prohibits the use of federal funds for the creation, destruction, or discarding of human embryos for research purposes, and also prohibits subjecting human embryos to a greater risk of injury or death than is allowed for research on fetuses in utero. Basically, Federal funding could not be used to derive hESC lines from human embryos for research purposes.

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4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

There is no research area in which additional investments should be made to bolster validated models to replace the use of human embryonic stem cells (hESCs).

Any additional investments made to bolster validated models to replace the use of hESCs would only result in additional waste of a staggering amount of taxpayer money on false promises and frauds, just like hundreds of billions of taxpayer money have been wasted on the fruitless efforts of iPSC fraud in the last 20 years.

hESC research holds the greatest benefit to humankind and has overwhelming public support. Prioritizing hESC research is vital to addressing childhood chronic diseases and ending the chronic disease epidemic. It is bad policy to ban hESC research or replace hESC research with adult stem cell scams and scientific frauds that would result in enormous waste of taxpayer money just like the massive fraud and waste iPSCs did in the last 20 years, stall any progress on life-saving solutions for many chronic diseases, deny access of millions of patients to life-saving treatments or cures brought by the breakthrough medical innovations of hESC research, cause public outrage, and push scientific research back to a dark era even worse than the Bush administration.

hESC research holds huge promises for treating major chronic diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable neurological and heart diseases, including Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure that cost trillions and affect millions. Millions of people are pinning their hopes on hESC research. Even President Bush didn't ban hESC research 25 years ago, but allowed hESC research

continue with Federal Funding, so someday, we could find lifesaving treatments and cures for a host of chronic diseases that destroy lives. There is no alternative for hESC research. And the so-called adult alternative to hESCs --- induced pluripotent stem cells (iPSCs) of ISSCR endorsed by the Nobel Foundation with Nobel Prize --- are in fact cancer cells reprogrammed with oncogenes, a massive scientific fraud and adult stem cell scam that has wasted a lot of government research funding in staggering amounts of hundreds of billions of taxpayer dollars, but produced absolutely nothing hopeful for any diseases. Adult stem cells and iPSCs have not created any life-saving treatments for any diseases and conditions, and iPSCs have failed safety tests in clinical trials by causing serious spontaneous mutations and harming patients just like cancer cells would do. Please see sdrmi.org for more.

The so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Despite false claim that “the adult alternative iPSCs and hESCs are identical”, iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells. hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.

Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.

In 2009, President Obama lifted Bush administration's restriction on NIH. As a result, the NIH registry has been expanded to include hundreds of hESC lines since. So far, those hESC lines on NIH registry are exclusively for research purpose only, but none of the hESC lines eligible for Federal funding are biologics-free, clinical-grade hESCs suitable for patient uses or clinical trials. hESC research has been surrounded by decades of social and legal controversy. The central ethical concern and controversy surrounding hESC research is the derivation of hESC lines, because it involves the destruction of human embryos to obtain stem cells, raising questions about the moral status of an early embryo and whether it constitutes a human life, with proponents arguing for the potential medical benefits of stem cell research while opponents believe it is morally wrong to destroy embryos for research purposes. So far, all hESC lines in NIH registry eligible for Federl funding were derived from surplus embryos with funding from private sector or the State (e.g., CIRM), that were in excess from IVF procedures and otherwise destined for destruction, and that were donated under IRB-approved guidelines that mandated informed consent, protection of the donor's identity, and strict ethical research practices. Despite some progresses, Federal funding remains barred from any activities associated with the derivation of hESC lines from IVF leftover embryos for research purposes by the Dickey-Wicker Amendment, a federal law that prohibits the use of federal funds to support research that destroys or harms human embryos, or prohibits the use of federal funds for the creation, destruction, or discarding of human embryos for research purposes, and also prohibits subjecting human embryos to a greater risk of injury or death than is allowed for research on fetuses in utero. Basically, Federal funding could not be used to derive hESC lines from human embryos for research purposes.

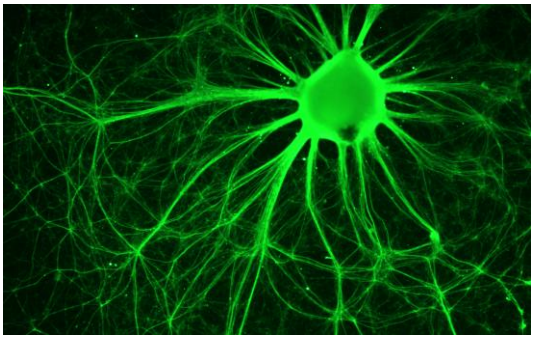
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Description: SDRMI Response to NOT-OD-26-031 “NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell (hESC) Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research”



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Human Embryonic Stem Cell Therapy
Unleashing the Power of Life Science

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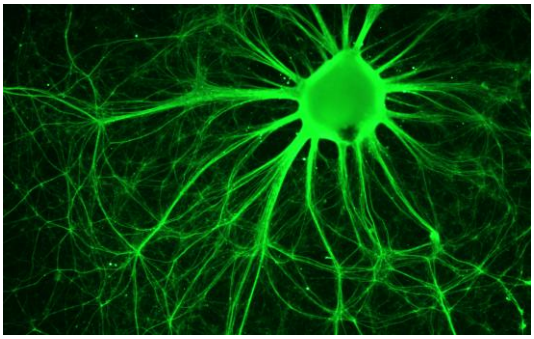
Response to NOT-OD-26-031 "NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell (hESC) Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research"

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed;

All the NIH-approved human embryonic stem cell (hESC) lines currently on the NIH hESC Registry are research-grade for research purposes only, only suitable for preclinical research. The NIH hESC Registry has no clinical-grade hESC lines suitable for therapeutic purposes, clinical applications, human trials, or patient uses.

All the currently approved hESC lines on the NIH hESC Registry are research-grade exclusively for preclinical research only, but none of those hESC lines eligible for Federal finding are biologics-free, clinical-grade hESCs suitable for therapeutic purposes, clinical applications, human trials, or patient uses. Because all the NIH-approved hESC lines were initially derived and maintained on mouse feeder cells and proteins, therefore, such hESC lines have been contaminated with animal cells, biologics, and genetic materials, unsuitable for clinical applications to patients or not clinically compatible. Using mouse feeder cells and foreign biologics for derivation, maintenance, and differentiation of these hESC lines currently on the NIH hESC Registry has compromised their therapeutic potential because of the risk of transmitting xeno-biologics and xeno-pathogens, altering genetic background, and promoting the expression of immunogenic proteins.

Although the NIH hESC registry currently has approximately 486 approved hESC lines, only a few, about 4-6 hESC lines, are commercially available for research purposes only, all from the Wicell Research Institute. Due to early improper handlings during passaging, most of the hESC lines currently on the NIH hESC registry are in extremely low quality or already dead, and therefore, could not be used for research anymore. For example, some of these NIH-approved hESC lines could not even be thawed alive from cryo-freezers. Even though some of these hESC lines could be grown back from cryo-freezers, they were found no longer at the pluripotent stage (e.g., no longer express pluripotent markers like Oct-4, SSEA-4), and therefore, no longer useful to get any

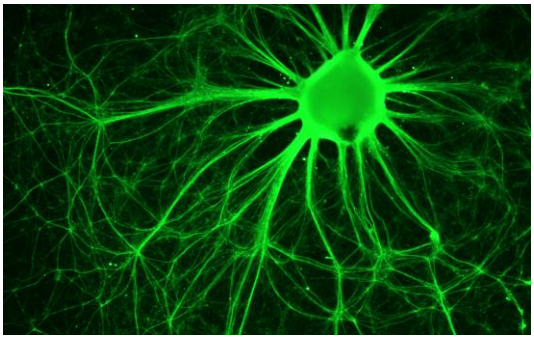


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hESC research going. All the NIH-approved hESC lines were initially derived and maintained using mouse supporting cells. Mouse cells grow much faster than human cells and survive harsh handlings during passaging much better than hESCs too. As a result, some of these NIH-approved hESC lines (e.g., Doug Melton's lines of Harvard) have apparently been contaminated or altered by mouse cells, because those cells actually express mouse cell markers (e.g., SSEA-1), but not hESC markers (e.g., SSEA-4), and behave more like mouse cells too. Therefore, it is essential for NIH to authenticate all the NIH-approved hESC lines and assess the quality of all the hESC lines currently on the NIH hESC Registry to ensure they are actually pluripotent hESC lines and in good quality for hESC research.

High-quality, biologics-free, clinical-grade new hESC lines are needed for clinical translation of hESC research and therapeutic applications, such as developing hESC-based stem cell therapies for tissue and function restoration and bio-fabrication of human replacement tissues/organs. Breakthroughs and advances in the last 20 years of hESC research have established defined hESC culture platforms to provide biologics-free (e.g., feeder-free, xeno-free, conditioned-medium-free, serum-free), defined culture systems for well-controlled, efficient derivation, maintenance, and differentiation of clinical-grade, high quality, cGMP compatible, stable hESC lines [e.g., Parsons**.** 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. *Gene and Cell Therapy: Therapeutic Mechanisms and Strategies,* Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318; Parsons, *et al*. 2012, Defining conditions for sustaining epiblast pluripotence enables direct induction of clinically-suitable human myocardial grafts from biologics-free hESCs. *J. Clinic. Exp. Cardiology* 2012;S9-001]. Defined hESC culture platforms allow all poorly-characterized and unspecified biological components and substrates in the culture system, including those derived from animals, to be removed, substituted, and optimized with defined human alternatives for *de novo* derivation and long-term maintenance of cGMP-quality, xeno-free, stable hESC lines and their human cell therapy derivatives, which have never been contaminated with animal cells and proteins, thus suitable for therapeutic development and clinical applications. Such breakthroughs in hESC research have overcome some major obstacles in bringing hESC therapy to the clinic, enabling *de novo* derivation of clinical-grade, cGMP compatible, stable hESC lines from human blastocysts that have never been contaminated by animal cells and proteins, and direct conversion of such pluripotent hESCs into a large supply of clinical-grade, functional human neurons and cardiomyocytes to be translated to patients for mending the damaged CNS and heart.

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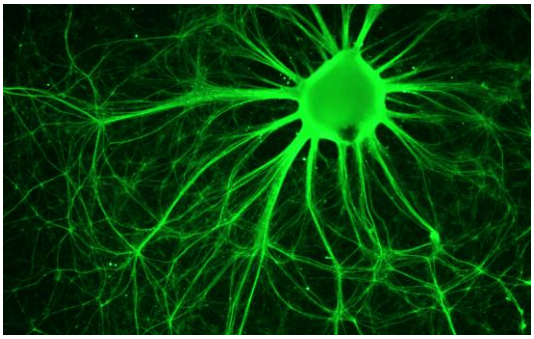
for a host of incurable or hitherto untreatable disorders that destroy lives, speed hESC medical breakthroughs to patients, and drive real progress on ending the chronic disease epidemic.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable;

2.1. Human embryonic stem cells (hESCs) are the gold standard of regenerative medicine in restoring vital tissue and function for a wide range of incurable or hitherto untreatable chronic diseases. hESCs offer the only scalable health solution to address the unmet medical needs of many costly and devastating chronic diseases. Those life-threatening chronic diseases are major health problems, cost trillions in healthcare, affect millions of people, and could not be pursued or solved if hESCs were unavailable.

Chronic diseases are major causes of morbidity and mortality in US and leading drivers of health care costs. Many chronic diseases, including heart disease and failure, stroke, Parkinson's disease (PD), Alzheimer disease (AD), spinal cord injury (SCI), traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), Type 1 diabetes, liver diseases, lung diseases are caused by damage or loss of tissue that leads to impairment or loss of function. Those devastating and life-threatening diseases are leading causes of death or permanent disability and major health problems that cost trillions in healthcare annually and affect millions of people in the US, but there is no effective treatment or drug that can restore the damaged or lost tissue and function. The limit capacity of cardiomyocytes (the mature contracting heart muscle cells) of the heart as well as neuron circuitries of the brain/spinal-cord for self-repair constitutes a significant challenge to traditional medicine for tissue and function restoration in seeking cures for those serious life-threatening diseases and injuries. To date, the need to restore vital tissue and function for a wide range of chronic diseases remains a daunting challenge to the conventional mode of drug development.

The successful derivation of hESC lines from the *in vitro* fertilization (IVF) leftover embryos is considered as one of the major breakthroughs of the 20th century life sciences. Pluripotent hESCs can maintain long-term, stable growth and differentiate into clinically-relevant lineages, providing an inexhaustible source of replacement cells for human tissue and function restoration. It is public consensus that hESC research holds huge promise for treating major human diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable chronic diseases. Millions of people are pinning their hopes on hESC research. Despite these devastating and life-threatening chronic diseases are leading causes of death or permanent disability, yet, there is no effective treatment or drug available. hESCs are genetically stable with unlimited expansion ability and unrestricted plasticity, proffering a pluripotent reservoir for *in vitro* derivation of a large supply of disease-targeted human somatic cells that are restricted to the lineage in need of repair. Therefore, they have been regarded as an ideal source to provide an unlimited supply of large-scale, well-

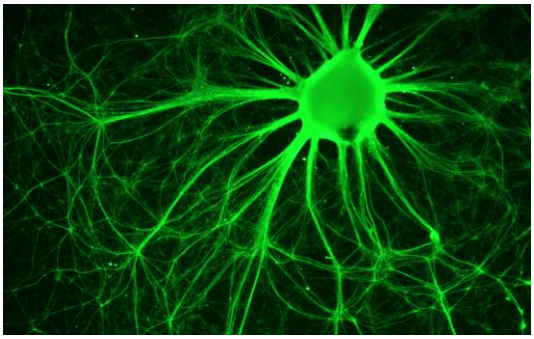


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characterized human specialized cell types for cell-based therapies to resolve some worldwide major health problems, such as neurodegenerative diseases, paralysis, diabetes, and heart diseases. So far, hESCs are the gold standard of regenerative medicine in restoring vital tissue and function for a wide range of incurable or hitherto untreatable chronic diseases. hESCs offer the only scalable health solution to address the unmet medical needs of many costly and devastating chronic diseases. Those life-threatening chronic diseases are major health problems, cost trillions in healthcare, affect millions of people, and could not be pursued or solved if hESCs were unavailable.

The rising prevalence of chronic diseases, coupled with increased healthcare costs, has fueled the exponential growth of the cell-based regenerative medicine market over the last 2 decades, to address the need to repair, replace, or regenerate the damaged or lost tissue or organ for many incurable or hitherto untreatable chronic diseases that have been challenging to traditional medicine. Although stem cell therapy represents a promising regenerative medicine approach closest to provide a cure for those diseases, demonstrating stem cell production at the scale and product purity adequate to heal the damaged or lost tissues that have naturally limited capacity for repair, such as the human heart and brain, has been a big challenge for traditional adult stem cell sources or products, including the prototypical heart/CNS tissue-derived epithelial-like Nestin+ human cardiac/neural stem cells (hCSC/hNSC), mesenchymal stem cells (MSC), bone marrow-derived stem cells (BMSC), and the so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Adult cell therapy products currently in clinical trials or on the market for heart and neurological indications, if any, have not demonstrated production at scale as well as any regenerative potential for heart muscle or neuron circuitry repair. So far, there is no evidence that any traditional adult stem cells are able to give rise to the contractile heart muscle cells (cardiomyocytes [CM]) or functional neurons following transplantation into the heart/CNS, thus achieving graft-dependent myocardium/CNS regeneration. Despite significant research efforts, the overwhelming majority of human trials with such traditional adult stem cells have failed to demonstrate clinical efficacy and benefit. Those clinical studies have revealed that most cell types are safe, but exert their therapeutic effects primarily through anti-inflammatory and protective actions to prolong the survival and function of existing cardiomyocytes/neurons, rather than mediate graft-dependent cardiomyocyte/neuron cell regeneration/replacement, suggesting that such therapeutic effects that primarily produce trophic or protective factors to rescue endogenous host cardiomyocytes/neurons or enhance endogenous cardiac/neural repair provide no substantial improvement in clinical end points and have no effect on overall survival. The over 2 decades of



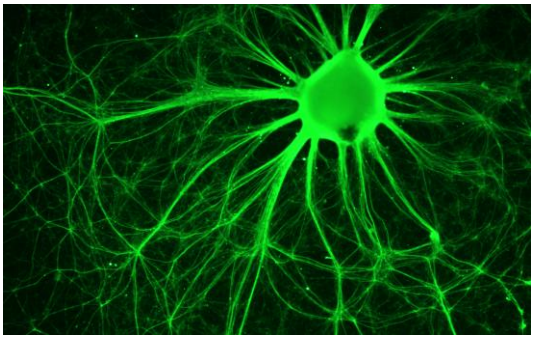
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clinical studies have identified the urgent need for safe and effective therapeutic stem cell sources adequate to regenerate the damaged/lost myocardium/nerve tissues.

Technology breakthroughs and advances in hESC research over the last 2 decades have provided innovative, scalable, and reproducible platforms to ensure high degrees of efficacy and safety of the hESC-derived regenerative medicine advanced therapy (RMAT) products, thus robust clinical benefit leading to therapies, which not only constitutes clinically representative progresses in both human neuronal and cardiac therapeutic products for treating a wide range of incurable or hitherto untreatable neurological and cardiovascular diseases, but also offers manufacturing innovation for production scale-up and creation or bio-fabrication of replacement tissue/organ products, such as the human heart and brain [e.g., Parsons**.** 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. *Gene and Cell Therapy: Therapeutic Mechanisms and Strategies,* Chapter 31:795-818; Parsons XH. Direct conversion of pluripotent hESC under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. *Methods Mol. Biol*. 2016;1307:299-318. DOI: 10.1007/7651_2014_69. PMID: 24500898].

Due to lack of a scalable human neuron source, the need to restore vital tissue and function for a wide range of neurological diseases and injuries remains a daunting challenge to conventional drug development. Technology breakthrough in hESC research enables direct conversion of non-functional, clinical-grade hESCs at the pluripotent stage by small molecule induction uniformly into a large supply of human neuronal progenitor cells and functional neurons [e.g., patent: USPTO# 8,716,017; Parsons**.** 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. *Gene and Cell Therapy: Therapeutic Mechanisms and Strategies,* Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318], providing the scalable manufacturing capability for large scale production of high quality clinical-grade human neuronal cells adequate for neuron circuitry repair and nerve tissue bio-fabrication to fill the capability gap in nerve tissue and neurological/motor function restoration for a wide range of incurable or hitherto untreatable neurological diseases. So far, hESCs offer the only scalable source of human neurons adequate for neuron regeneration and neurological function restoration to treat serious, life threatening, progressive or fatal neurodegenerative diseases such as Parkinson’s disease (PD), Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and injuries such as spinal cord injury (SCI), traumatic brain injury (TBI), and strokes. hESCs offer a novel, advanced therapeutic strategy for a wide range of incurable or hitherto untreatable neurological disorders that destroy lives, and those urgently needed cutting-edge stem cell therapy solutions could not be pursued if hESCs were unavailable.

Lack of a scalable human cardiac stem cell source with adequate heart muscle regeneration potential remains a major setback for heart replacement, and fabricating a human heart is still beyond reach. Technology

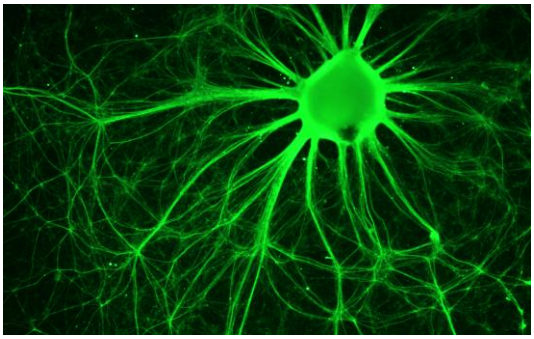


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breakthrough in hESC research enables direct conversion of non-functional clinical-grade hESCs at the pluripotent stage by small molecule induction uniformly into a large supply of human cardiac precursor cells and contractile cardiomyocytes [e.g., patent: USPTO# 9,428,731; Parsons**.** 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. *Gene and Cell Therapy: Therapeutic Mechanisms and Strategies,* Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318], providing the scalable manufacturing capability for large-scale production of high-quality clinical-grade human heart muscle cells adequate for heart muscle regeneration and bio-fabrication to fill the capability gap in myocardial tissue and contractile function restoration for heart disease and failure. So far, hESCs offer the only scalable source of human cardiomyocytes adequate for heart muscle regeneration and contractile function restoration to treat heart disease and failure. hESCs offer a novel, advanced therapeutic strategy for cardiovascular diseases (CVD), and those urgently needed cutting-edge stem cell therapy solutions could not be pursued if hESCs were unavailable.

Despite false claim that “the adult alternative iPSCs and hESCs are identical”, iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells. hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.

Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.



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Today, cutting-edge hESC technology platforms have been developed, some even commercialized, for defined media and culture systems to derive high quality, clinical-grade, stable hESC lines suitable for human trials and patient uses, for large-scale production of clinical-grade hESC-derived CNS/heart-related human stem/progenitor/precursor cells, accessory cells, and functional human CNS/heart cell/tissue/organ products to support clinical trials of regeneration or replacement therapies as well as tissue/organ biofabrication for those most-costly and devastating chronic diseases. Innovative hESC technology platforms and products have broad applications for a wide range of chronic diseases that destroy lives, thus providing high-impact therapeutic solutions across a wide spectrum of life-threatening chronic diseases, and ultimately, relieving the high burdens of diseases, and generating high-yield return for public investment.

Current state of hESC research has provided much-need therapeutic solutions for a wide range of incurable or hitherto untreatable chronic diseases, and has laid the foundation for CNS/heart tissue and function restoration as well as for bridging the key knowledge gaps in human CNS/heart development. Despite the social and legal controversies constantly surrounding hESC research, advances in the last 20 years of hESC research have presented hESCs as a novel, advanced therapeutic strategy for a host of chronic diseases that destroy lives, thus warranting continued public support and Federal investment. It is crucial for the Federal government to prioritize such frontiers of regenerative medicine to ensure that these reachable, urgently-needed, better treatments and new cures brought by the breakthrough medical innovations of hESC research for those costly and devastating chronic diseases are near, thus ensuring taxpayer money be used to pave a successful path in the war against diseases.

2.2. hESCs are the gold standard for understanding human embryonic development, providing much-needed human model systems to unlock the mysteries of human development and disorders, and facilitating rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

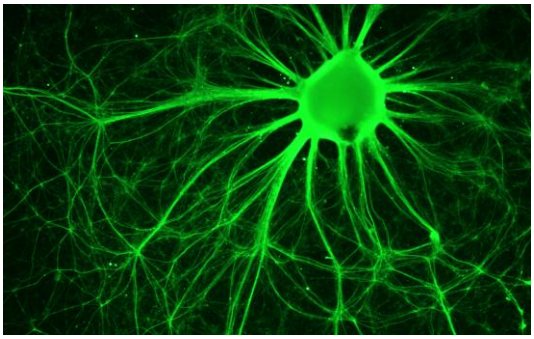
Traditional drug development usually starts with drug leads discovered in non-human simple model organisms, thus requires lengthy and costly both demonstration in animal model testing and establishment of proof-of-concept and safety in human trials. As a result, millions of drug leads have vanished before even reach clinical trials, and for few lucky ones, have encountered the very high drug failure rate in human trials. Among those very few drugs that eventually obtained their market approvals, there were not any cures, or even meaningfully effective treatments, for Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure, or a host of other chronic diseases that destroy lives. The difficulty of crossing the gulf

between finding a promising new agent and demonstrating its safety and efficacy in humans in biomedical research has been referred as “the valley of death”.

The difficulty of crossing “the valley of death” in drug development is the pounding consequence of a vast amount of Federal and private investments only go to maintain the status quo of mainstream biomedical research in the non-human, lower organism models or systems that do not reflect the complexity of humans, thus have little implications for the prevention and treatment of human diseases. Without a readily accessible and effective human model system to unlock the mysteries of human development and disorders, the road of desperately seeking cures has become all but a dead end to real world remedy.

Due to the restrictions on human embryonic and fetal materials that significantly limit their availability for study, there is a fundamental gap in our knowledge regarding the molecular networks and pathways underlying human embryogenesis. Derivation of hESCs provides powerful *in vitro* model systems to remove limitations at the cellular or biological systems levels that stymie progress towards developing human-based tools and platforms that can apply to a broad range of human diseases. Development and utilization of hESC models of human embryonic development facilitate rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of human diseases. Technology breakthroughs in the last 20 years of hESC research enable neuronal or cardiac lineage-specific differentiation direct from the pluripotent state of hESCs with small molecule induction, which have provided much-needed *in vitro* model systems for bridging the key knowledge gaps in human CNS (central nervous system) and heart development [e.g., Parsons**.** 2025, Directing pluripotent hESCs towards lineage-specific cell therapy derivatives for regenerative medicine. *Gene and Cell Therapy: Therapeutic Mechanisms and Strategies,* Chapter 31:795-818; Parsons. 2016, Direct conversion of pluripotent hESCs under defined culture conditions into human neuronal or cardiomyocytes cell therapy derivatives. Methods Mol. Biol. 2016;1307:299-318]**.** It opens the door for further unveiling genetic and epigenetic programs embedded in the human CNS and heart formation during human embryogenesis using genome-wide high-throughput high resolution profiling approaches. Therefore, hESCs are gold standard for understanding human embryonic development, providing much-needed human model systems to unlock the mysteries of human development and disorders, and facilitating rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

2.3. hESCs are the gold standard for developing human-based risk testing systems for rapid and high-fidelity safety evaluation of health risks, particularly cumulative health risks, of developmental toxins with sensitivity equivalent to vulnerable children, infants, and fetuses, thus uncovering the root causes of



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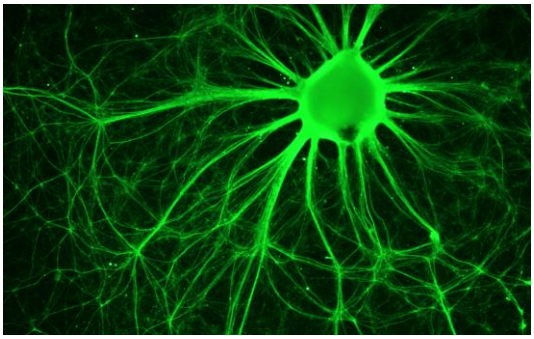
childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

In order for a drug to be approved in the US, the FDA typically requires preclinical toxicity tests and animal model studies on small and large animals to provide sufficient evidence of proof-of-concept for the prospect of safety and efficacy to justify an Investigational New Drug (IND) application for the proposed clinical investigation of a new drug. Companies use tens of thousands of animals for such tests each year. Yet more than nine in 10 drugs that enter human clinical trials fail because they are unsafe or ineffective.

Thus far, testing potential therapeutic strategies has largely relied on animal models for evaluating the behavior, safety, and efficacy of therapeutic candidates and human cell therapy products. However, because of interspecies differences, conventional studies using animal models are often poor predictors of human efficacy and safety. Animal models are xeno-hosts for the transplantation of human cells, not ideal for testing the behavior, safety, and efficacy of therapeutic outcomes of human stem cells. Large primate models are very costly and often taken years to obtain results. In addition, the results of animal studies can be highly variable and difficult to reproduce, making them unreliable as benchmarks for decisions on humans in clinical trials. Preclinical data using animal models, even results of large animal models, do not necessarily provide the benchmarks or indicators for safety and efficacy in human trials.

Children are still in a sensitive developmental stage, uniquely vulnerable to environmental chemical exposures, including pesticides, microplastics, dioxins, flame retardants, BPA, PFSA, fluoride, EMR, Phthalates, Bisphenols, herbicides, and insecticides. Since President Clinton's executive order 13045 in 1997, childhood health has largely worsened, and the chemicals children are exposed to have grown. There is a growing concern about the link between environmental health risks, particularly cumulative health risks, and chronic diseases. The emerging crisis of overmedication and the growth of childhood vaccine schedule also compound the health risks, particularly cumulative health risks, of childhood environmental chemical exposures, drugs, and vaccines to vulnerable children who are still in a sensitive developmental stage. Such health risks, particularly cumulative health risks, could be the root causes of childhood chronic disease epidemic that warrant scientific investigations.

However, scientific inquiry into the links between the health risks of childhood environmental chemical exposures, drugs, and vaccines to chronic diseases, has been hindered by the lack of a human-based risk testing system with sensitivity equivalent to that of vulnerable children, infants, and fetuses. In the US, federal regulations do not allow research that presents "greater risks than minimal" on children. In addition, federal restrictions on human embryonic and fetal materials significantly limit their availability for study. As a result,

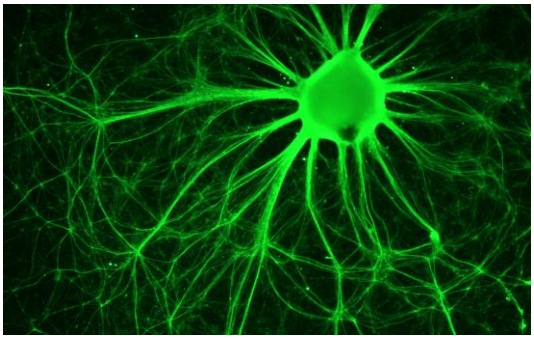


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there are significant gaps in available data regarding the effects of developmental toxins that may play a crucial role in the rising prevalence of childhood chronic diseases.

The advances in pluripotent hESC research have provided the unique opportunity to develop human-based risk testing systems for rapid and high-fidelity safety evaluation of developmental toxins with sensitivity equivalent to that of vulnerable children, infants, and fetuses. Human embryo-originated hESC and their cell/tissue/organ products/models offer viable, adequate, timely, cost-effective, sensitive, and superior alternatives that meet higher quality and safety standards than current animal testing systems and other human adult cell/tissue/organ-based testing systems. hESCs are derived from human embryos, negating the species-species differences observed in animal testing. hESCs and their derivatives have a very low tolerance threshold and are highly sensitive to any toxic chemicals/drugs/products/vaccines, providing scalable, more timely, predictive, reliable alternative methods to current animal testing systems and other human adult cell/tissue/organ-based testing systems, ensuring higher quality and safety standards, and reducing the time and cost. hESC-based human cell/tissue/organ products or models offer rapid, cost-effective, and high-fidelity safety evaluation of developmental toxins with sensitivity equivalent to that of vulnerable children, infants, and fetuses.

FDA Modernization Act 2.0 legitimizes alternatives to animal testing for advancing a drug or product to human trials. Enacting such a law for a drastic change in FDA regulation, passed by Congress and welcomed by animal welfare groups, was only made possible by advances in hESC research that have begun to offer increasingly viable alternatives to animal testing. However, many of the new approach methodologies (NAMs) proposed by the FDA in the “Roadmap to Reducing Animal Testing in Preclinical Safety Studies”, such as adult-cell/tissue/organ-based organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays, are unable to provide higher quality and safety standards than animal testing. For example, organ chips and organoids based on adult stem/cancer cells (e.g., iPSCs that are in fact adult cells reprogrammed with oncogenes or actually cancer cells) have proven to be inadequate as alternatives to animal toxicity testing because the tolerance threshold of adult/cancer cells/iPSCs to toxic chemicals/drugs is much higher than the tolerance threshold of normal human tissues or organs. Such as, the drugs screened by the liver chips of Emulate based on iPSCs either failed in clinical trials because they were toxic to the liver or were approved for market but then withdrawn or scaled back because of liver damage (see the New York Times report “Could the next blockbuster drug be lab-rat few?”). In addition, reprogrammed-adult-cell or iPSC-based organoids or organ-on-a-chip systems do not authentically replicate the in vivo human development or organ systems. Reprogrammed-adult-cell or iPSC-based brain organoids or organ-on-a-chip systems are insensitive to any toxic chemicals/drugs/vaccines/products, inadequate and unreliable to test the safety of chemicals/drugs/vaccines/products, thus unable to provide any meaningful knowledge to fill the gaps in available data regarding the effects of neurodevelopmental toxicants on children’s brain development. Therefore, those iPSC-based NAMs (e.g., brain organoids) in FDA proposed Roadmap are inadequate and insufficient to uncover the root causes of childhood chronic diseases.



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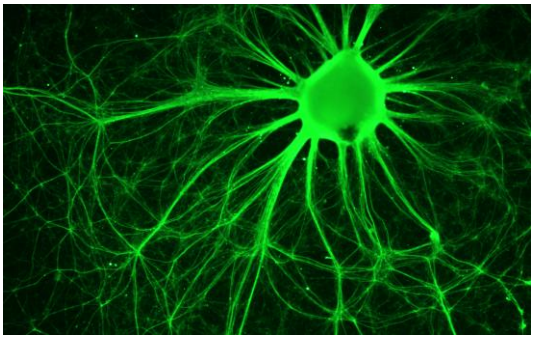
The hESC-based innovative platforms provide scale-up capability for the creation of human replacement CNS and heart, such as micro-brains, micro-spinal-cords, and micro-hearts, thereby increasing the biological complexity of human-based *in vitro* models and assays to mimic the *in vivo* structure, behavior, and function of the human CNS and heart. These hESC-based *in vitro* models and assays are controllable, reproducible, and scalable, and can be monitored and validated against responses on multiple hierarchical levels. Development and utilization of complex 3D multi-cellular models of human embryogenesis and organogenesis using hESCs provide a highly-sensitive, authentic, and reliable *in vitro* tool for rapid and high-fidelity safety evaluation of developmental toxins that may play a crucial role in the rising prevalence of childhood chronic diseases, thus uncovering the root causes that will lead to better prevention strategies and evidence-based therapeutic solutions to end the childhood chronic disease epidemic. Therefore, hESCs are the gold standard for developing human-based risk testing systems for rapid and high-fidelity safety evaluation of health risks, particularly cumulative health risks, of developmental toxins with sensitivity equivalent to vulnerable children, infants, and fetuses, thus uncovering the root causes of childhood chronic diseases. Such research areas critical to ending the childhood chronic disease epidemic could not be pursued or solved if hESCs were unavailable.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells (iPSCs), adult stem cells, etc., can replace the use of hESCs;

There is no research area in any emerging biotechnologies that can replace the use of hESCs.

Any efforts to replace the use of human embryonic stem cells (hESCs) would only result in additional waste of a staggering amount of taxpayer money on false promises and frauds, just like hundreds of billions of taxpayer money have been wasted on the fruitless efforts of iPSC fraud in the last 20 years.

hESC research holds the greatest benefit to humankind and has overwhelming public support. Prioritizing hESC research is vital to addressing childhood chronic diseases and ending the chronic disease epidemic. It is bad policy to ban hESC research or replace hESC research with adult stem cell scams and scientific frauds that would result in enormous waste of taxpayer money just like the massive fraud and waste iPSCs did in the last 20 years, stall any progress on life-saving solutions for many chronic diseases, deny access of millions of patients to life-saving treatments or cures brought by the breakthrough medical innovations of hESC research, cause public outrage, and push scientific research back to a dark era even worse than the Bush administration.



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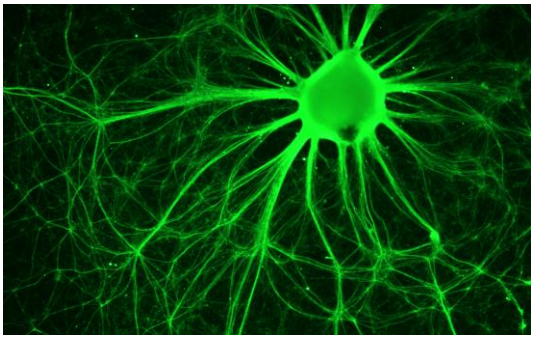
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hESC research holds huge promises for treating major chronic diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable neurological and heart diseases, including Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure that cost trillions and affect millions. Millions of people are pinning their hopes on hESC research. Even President Bush didn't ban hESC research 25 years ago, but allowed hESC research continue with Federal Funding, so someday, we could find lifesaving treatments and cures for a host of chronic diseases that destroy lives. There is no alternative for hESC research. And the so-called adult alternative to hESCs --- induced pluripotent stem cells (iPSCs) of ISSCR endorsed by the Nobel Foundation with Nobel Prize --- are in fact cancer cells reprogrammed with oncogenes, a massive scientific fraud and adult stem cell scam that has wasted a lot of government research funding in staggering amounts of hundreds of billions of taxpayer dollars, but produced absolutely nothing hopeful for any diseases. Adult stem cells and iPSCs have not created any life-saving treatments for any diseases and conditions, and iPSCs have failed safety tests in clinical trials by causing serious spontaneous mutations and harming patients just like cancer cells would do. Please see sdrmi.org for more.

The so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Despite false claim that "the adult alternative iPSCs and hESCs are identical", iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells. hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.



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Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.

In 2009, President Obama lifted Bush administration's restriction on NIH. As a result, the NIH registry has been expanded to include hundreds of hESC lines since. So far, those hESC lines on NIH registry are exclusively for research purpose only, but none of the hESC lines eligible for Federal funding are biologics-free, clinical-grade hESCs suitable for patient uses or clinical trials. hESC research has been surrounded by decades of social and legal controversy. The central ethical concern and controversy surrounding hESC research is the derivation of hESC lines, because it involves the destruction of human embryos to obtain stem cells, raising questions about the moral status of an early embryo and whether it constitutes a human life, with proponents arguing for the potential medical benefits of stem cell research while opponents believe it is morally wrong to destroy embryos for research purposes. So far, all hESC lines in NIH registry eligible for Federl funding were derived from surplus embryos with funding from private sector or the State (e.g., CIRM), that were in excess from IVF procedures and otherwise destined for destruction, and that were donated under IRB-approved guidelines that mandated informed consent, protection of the donor's identity, and strict ethical research practices. Despite some progresses, Federal funding remains barred from any activities associated with the derivation of hESC lines from IVF leftover embryos for research purposes by the Dickey-Wicker Amendment, a federal law that prohibits the use of federal funds to support research that destroys or harms human embryos, or prohibits the use of federal funds for the creation, destruction, or discarding of human embryos for research purposes, and also prohibits subjecting human embryos to a greater risk of injury or death than is allowed for research on fetuses in utero. Basically, Federal funding could not be used to derive hESC lines from human embryos for research purposes.

However, breakthroughs and advances in the last 20 years of hESC research have changed the premise of the Dickey-Wicker Amendment, the federal law that prohibits the use of federal funds to derive hESC lines from human embryos for RESEARCH PURPOSES only.

In August, 2001, when President Geroge W. Bush announced the restriction of Federal funding to hESC lines derived before his announcement, he basically provided a compromised solution to both pros and cons. To those

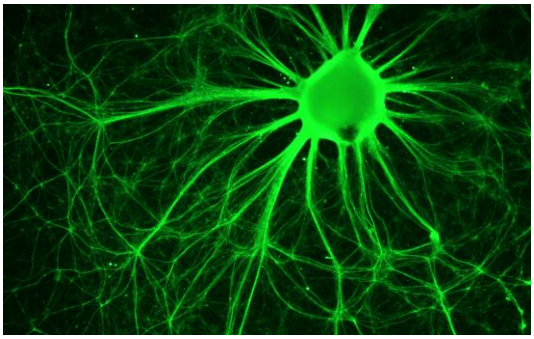
who supported hESC research, he allowed hESC research continue with NIH funding in the hope that it would provide scientific evidence of medicinal uses of hESC for many diseases to warrant continued Federal funding and public support for hESC research in future. To those who were against hESC research, he also ended derivation of more hESC lines by destroying embryos. 25 years later, his policy to invest Federal funding in hESC research has paid off. Breakthroughs and advances in the last 20 years of hESC research have provided scientific evidence of medicinal uses of hESCs for many life-threatening and devastating diseases to warrant continued Federal funding and public support for hESC research. Those original hESC studies in the last 20 years have presented hESCs as a novel, advanced therapeutic strategy for a host of chronic diseases that destroy lives. The IVF techniques offer a small portion of the millions of excess embryos currently stored in the IVF clinics worldwide, which are otherwise destined for destruction, to be an unlimited source that could potentially deliver in future a whole range of therapeutic treatments or cures to patients with life-threatening and devastating diseases for tissue and function restoration. The breakthroughs and advances in the last 20 years of hESC research have laid the foundation for relaxing Federal policy to allow Federal funding to be used to derive biologics-free, clinical-grade hESC lines from human embryos for THERAPEUTIC PURPOSES, CLINICAL APPLICATIONS, PATIENT USES, OR HUMAN TRIALS. Such deregulation efforts will dramatically increase the overall turnover of investments in biomedical research, deliver urgently-needed treatments or cures for a host of incurable or hitherto untreatable disorders that destroy lives, speed hESC medical breakthroughs to patients, and drive real progress on ending the chronic disease epidemic.

4. Research areas in which additional investments should be made to bolster validated models to replace the use of hESCs.

There is no research area in which additional investments should be made to bolster validated models to replace the use of human embryonic stem cells (hESCs).

Any additional investments made to bolster validated models to replace the use of hESCs would only result in additional waste of a staggering amount of taxpayer money on false promises and frauds, just like hundreds of billions of taxpayer money have been wasted on the fruitless efforts of iPSC fraud in the last 20 years.

hESC research holds the greatest benefit to humankind and has overwhelming public support. Prioritizing hESC research is vital to addressing childhood chronic diseases and ending the chronic disease epidemic. It is bad policy to ban hESC research or replace hESC research with adult stem cell scams and scientific frauds that would result in enormous waste of taxpayer money just like the massive fraud and waste iPSCs did in the last 20 years, stall any progress on life-saving solutions for many chronic diseases, deny access of millions of patients to life-saving treatments or cures brought by the breakthrough medical innovations of hESC research, cause public outrage, and push scientific research back to a dark era even worse than the Bush administration.



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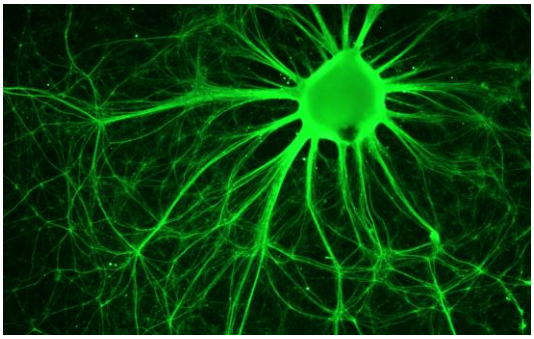
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Email: parsons@sdrmi.org

hESC research holds huge promises for treating major chronic diseases that have been challenging for traditional medicine, such as a wide range of incurable or hitherto untreatable neurological and heart diseases, including Parkinson's disease, Alzheimer disease, stroke, spinal cord and brain injuries, heart disease and failure that cost trillions and affect millions. Millions of people are pinning their hopes on hESC research. Even President Bush didn't ban hESC research 25 years ago, but allowed hESC research continue with Federal Funding, so someday, we could find lifesaving treatments and cures for a host of chronic diseases that destroy lives. There is no alternative for hESC research. And the so-called adult alternative to hESCs --- induced pluripotent stem cells (iPSCs) of ISSCR endorsed by the Nobel Foundation with Nobel Prize --- are in fact cancer cells reprogrammed with oncogenes, a massive scientific fraud and adult stem cell scam that has wasted a lot of government research funding in staggering amounts of hundreds of billions of taxpayer dollars, but produced absolutely nothing hopeful for any diseases. Adult stem cells and iPSCs have not created any life-saving treatments for any diseases and conditions, and iPSCs have failed safety tests in clinical trials by causing serious spontaneous mutations and harming patients just like cancer cells would do. Please see sdrmi.org for more.

The so-called adult cell alternative to hESCs --- induced pluripotent adult/stem cells (iPSCs) that are in fact adult cells reprogrammed with oncogenes or cancer cells harboring oncogenes. iPSCs contain oncogenes because the process of creating them often involves using oncogenes or genes that are linked to tumorigenesis. Key reprogramming factors like c-Myc, Klf4, Oct4, Sox2 are well-known oncogenes and have links to tumor formation. It is common scientific knowledge that gene reprogramming is in fact oncogenesis. While these genes are necessary for reprogramming, their presence means iPSCs inherently carry an oncogenic risk that must be addressed, particularly for clinical applications.

Despite false claim that "the adult alternative iPSCs and hESCs are identical", iPSCs and hESCs are actually not identical, but distinctly different. The so-called adult alternative iPSCs are not pluripotent stem cells, but bioengineered pluripotent cancer cells reprogrammed from adult cells with oncogenes, distinctly different from embryo-originated hESCs that are the real, natural pluripotent stem cells. hESCs derived from embryos are highly acetylated and unmethylated, genetically stable with unlimited expansion ability and unrestricted plasticity, sustaining epiblast pluripotency, maintaining genomic/epigenomic/cell-line homogeneity across all hESC lines, and respond to developmental signals at embryonic or epiblast stage. In contrast, the so-called adult cell alternative iPSCs are in fact reprogrammed from different adult cells or different tissues with different oncogenes, deacetylated and highly-methylated, having different differentiation potential and cell line variations, displaying genomic heterogenicity and instability because the different tissues they used for reprogramming have different genomic imprints that could not be simply reversed by genes, not responding to developmental signals at embryonic or epiblast stage, displaying uncontrolled growth, just like cancer cells.



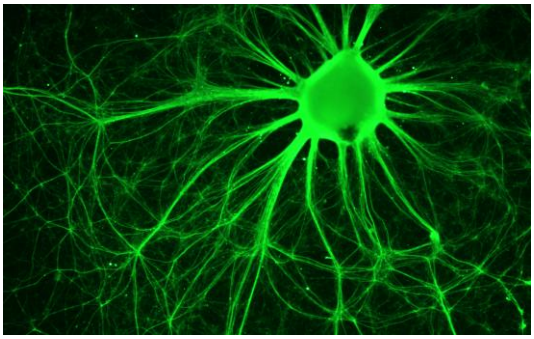
Website: https://www.sdrmi.org
Email: parsons@sdrmi.org

hESC discoveries and breakthroughs do not apply for iPSCs, and hESC technologies and platforms do not work for iPSCs either.

Ironically, most of the Federal funding for stem cell research during the Obama, Trump, and Biden Administrations has been allocated to waste on the false promise --- so-called adult alternative iPSCs, which, despite well-funded, have generated neither intended public interests nor promised medicinal benefits to really push the regenerative medicine field forward. hESC research is irreplaceable in developing innovative regenerative medicine technologies for a host of chronic diseases that destroy lives and improving our understanding of the dynamics and complexity of the human tissue and organ function in development and disorders. Future efforts to relax Federal policy and prioritize funding to support such cutting-edge hESC research are crucial in order to dramatically increase the overall turnover of investments in biomedical research.

In 2009, President Obama lifted Bush administration's restriction on NIH. As a result, the NIH registry has been expanded to include hundreds of hESC lines since. So far, those hESC lines on NIH registry are exclusively for research purpose only, but none of the hESC lines eligible for Federal funding are biologics-free, clinical-grade hESCs suitable for patient uses or clinical trials. hESC research has been surrounded by decades of social and legal controversy. The central ethical concern and controversy surrounding hESC research is the derivation of hESC lines, because it involves the destruction of human embryos to obtain stem cells, raising questions about the moral status of an early embryo and whether it constitutes a human life, with proponents arguing for the potential medical benefits of stem cell research while opponents believe it is morally wrong to destroy embryos for research purposes. So far, all hESC lines in NIH registry eligible for Federl funding were derived from surplus embryos with funding from private sector or the State (e.g., CIRM), that were in excess from IVF procedures and otherwise destined for destruction, and that were donated under IRB-approved guidelines that mandated informed consent, protection of the donor's identity, and strict ethical research practices. Despite some progresses, Federal funding remains barred from any activities associated with the derivation of hESC lines from IVF leftover embryos for research purposes by the Dickey-Wicker Amendment, a federal law that prohibits the use of federal funds to support research that destroys or harms human embryos, or prohibits the use of federal funds for the creation, destruction, or discarding of human embryos for research purposes, and also prohibits subjecting human embryos to a greater risk of injury or death than is allowed for research on fetuses in utero. Basically, Federal funding could not be used to derive hESC lines from human embryos for research purposes.

However, breakthroughs and advances in the last 20 years of hESC research have changed the premise of the Dickey-Wicker Amendment, the federal law that prohibits the use of federal funds to derive hESC lines from human embryos for RESEARCH PURPOSES only.



San Diego Regenerative Medicine Institute

Human Embryonic Stem Cell Therapy
Unleashing the Power of Life Science

Website: https://www.sdrmi.org
Email: parsons@sdrmi.org

In August, 2001, when President Geroge W. Bush announced the restriction of Federal funding to hESC lines derived before his announcement, he basically provided a compromised solution to both pros and cons. To those who supported hESC research, he allowed hESC research continue with NIH funding in the hope that it would provide scientific evidence of medicinal uses of hESC for many diseases to warrant continued Federal funding and public support for hESC research in future. To those who were against hESC research, he also ended derivation of more hESC lines by destroying embryos. 25 years later, his policy to invest Federal funding in hESC research has paid off. Breakthroughs and advances in the last 20 years of hESC research have provided scientific evidence of medicinal uses of hESCs for many life-threatening and devastating diseases to warrant continued Federal funding and public support for hESC research. Those original hESC studies in the last 20 years have presented hESCs as a novel, advanced therapeutic strategy for a host of chronic diseases that destroy lives. The IVF techniques offer a small portion of the millions of excess embryos currently stored in the IVF clinics worldwide, which are otherwise destined for destruction, to be an unlimited source that could potentially deliver in future a whole range of therapeutic treatments or cures to patients with life-threatening and devastating diseases for tissue and function restoration. The breakthroughs and advances in the last 20 years of hESC research have laid the foundation for relaxing Federal policy to allow Federal funding to be used to derive biologics-free, clinical-grade hESC lines from human embryos for THERAPEUTIC PURPOSES, CLINICAL APPLICATIONS, PATIENT USES, OR HUMAN TRIALS. Such deregulation efforts will dramatically increase the overall turnover of investments in biomedical research, deliver urgently-needed treatments or cures for a host of incurable or hitherto untreatable disorders that destroy lives, speed hESC medical breakthroughs to patients, and drive real progress on ending the chronic disease epidemic.

23. Dr. David M. Gilbert

I am responding: On behalf of myself

Name: Dr. David M. Gilbert

Name of Organization: San Diego Biomedical Research Institut

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 03/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
We will always need fresh cell lines for reasons that are well known (genetic and epigenetic load increases with passage, immune rejection requires off the shelf reagents for all patient, iPSCs are not yet as safe or proven, hESCs will always be needed as benchmarks). Which of the current and future lines should be pursued requires research and protocol optimization - how about an RFA to weed out existing lines on the registry that are not useful, honing the 503 down to the real list, and then take a look at the immunological diversity as therapeutics and seek lines that fill the gap.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Gold standards will shift as passage numbers increase. New lines will be needed.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Currently nothing can "replace" hESCs. They are the native tissue. You benchmark against them and they are more youthful and protected from genetic load for therapeutic purposes.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
hESCs are not to be "replaced". Reduced use or reduced need does not warrant elimination of the ground truth, the native material. Feel free to read this:
https://davidmgilbert.substack.com/p/questionable-logic-in-nih-policy

24. Victor Corces

I am responding: On behalf of myself

Name: Victor Corces

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 03/26/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
None

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
All

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
None. If you want to learn about the biology of hESCs, and of the cell types and tissues derived from these cells, there are no areas in which the currently available ones are enough. The trend should go in the oposite direction, e. i. make more cell lines available to avoid making conclusions based on existing ones, which are contaminated by viruses and were derived long ago. If you saw the movie Risky Business, you may remeber when Tom Cruise said "Porsche. There is no subtitute". The same applies to hESCs. hESCs are not the same as iPSCs, which have been reprogram to a certain extent but still retain partial memory of their differentiated state.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Why do this? What would be the point of spending research funds to find a replacement for something that already exist and the replacement will not be as good?

25. Stewart Anderson

I am responding: On behalf of myself

Name: Stewart Anderson

Name of Organization: Children's Hospital of Philadelphia/UPenn School of Medicine

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/03/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
IPSCs generally exist at a more differentiated/less fully pluripotent state than hESCs. For this reason they can be, for lines that are reasonably low passage and properly QC'd, superior to IPSCs for testing isogenic pairs of lines in which a disease related mutation is introduced and compared to the parent line. This can be particularly for testing mutational effects on highly differentiated cells, such as neuronal subtypes, that can be particularly challenging due to line to line idiosyncracies.

In addition, as many dozens of hESC lines have been in use for 10+ years, and are tremendously useful for many purposes--i.e. containing fluoroescent reporters of a particular cell type or lineage, it would be tremendously wasteful if NIH, which has supported that generation and use of these cells previously, to limit their use going forward. True, many lines could be re-made on IPSC backgrounds, but the cost to replace the existing line librarry would be extreme.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
as above

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
as above

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
further studying how to de-volve IPSCs into the sometimes-more pluripotent state if hESCs.

26. Philip Jordan

I am responding: On behalf of myself

Name: Philip Jordan

Name of Organization: Uniformed Services University of the Health Sciences (primary) and Johns Hopkins University (adjunct)

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/08/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Sufficiency of Current Lines: For general proof-of-concept studies and basic developmental biology, the 503+ lines currently on the NIH Registry provide a robust genetic diversity. These lines are essential for the ongoing development of New Approach Methodologies (NAMs) because they offer a longitudinal history of data that allows researchers to cross-reference results globally.

Need for New Lines: New hESC lines are critically needed to represent ancestral genetic diversity that is currently underrepresented in the Registry. Furthermore, new lines derived under clinical-grade (cGMP) conditions are necessary for modern regenerative medicine. Without new, high-diversity, and clinical-grade hESC lines, we risk developing NAMs and therapies that are not universally applicable or safe for all populations.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Benchmarking Epigenetic Integrity: hESCs remain the only source of "virgin" pluripotency. Unlike iPSCs—which carry "epigenetic memory" from their somatic origins (e.g., skin or blood) and accumulated mutations from the donor's life—hESCs represent the baseline state of human development. They are the essential control group for validating whether an organoid or MPS has reached a truly "embryonic-like" or "mature" state.

Early Embryogenesis and Gastrulation Modeling: Research into the first few days of human life—critical for understanding miscarriage and congenital disabilities—cannot be reliably performed with iPSCs, which often exhibit "skewed" differentiation potential due to residual epigenetic marks.

Microphysiological Systems (MPS) Validation: When building "organs-on-a-chip," hESCs serve as the gold standard to ensure the biological responses observed are due to the system's design and not the underlying genetic instability or "reprogramming noise" inherent in many iPSC lines.

hESCs are the "True North"

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

Patient-Specific Disease Modeling: iPSCs are the superior choice for studying specific genetic diseases (e.g., Cystic Fibrosis or Alzheimer's) because they carry the exact genetic mutations of the patient. In these cases, the "life lived" by the cell is a feature, not a bug.

Drug Metabolism and Safety Screening: For high-throughput toxicology screening where a "population-in-a-dish" approach is required, the scalability of iPSCs makes them a functional replacement for hESCs, provided they are initially validated against hESC benchmarks.

Adult Stem Cells (ASCs): In localized tissue repair (e.g., bone marrow transplants or corneal repair), ASCs are already the clinical standard and have effectively replaced the need for pluripotent sources in those specific applications.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Epigenetic "Resetting" Technologies: Funding for research that can completely "erase" the epigenetic memory of iPSCs to make them functionally indistinguishable from hESCs.

Standardization of NAMs/Organoids: Investment in large-scale "Characterization Biobanks" that use hESCs to create a universal proteomic and transcriptomic map. This map would allow researchers to verify their iPSC-derived models without needing to run side-by-side hESC trials every time.

We are not yet in a place to put hESCs aside. This is a critical moment in creating human model systems that can essentially change the shape of medicine and personalized treatments and cures. On the contrary, we need hESCs now to provide the benchmark and drive technologies forward.

27. Federation of American Societies for Experimental Biology (FASEB)

I am responding: On behalf of an organization

Name: Eric E. Kelly, PhD

Name of Organization: Federation of American Societies for Experimental Biology (FASEB)

Type of Organization: Professional Organization/Association

Role: Organizational Official

Date Submitted: 04/14/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The last decade marked a shift in the use of stem cells in biomedical research from hESC lines to increased use and reliance on induced pluripotent stem cells (iPSC), prompted in part by federal policies that limited the use and development of hESC lines. Despite considerable progress toward meeting the utility of hESCs with iPSCs, important differences exist between hESCs and iPSCs that prevent total interchangeability. Currently, existing hESC lines sufficiently meet the needs of the research community to assess new iPSC pluripotency; however, given ongoing uncertainty surrounding the definition of distinct pluripotent states, FASEB recommends that NIH lift the current pause on the registration of new hESC lines to ensure lines available through the registry reflect technological advancements and scientific potential. FASEB also encourages NIH to establish clear scientific criteria to determine when the registration of new hESC lines is necessary. Such criteria should highlight why a new hESC line is necessary to elucidate scientific insights and address specific research questions that cannot be pursued through existing hESC lines, iPSC models, or other validated systems.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
As the research community continues to make progress toward the development of models to replace hESCs, there are several areas for which targeted investments should be prioritized:

1. Additional funding for infrastructure to support iPSC standardization and quality control, including benchmarking genetic stability and differentiation, is critical as the field moves toward widespread adoption of iPSC methodologies. Such investments will support the agency's continued efforts to bolster rigor and reproducibility.

2. Support for the establishment of large, well-annotated iPSC reference panels and banks of patient-derived and disease-specific lines that are linked with whole-genome databases to enable population-

scale and ancestry-aware studies that accelerate research examining human rare diseases, common diseases for which diverse populations are differentially susceptible, population variants in infectious disease susceptibility, and population-based medicine.

3. Additional investments in iPSC-based embryoid and organoid models to support the replacement of hESC use in embryology and organogenesis. NIH should also consider developing clear guidance for the use of hESCs and iPSCs in developmental biology research.

4. Additional support to develop validated lineage-restricted cell systems, including trophoblast and organ-specific progenitors, will strengthen methodologies that may more accurately reflect in vivo biology.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/FINAL_FASEB-Comments-on-NIH-hESC-RFI_20260414-letterhead.pdf

Description: Comments from the Federation of American Societies for Experimental Biology (FASEB), formatted on letterhead and including introductory/concluding text.

FASEB
Federation of American Societies for Experimental Biology

Representing Over 100,000 Researchers

6120 Executive Blvd., Suite 230, Rockville, MD 20852 | faseb.org

April 14, 2026

Lyric Jorgenson, PhD
Associate Director for Science Policy
National Institutes of Health
6705 Rockledge Drive
Bethesda, MD 20817

RE: Response to Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

Transmitted electronically via online form.

Dear Dr. Jorgenson,

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to provide feedback on the Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031), which seeks input on the utility of human embryonic stem cells (hESCs) in biomedical research. FASEB is a coalition of 20 scientific societies representing over 100,000 individual biological and biomedical researchers, many of whom utilize hESC lines in their research programs. Given the ever-changing nature of biomedical and biological science research, our community acknowledges the importance of continuously assessing available methodologies to maximize available resources.

Below, FASEB offers comments addressing questions 1 and 4. These comments recommend that NIH resume review of new hESC lines for inclusion in the Human Embryonic Stem Cell Registry. The Federation also highlights several research areas for which additional investments could bolster the development, validation, and application of hESC alternatives.

Question 1: Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed

The last decade marked a shift in the use of stem cells in biomedical research from hESC lines to increased use and reliance on induced pluripotent stem cells (iPSC), prompted in part by federal policies that limited the use and development of hESC lines. Despite considerable progress toward meeting the utility of hESCs with iPSCs, important differences exist between hESCs and iPSCs that prevent total interchangeability. Currently, existing hESC lines sufficiently meet the needs of the research community to assess new iPSC pluripotency; however, given ongoing uncertainty surrounding the definition of distinct pluripotent states, FASEB recommends that NIH lift the current pause on the registration of new hESC lines to ensure lines available through the registry reflect technological advancements and scientific potential. FASEB also encourages NIH to establish clear scientific criteria to determine when the registration of new hESC lines is necessary. Such criteria should highlight why a new hESC line is necessary to elucidate scientific insights and address specific research questions that cannot be pursued through existing hESC lines, iPSC models, or other validated systems.

Question 4: Research areas in which additional investments should be made to bolster validated models to replace use of hESCs

As the research community continues to make progress toward the development of models to replace hESCs, there are several areas for which targeted investments should be prioritized:

1. Additional funding for infrastructure to support iPSC standardization and quality control, including benchmarking genetic stability and differentiation, is critical as the field moves toward widespread adoption of iPSC methodologies. Such investments will support the agency's continued efforts to bolster rigor and reproducibility.
2. Support for the establishment of large, well-annotated iPSC reference panels and banks of patient-derived and disease-specific lines that are linked with whole-genome databases to enable population-scale and ancestry-aware studies that accelerate research examining human rare diseases, common diseases for which diverse populations are differentially susceptible, population variants in infectious disease susceptibility, and population-based medicine.
3. Additional investments in iPSC-based embryoid and organoid models to support the replacement of hESC use in embryology and organogenesis. NIH should also consider developing clear guidance for the use of hESCs and iPSCs in developmental biology research.
4. Additional support to develop validated lineage-restricted cell systems, including trophoblast and organ-specific progenitors, will strengthen methodologies that may more accurately reflect *in vivo* biology.

FASEB appreciates the opportunity to comment as policies surrounding hESC development and registration are revisited. In our comments, we recommend that NIH resume registration of new hESC lines and highlight several areas for which additional investment will support development of alternative methodologies to complement knowledge gained through studies using hESCs.

Please do not hesitate to contact me should you have any questions related to our comments.

Sincerely,



Eric E. Kelley, PhD
FASEB President

28. Bernard Khor

I am responding: On behalf of myself

Name: Bernard Khor

Name of Organization: N/A

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/14/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Human embryonic stem cells (hESCs) are irreplaceable for studying early developmental events in humans. They are stable and hundreds of genetic tools have been generated by editing the NIH-approved hESCs during the last two decades. These lines are an invaluable resource for the research community and it would take decades and millions of dollars to regenerate all of these edits in new, non-embryonic lines.

Although hESCs are more stable than induced pluripotent stem cells (iPSCs), they still exhibit similar technical problems at high passage numbers, including genetic instability and increased senescence. Furthermore, the current NIH-approved hESC list does not accurately reflect the genetic diversity present in humans. Therefore, the generation of new hESC lines is needed to better understand the biological underpinnings of early human development.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs remain the gold standard for several research areas. As mentioned in point 1, hESCs are unique because they can be differentiated into any cell type in the body, and, as compared to iPSCs, are more genetically stable. Importantly, there are several ongoing clinical trials that use hESCs to generate differentiated cells for transplantation in diseases that affect individuals with Down syndrome:

Neurona Therapeutics is differentiating hESCs into GABAergic interneurons for transplantation into the hippocampus of patients with mesial temporal lobe epilepsy. This clinical trial is already in Phase I/II and is showing promising results (PMID: 37802038). A clinical trial for the transplantation of myelinating glial cells is also planned to start in the near future. This will be of particular interest for individuals with Down syndrome, who have demonstrated deficits in myelination.
Multiple clinical trials (Viacyte, Vertex, CRISPR Therapeutics) are using hESCs to treat type 1 diabetes (PMIDs: 41638426, 39575893). Here, the goal is to replace the lost insulin-producing β-islet pancreatic cells. Some of these clinical trials are in Phase I or I/II, and one is in Phase III (Vertex, VX-880). Thus, there is very strong evidence of hESCs enabling important clinical advances. Individuals with Down syndrome are at a much higher risk of developing Type 1 diabetes (PMID: 32521135); therefore, these advances, which were made possible by hESCs, are vital to the T21RS and Down syndrome community.
There is a higher prevalence of macular degeneration and other ocular conditions in people with Down syndrome (PMID: 39613904). hESCs are being used in numerous Phase 1 and 2 clinical trials for these

ocular diseases, and are showing high therapeutic potential (PMID: 40830295).

These examples of highly promising clinical trials highlight the essential role of hESCs in personalized medicine. While iPSCs are powerful tools and mimic many properties of hESCs, they retain residual epigenetic memory from their tissue of origin, limiting their use in regenerative medicine. Furthermore, hESCs allow researchers to maintain a consistent genetic background for their experiments and even compare results across different conditions and diseases. Importantly, because hESCs have been successfully used in transplantation studies, we know they are a valid and safe approach.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
With the current technology, hESCs cannot be fully replaced by other stem cell platforms. Induced pluripotent stem cells are an extremely powerful model system and offer some advantages over hESCs, including being patient-specific, more accessible, and avoiding the inherent ethical concerns associated with hESCs.

However, as detailed in point 1, they also have some disadvantages, such as residual molecular signatures retained from the adult cells they were derived from, and the lack of genetic tools that have already been edited into the approved hESCs. Thus, to best promote translational research and clinical innovation, these two model systems should be used in parallel.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Several recent technological advances enable researchers to perform in-depth analyses of other pluripotent stem cells and compare them to hESCs. For example, analyses of nuclear architecture, chromatin accessibility, transcriptomics, proteomics, metabolomics, and physiology of hESCs will be essential to understand the residual adult signatures of iPSCs. By comparing these pluripotent cells, researchers will be able to improve the next generation of iPSCs and potentially make them more similar to hESCs. As mentioned above, it is paramount to retain hESCs as a benchmark for refinement of iPSCs as new technologies emerge. Furthermore, the resources invested in developing the genetic tools available in hESCs and their downstream applications should not be limited, as this would create a significant roadblock to future research. Instead, NIH should continue to invest in hESCs in parallel with novel applications and approaches utilizing iPSCs.

29. Justin Westhoff

I am responding: On behalf of myself

Name: Justin Westhoff

Name of Organization: Medical College of Wisconsin

Type of Organization: Academic Institution

Role: Other

Role - Other: Research Technologist 3

Date Submitted: 04/15/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Embryonic Stem Cells should never be used for any medical purpose as it violates the dignity of human life. Use adult stem cells only

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
They should never be seen as the gold standard and alternatives should absolutely be explored.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Pluripotent and adult stem cells are a much, much better option for using stem cells.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Any exploration of other sources of stem cells outside on embryonic should be encouraged

30. Lizbeth Nunez

I am responding: On behalf of myself

Name: Lizbeth Nunez

Name of Organization: Medical College of Wisconsin

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/15/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Currently approved hESC lines are sufficient for many standard applications, including basic pluripotency research, differentiation protocol development, lineage tracing, toxicology, organoid development, and benchmarking of other human pluripotent stem cell systems. In many labs, approved hESC lines already support work in developmental biology, neurobiology, retinal biology, cardiometabolic differentiation, and translational cell manufacturing. At the same time, new hESC lines are still needed. One major reason is genetic diversity. Widely used hESC resources do not adequately capture the diversity of human populations, and whole-genome analysis has shown that many commonly used hESC lines are closely related, including sibling relationships among roughly one-third of sequenced lines. That means the existing pool does not fully represent human genetic variation for disease modeling, drug response, developmental biology, or immune compatibility studies.

New lines are also needed for disease-associated genotypes, better HLA representation, and updated clinical-grade derivation and manufacturing standards. Those needs are especially important for transplantation-oriented research, where immune compatibility and reproducible product quality matter greatly.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs remain the gold standard in several areas because they are the original and most direct human pluripotent reference state against which other systems are compared. Even where iPSCs are highly useful, they are still commonly evaluated relative to hESC benchmarks for pluripotency, differentiation fidelity, epigenetic state, and developmental potential. Ongoing efforts to standardize iPSC testing reflect that the field still needs robust reference standards.

Besides the obvious early human development and embryo-model research there are many other areas that benefit from hembryonic stem cells. For example, cell replacement and regenerative medicine, where hESC-derived products have already reached human clinical trials. Recent and ongoing examples include:

Type 1 diabetes: Vertex’s zimislecel/VX-880 program uses stem-cell-derived insulin-producing islet cells and has reported encouraging clinical results in people with severe type 1 diabetes.
Parkinson’s disease: a 2025 Nature paper reported phase I trial results for dopaminergic neuron

progenitors derived from hESCs.
Retinal disease: multiple ClinicalTrials.gov studies have tested hESC-derived retinal pigment epithelium for macular degeneration and related retinal disorders.
Spinal cord injury: hESC-derived oligodendrocyte progenitor cell programs have advanced through clinical testing and long-term safety follow-up.

Removing hESCs would not just slow these areas; it would undermine the evidence base that made them possible. In translational medicine, hESCs are not merely historical tools. They are active inputs into product development, potency benchmarking, manufacturing optimization, and first-in-human studies.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
There are definitely research areas where alternatives can reduce hESC use. iPSCs are especially strong for patient-specific disease modeling, genetic disease studies, drug screening, gene-editing workflows, and some forms of regenerative medicine development. Because they can be derived from living donors, they are also highly valuable for personalized models and autologous or HLA-matched strategies.

Adult stem cells can replace hESCs in some narrower tissue-specific contexts, especially where the question is about adult tissue repair or lineage-restricted regeneration rather than broad human pluripotency.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
iPSC standardization and cross-lab validation, including genomic stability, differentiation reproducibility, potency assays, and agreed-upon reference standards.

Immune-compatible pluripotent stem cell resources, including HLA-matched and engineered lines, to improve transplantation relevance.

Stem cell-based embryo models and organoid systems, where careful validation against known developmental biology is still needed.

Head-to-head validation studies directly comparing hESCs, iPSCs, and adult stem-cell-derived systems for specific use cases rather than assuming interchangeability

31. Kristy Welshhans

I am responding: On behalf of myself

Name: Kristy Welshhans

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Investigator/Researcher

Date Submitted: 04/15/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Human embryonic stem cells (hESCs) are irreplaceable for studying early developmental events in humans. They are stable and hundreds of genetic tools have been generated by editing the NIH-approved hESCs during the last two decades. These lines are an invaluable resource for the research community and it would take decades and millions of dollars to regenerate all of these edits in new, non-embryonic lines.

Although hESCs are more stable than induced pluripotent stem cells (iPSCs), they still exhibit similar technical problems at high passage numbers, including genetic instability and increased senescence. Furthermore, the current NIH-approved hESC list does not accurately reflect the genetic diversity present in humans. Therefore, the generation of new hESC lines is needed to better understand the biological underpinnings of early human development.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs remain the gold standard for several research areas. As mentioned in point 1, hESCs are unique because they can be differentiated into any cell type in the body, and, as compared to iPSCs, are more genetically stable. The research in my lab focuses on Down syndrome. Importantly, there are several ongoing clinical trials that use hESCs to generate differentiated cells for transplantation in diseases that affect individuals with Down syndrome:

Neurona Therapeutics is differentiating hESCs into GABAergic interneurons for transplantation into the hippocampus of patients with mesial temporal lobe epilepsy. This clinical trial is already in Phase I/II and is showing promising results (PMID: 37802038). A clinical trial for the transplantation of myelinating glial cells is also planned to start in the near future. This will be of particular interest for individuals with Down syndrome, who have demonstrated deficits in myelination.

Multiple clinical trials (Viacyte, Vertex, CRISPR Therapeutics) are using hESCs to treat type 1 diabetes (PMIDs: 41638426, 39575893). Here, the goal is to replace the lost insulin-producing β-islet pancreatic cells. Some of these clinical trials are in Phase I or I/II, and one is in Phase III (Vertex, VX-880). Thus, there is very strong evidence of hESCs enabling important clinical advances. Individuals with Down syndrome are at a much higher risk of developing Type 1 diabetes (PMID: 32521135); therefore, these advances, which were made possible by hESCs, are vital to the T21RS and Down syndrome community.

There is a higher prevalence of macular degeneration and other ocular conditions in people with Down syndrome (PMID: 39613904). hESCs are being used in numerous Phase 1 and 2 clinical trials for these ocular diseases, and are showing high therapeutic potential (PMID: 40830295).

These examples of highly promising clinical trials highlight the essential role of hESCs in personalized medicine. While iPSCs are powerful tools and mimic many properties of hESCs, they retain residual epigenetic memory from their tissue of origin, limiting their use in regenerative medicine. Furthermore, hESCs allow researchers to maintain a consistent genetic background for their experiments and even compare results across different conditions and diseases. Importantly, because hESCs have been successfully used in transplantation studies, we know they are a valid and safe approach.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
With the current technology, hESCs cannot be fully replaced by other stem cell platforms. Induced pluripotent stem cells are an extremely powerful model system and offer some advantages over hESCs, including being patient-specific, more accessible, and avoiding the inherent ethical concerns associated with hESCs.

However, as detailed in point 1, they also have some disadvantages, such as residual molecular signatures retained from the adult cells they were derived from, and the lack of genetic tools that have already been edited into the approved hESCs. Thus, to best promote translational research and clinical innovation, these two model systems should be used in parallel.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Several recent technological advances enable researchers to perform in-depth analyses of other pluripotent stem cells and compare them to hESCs. For example, analyses of nuclear architecture, chromatin accessibility, transcriptomics, proteomics, metabolomics, and physiology of hESCs will be essential to understand the residual adult signatures of iPSCs. By comparing these pluripotent cells, researchers will be able to improve the next generation of iPSCs and potentially make them more similar to hESCs. As mentioned above, it is paramount to retain hESCs as a benchmark for refinement of iPSCs as new technologies emerge. Furthermore, the resources invested in developing the genetic tools available in hESCs and their downstream applications should not be limited, as this would create a significant roadblock to future research. Instead, NIH should continue to invest in hESCs in parallel with novel applications and approaches utilizing iPSCs.

32. Karen Vonhof

I am responding: On behalf of myself

Name: Karen Vonhof

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Other

Role - Other: I am part of a familial study for Neuroendocrine Cancer at NIH. I am Pro-Life and firmly believe in the sanctity of human life. I therefore vehemently disagree with NIH using any part of aborted babies.

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
I am Pro-Life and firmly believe in the sanctity of human life. I therefore vehemently disagree with NIH using any part of aborted babies.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
I am Pro-Life and firmly believe in the sanctity of human life. I therefore vehemently disagree with NIH using any part of aborted babies.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Adult stem cells and induced pluripotent stem cells (iPSCs) have emerged as safe, versatile, and highly effective alternatives.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

33. Marcia Leese

I am responding: On behalf of myself

Name: Marcia Leese

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Public Comment on NIH Proposed Changes to Human Embryonic Stem Cell Research To the National Institutes of Health:

I respectfully submit this comment in strong support of the NIH's decision to reconsider and restrict the use of human embryonic stem cells (hESC) in federally funded research. Please urge the NIH to prohibit all future federal funding for hESC research.

I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Rresearch has failed to deliver the anticipated breakthroughs. After more than 25 years, there's been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer.

Every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings capable of growth, laughter, and love, of forming relationships, and experience the full beauty of human life. To deliberately end that life and potential is morally reprehensible.

No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

Instead, direct all NIH funding toward alternative stem cell sources to such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

I sincerely urge the NIH to take steps to end all taxpayer funding for human embryonic stem cell research.

Thank you.

Marcia Leese
[redacted]
Retired, concerned citizen

34. Tina Smith

I am responding: On behalf of myself

Name: Tina Smith

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Quit taking innocent lives

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
and more children live

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
murder

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
you are so smart figure it out yourself

35. Ronald McElfresh

I am responding: On behalf of myself

Name: Ronald McElfresh

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Other

Role - Other: N/A

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

36. L. G.

I am responding: On behalf of myself

Name: L. G.

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
No. It is wrong to use embryonic stem cells in this way. Use adult stem cells or iPSCs or find another way that doesn't use embryonic cells.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
No. It is wrong to use embryonic stem cells in this way. Use adult stem cells or iPSCs or find another way that doesn't use embryonic cells.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
YES. Use adult stem cells or iPSCs or find another way that doesn't use embryonic cells.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Agreed. The use of embryonic stem cells is inherently wrong, and not necessary.

37. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/Comments-on-NIH-Proposed-Changes-to-Human-Embryonic-Stem-Cell-Research.docx

To the National Institutes of Health:

I respectfully submit this comment in strong support of the NIH's decision to reconsider and restrict the use of human embryonic stem cells (hESC) in federally funded research. I urge the NIH to make the current pause permanent and prohibit all future federal funding for hESC research.

I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.

More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.

No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of *Chevron* deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Fred Eisenmann
[redacted]

38. Sandra Singleton

I am responding: On behalf of myself

Name: Sandra Singleton

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Public Comment on NIH Proposed Changes to Human Embryonic Stem Cell Research

To the National Institutes of Health:

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I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.

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No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of *Chevron* deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research so that these human embryos will have the opportunity to grow into a viable person contributing to society

Sincerely,

Sandra Singleton Full Name]
[redacted]]
Nurse

39. Ruth Furfaro

I am responding: On behalf of myself

Name: Ruth Furfaro

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/17/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

40. Cathryn Villasenor

I am responding: On behalf of myself

Name: Cathryn Villasenor

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/18/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

41. William L

I am responding: On behalf of myself

Name: William L

Name of Organization: N/A

Type of Organization: Other

Type of Organization - Other: N/A

Role: Member of the Public

Date Submitted: 04/19/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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To the National Institutes of Health:

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No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of Chevron deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

[redacted]

[redacted]
(Retired)

42. Richard Tennant

I am responding: On behalf of myself

Name: Richard Tennant

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Other

Role - Other: N/A

Date Submitted: 04/19/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
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I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Richard Tennant

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

43. Luke Harvey

I am responding: On behalf of myself

Name: Luke Harvey

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/19/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
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It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of Chevron deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human

embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Luke Harvey
[redacted]

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Public Comment on NIH Proposed Changes to Human Embryonic Stem Cell Research

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I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Luke Harvey
[redacted]

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
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To the National Institutes of Health:

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I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Luke Harvey
[redacted]

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Public Comment on NIH Proposed Changes to Human Embryonic Stem Cell Research

To the National Institutes of Health:

I respectfully submit this comment in strong support of the NIH's decision to reconsider and restrict the use of human embryonic stem cells (hESC) in federally funded research. I urge the NIH to make the current pause permanent and prohibit all future federal funding for hESC research.

I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.
More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.
No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.
It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of Chevron deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Luke Harvey
[redacted]

44. James L. Sherley

I am responding: On behalf of myself

Name: James L. Sherley

Name of Organization: Science Alliance for Life and Technology

Type of Organization: Professional Organization/Association

Role: Organizational Official

Date Submitted: 04/19/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The professed needs for hESCs for research never ethically justified the methods by which hESCs were and are produced; and it follows that there are no current needs for hESCs in research that ethically justifies their current or future production.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
This is a highly prejudicial, presumptuous prompt. There are no research areas for which "hESCs are the gold standard" given that any current hESC research is unethical. In any case, iPSCs are now established, alternative, ethically-sourced cells with essentially identical properties to hESCs.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Any and all areas of ethical biomedical research can use iPSCs, perinatal tissue stem cell cells, and postnatal tissue stem cells to replace the use of hESCs. Examples include microphysiological systems, organoid cultures, and continued primary human tissue cell culture and animal tissue cell culture.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Human and animal tissue cell biomanufacturing
Methods for accurate, differential tissue stem cell counting
Human and animal tissue cell genetic engineering
Human and animal tissue stem cell genetic engineering

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/hESC-Alternatives-Comment_JS_2026.04.19.docx

Description: Comment: Alternatives to hESC Research

Comment on Alternatives for hESC Research

The controversial era of human embryonic stem cell (hESC) research began with the 1998 scientific report of methods for deriving embryonic stem cells from human embryos conceived by *in vitro* fertilization [**1**]. The morality and ethics of the ensuing research interest was immediately called into question, erupting into public debates on hESC research by 2001. The ethical arguments were clear and the focus of debate, but important scientific arguments were largely ignored [**2**].

Scientists promoting hESC research led with the utilitarian promise that the research would yield medical treatments and cures that otherwise would not be possible to achieve. They ignored the existence of alternative approaches to the same medical goals. In particular, they highlighted biological properties of hESCs that other types of stem cells, which could be ethically obtained with no moral objections, did not have. These were perinatal and postnatal tissue stem cells, referred to at the time as adult stem cells or somatic stem cells.

One commonly recognized important scientific argument against hESC research's promise of unique medical treatments for children and adults was remarkably minimized. HESCs could not be implanted to repair of restore diseased or damaged organs and tissues, – the impression given to the public – because the cells form tumors after implantation. In fact, this property was used to characterize hESCs! Promoting scientists assured the public that this gaping shortcoming could be solved. Opposing scientists warned that this fundamental biological nature of hESCs would never be controlled. Twenty-five years later, it still has not been.

A related, equally important scientific argument, was completely ignored. Unlike tissue stem cells, hESCs cannot maintain their stem cell property while simultaneously continuously replenishing short-lived mature cells, which complete their limited lifetime in tissues and organs, die, and must be replaced. This tissue cell replenishment, or renewal, is the function of tissue stem cells [**2,3**].

Scientists pursuing hESC-based cell therapies have used the cells to produce mature cells for investigations with the goal of developing new organ and tissue cell replacement therapies. Theoretically, if all the source hESCs can be removed from mature, non-multiplying cell preparations, these therapies may avoid the tumor formation risk. But this risk is still quite significant for hESC-derived mature cells that are able to multiply. However, neither type of hESC-derived mature cells can provide the essential function of tissue cell renewal, which is only provided by natural tissue stem cells.

An important alternative to hESC research is induced pluripotent stem cell (iPSC) research. IPSCs offered a morally and ethically acceptable alternative for scientists who wished to pursue research with cells that have the properties of hESCs. No human beings are conceived or injured for the production and study of iPSCs. Many years of research now in countless laboratories have

established the near-identity of hESCs and iPSCs, with many groups having now shifted completely to iPSCs for their research.

Despite the availability of iPSCs, the most important alternative to both hESC and iPSC research for developing more effective cell-based therapies is continued investment in tissue stem cell research. The only approved stem cell therapies use tissue stem cells like blood hematopoietic stem cells. Unlike either hESCs or iPSCs, tissue stem cells inherently possess the essential cell therapy-enabling property of tissue cell renewal.

During many hESC debates, a leading contention was that tissue stem cells could not provide effective cell therapies because they were too difficult to identify and too difficult to produce. Promoting scientists proffered this justification for hESC research even though effective tissue stem cell transplantation therapies had been in routine clinical practice for decades. In the intervening 25 years, whereas hESC research is yet to yield even one promised medical advance, technologies for quantifying [**4**], producing [**5**], and standardizing [**6**] tissue stem cells for improved cell and gene therapies continue to advance.

References

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2. Sherley, J. L. (2008) “The Importance of Valid Disclosures in the Human Embryonic Stem Cell Research Debate,” *Cell Prolif*. 41 (Suppl. 1) 57-64.

3. Sherley, J. L. (2004) "Human Embryonic Stem Cell Research: No Way Around a Scientific Bottleneck," *J. Biomed. Biotech.* 2, 71-72.

4. Dutton, R., Abdi, F., Minnetyan, L. and Sherley, J. L. (2020) “A Computational Technology for Specific Counting of Perinatal and Postnatal Human Tissue Stem Cells for Transplantation Medicine,” *OBM Transplantation* 4(3):24; doi:10.21926/obm.transplant.2003117.

5. Paré, J.-F. and Sherley, J. L. (2006) “Biological Principles for Ex Vivo Adult Stem Cell Expansion,” in *Current Topics in Developmental Biology*, ed. G. Schatten, Elsevier, Inc. (San Diego), Vol. 73, pp. 141-171.

6. WK9536 Working Group (2025) “New Test Method for Differential Quantification of Stem Cells in Samples of Isolated Postnatal Vertebrate Tissue Cells,” https://www.astm.org/membership-participation/technical-committees/workitems/workitem-wk95346.

45. C Pettijohn

I am responding: On behalf of myself

Name: C Pettijohn

Name of Organization: Member of the public

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/19/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Description: Comment from a member of the public

Public Comment on NIH Proposed Changes to Human Embryonic Stem Cell Research

To the National Institutes of Health:

I respectfully submit this comment in strong support of the NIH's decision to reconsider and restrict the use of human embryonic stem cells (hESC) in federally funded research. I urge the NIH to make the current pause permanent and prohibit all future federal funding for hESC research.

I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.

More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.

No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of *Chevron* deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

[Your Full Name]
[Your City, State]
[Optional: Your Occupation or Affiliation]

46. Caroline Hogan

I am responding: On behalf of myself

Name: Caroline Hogan

Name of Organization: N/A

Type of Organization: Other

Type of Organization - Other: N/A

Role: Member of the Public

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
To the National Institutes of Health:
I respectfully submit this comment in strong support of the NIH's decision to reconsider and restrict the use of human embryonic stem cells (hESC) in federally funded research. I urge the NIH to make the current pause permanent and prohibit all future federal funding for hESC research.
I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.
More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.
No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.
It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.
Finally, with the recent overturning of Chevron deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.
I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.
Sincerely,

Caroline Hogan
[redacted]

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

47. Xinyu Zhao

I am responding: On behalf of myself

Name: Xinyu Zhao

Name of Organization: University of Wisconsin-Madison

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
My research focuses on understanding genetic mechanisms regulating neuronal development and their implications in human intellectual disabilities, including autism spectrum disorders (ASD) and Fragile X syndrome (FXS) for over 30 years. My research uses human pluripotent stem cells (hPSCs) including both human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) and has discovered novel mechanisms and therapeutic targets for FXS and ASD. These results have been published in over 100 peer reviewed publications and two patents. I have been continuously funded by multiple NIH since 2007. In addition, I serve as Co-Director of IDD Models Core of the Waisman Center IDDRC and the Director for Rodent Behavioral sub Core. I am currently a scientific review board member for IRSF and is a member of the NFXF Fragile X Clinical Trial Committee. Since 2019, I have been the leader/organizer of Human 3D Organoid Task Group of the Cross-IDDRC Stem Cell Consortium, with goal to establish consistent protocols and analytic methods for using Human 3D Organoids in studying IDD conditions, yielding several collaborative publications (Sandoval et al Stem Cell Reports 2024; PMID: 38759644). We have also been developing methods for assessing organoids as models for human brain development (He et al, Cell Report Methods 2023, PMID 36936070; STAR Protocol 2024, PMID: 39392746). Therefore I have extensive experience in working with both hESCs and hiPSCs and I am committed to using hPSCs to investigate human neurodevelopmental disorders.

The original five hESC lines created in 1998 (WA01, WA07, WA09, WA13, and WA14, AKA H1, H7, H9, H13, and H14) are the most widely used hESC lines used by researchers worldwide. Many researchers in both industry and academia, including basic scientists like me, have created gene deletion or insertions in these lines to study disease mechanisms. If we are not allowed to use these lines and their derived sub-lines, it will be a costly and significant loss for both research and drug development.

There are human brain disorders that require hESCs as models. For example, the hESC lines derived from FXS embryos do not have gene methylation but the gene is methylated during development. A major therapeutic effort is to prevent gene methylation to restore gene expression. However, hiPSC lines derived from patients' blood or skin cells already have gene methylation therefore they cannot be used for this research.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
The hiPSCs have residual epigenetic memory from the skin or blood cells they are derived from;

therefore they are not fully pluripotent. It is critical to use hESCs as guide for hiPSC quality assessment and differentiation optimization. Without hESCs, we will go blind in using hiPSCs for research and therapeutic development.

For example, the hESC lines derived from FXS embryos do not have gene methylation but the gene is methylated during development. A major therapeutic effort is to prevent gene methylation to restore gene expression. However, hiPSC lines derived from patients' blood or skin cells already have gene methylation therefore they cannot be used for this research.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
The use of hiPSCs have already become mainstream. However, as mentioned above, these cells must be compared to hESCs regularly to ensure they are pluripotent. Adult stem cells, particularly those from solid tissue such as brains, have limited capacity to be cultured in vitro which make them unsuitable for drug development.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Cross institutional collaborations such as what we have published "Rigor and reproducibility in human brain organoid research: Where we are and where we need to go" (Sandoval et al Stem Cell Reports 2024; PMID: 38759644) and computational methods for assessing organoids as models for human brain development (He et al, Cell Report Methods 2023, PMID 36936070; STAR Protocol 2024, PMID: 39392746) are good start. However, NIH funding are needed to expand these efforts to increase the impact.

48. Kristen Kroll

I am responding: On behalf of myself

Name: Kristen Kroll

Name of Organization: Washington University School of Medicine

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
[please see attached]

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
[please see attached]

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
[please see attached]

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
[please see attached]

49. Jon Odorico

I am responding: On behalf of myself

Name: Jon Odorico

Name of Organization: University of Wisconsin

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.

- hESC lines have been pivotal in a broad array of basic biological research studies including the use of genetically engineered lines, e.g. reporter lines, and expanding the genetic diversity as well as disease relevance with new hESC lines will provide for future advances.
- hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes, and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.
- New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

- hESC lines provide the "ground truth" of the earliest steps in human development because they are derived directly from the pre-implantation human embryo
- hESCs provide the only natural benchmark for defining human stem cells.
- hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
- Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
- The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
- Fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

- hESCs cannot be replaced by current alternative technologies and are needed as a reference

standard and a benchmark for future work and the development of these alternatives. Lack of this benchmark may slow technological advancement or create insufficient technologies.

- hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
- hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.
- Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.
- An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

- Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies
- Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.
- Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.
- Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

50. Michael W. Schoenwald

I am responding: On behalf of myself

Name: Michael W. Schoenwald

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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I request that the NIH clarify its guidelines and prevent future federal funds from being used for human embryonic stem cell research (hESC). Despite the early enthusiasm and lofty promises, science has shown that hESC research has failed to deliver the anticipated breakthroughs. After more than 25 years, there has been no serious progress in using hESCs to develop cures for spinal cord injuries, Parkinson's, Alzheimer's, or cancer. In fact, research has shown that hESCs can lead to tumor formation, including cancer.

More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.

No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of *Chevron* deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Michael W. Schoenwald
[redacted]

51. Marybeth Schoenwald

I am responding: On behalf of myself

Name: Marybeth Schoenwald

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/20/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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More importantly, every hESC research project results in the deliberate destruction of a living human embryo. At the moment of conception, these embryos possess the complete genetic information needed to become fully formed human beings. Given time and the proper environment, they would grow, laugh, love, form relationships, and experience the full beauty of human life. To deliberately end that life and potential at any stage — even a few days after conception — is morally reprehensible.

No federal funding should support such programs, especially not taxpayer dollars taken from millions of Americans who strongly oppose the destruction of these innocent human lives.

It would be far more ethical and scientifically effective for the NIH to direct funding toward alternative stem cell sources — such as adult stem cells and induced pluripotent stem cells (iPSCs) — which have already proven safe and successful in treating patients, without destroying human life.

Finally, with the recent overturning of *Chevron* deference, the legal foundation supporting the current NIH guidelines on hESC funding is now uncertain. This creates a perfect opportunity for the NIH to clarify its standards, prohibit federal funding for practices that destroy human embryos, and uphold the dignity and value of human life at every stage of development.

I sincerely urge the NIH to take this important step and end all taxpayer funding for human embryonic stem cell research.

Sincerely,

Marybeth Schoenwald
[redacted]

52. RAVIE DAVIS

I am responding: On behalf of myself

Name: RAVIE DAVIS

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
When it harms another, don't expect to succeed in going forward. A moral choice is not only not harmful to another, it is a key to success.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Please on every level make the right choice to not harm but also to help do right.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Go forward by making the right choice.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Research has already been done, so this should be a no-brainer.

53. California Institute for Regenerttive Medicine

I am responding: On behalf of an organization

Name: Geoffrey Lomax

Name of Organization: California Institute for Regenerttive Medicine

Type of Organization: Other

Type of Organization - Other: Medical Research Granting Agency

Role: Organizational Official

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The decline in requests to add new hESC lines to the registry may well be an indicator of the research community's adherence to high medical and ethical standards. While no new lines have been added to the registry since 2023, maintaining this appropriate pathway to expand the registry in the future is critical as future, unanticipated research needs evolve. Recognizing the value of hESCs in therapeutic development as well as research ethics, the existing guidelines (NIH and National Academies) strike the right balance in fostering innovation without compromising values and thus, should be maintained.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs have been used to create engineered lines designed to provide real-time monitoring of cell behavior. Known as "reporter lines", these tools have been developed at considerable expense. To highlight one use of these lines, they enable high-throughput screening of thousands of drug candidates simultaneously, allowing researchers to quickly identify which compounds promote or inhibit specific biological processes. This dramatically accelerates the drug discovery pipeline, particularly for rare diseases where time and resources are limited.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
While human induced pluripotent stem cells (hiPSC) represent a powerful complementary approach to hESC, they do not replace hESC. hESCs remain the gold standard for human pluripotent stem cell characteristics, and future basic and clinical research with hiPSC depends on benchmarking against hESC. For example, hiPSCs are generated through a reprogramming process that frequently introduces genetic mutations . Additionally, hiPSCs retain an epigenetic "memory" of the adult cell from which they were derived, which can influence their differentiation potential . It remains unknown whether hiPSC will be the optimal choice for all future applications of human pluripotent stem cells, and currently unforeseen new technologies may enable derivation of hESC lines with superior characteristics for certain applications, including clinical products.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
CIRM submits that the policy framework finalized in 2009, the NIH Guidelines for Human Stem Cell

Research (NIH Guidelines), strike an important balance that enables the American research community to remain competitive and responsive to the needs of the field while demonstrating adherence to stringent ethical standards. The NIH Guidelines ensure that hESC lines are created with voluntary, informed consent without coercion. This enables hESC research that advances our understanding of human disease and leads to desperately needed prevention and treatment strategies for patients. The NIH Guidelines complement the National Academies' Guidelines , which together represent a comprehensive and responsible approach for current and future research. As discussed below, in order to maintain the country's current position as a leader in the field and to ensure research is meeting high ethical standards, we encourage the NIH to resume accepting new submissions to the stem cell line registry as soon as possible and maintain the 2009 NIH Guidelines governing its requirements.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/hESC-RFI-4.21.26-Final.pdf

Description: Summary of comments attached

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

April 15, 2026

Public Comment: NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (Notice Number: NOT-OD-26-031)

Comments submitted electronically at https://osp.od.nih.gov/comment-form-reducing-reliance-on-human-embryonic-stem-cells-in-nih-supported-research/

To Whom It May Concern:

On behalf of the California Institute of Regenerative Medicine (CIRM), thank you for the opportunity to submit these comments in response to the Request for Information (RFI) on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research. This RFI accompanies an announcement from the National Institutes of Health (NIH) on its pause on new submissions to the NIH Human Embryonic Stem Cell (hESC) Registry. CIRM is a state agency created by the people of California to advance scientific research with the goal of generating stem cell and gene therapies.

CIRM submits that the policy framework finalized in 2009, the NIH Guidelines for Human Stem Cell Research (NIH Guidelines),[1] strike an important balance that enables the American research community to remain competitive and responsive to the needs of the field while demonstrating adherence to stringent ethical standards. The NIH Guidelines ensure that hESC lines are created with voluntary, informed consent without coercion. This enables hESC research that advances our understanding of human disease and leads to desperately needed prevention and treatment strategies for patients. The NIH Guidelines complement the National Academies' Guidelines[2], which together represent a comprehensive and responsible approach for current and future research. As discussed below, in order to maintain the country's current position as a leader in the field and to ensure research is meeting high ethical standards, **we encourage the NIH to resume accepting new submissions to the stem cell line registry as soon as possible and maintain the 2009 NIH Guidelines governing its requirements.**

Current NIH Guidelines Align with Administration Priorities

hESCs are a foundational pillar supporting the development of stem cell therapies for intractable disease. The focal point of stem cell research has been conditions that are difficult or impossible to relieve, manage, or cure with standard treatments, medications, or therapies, necessitating more novel approaches. Many of these conditions meet rare or ultra rare disease designations, with some affecting fewer than 1 in 50,000 individuals or less than 7000 people in the United States.[3] The Administration has taken significant steps forward to support innovative biomedical research in rare disease such as expanding Right to Try authorities, funding the work of the Food and Drug Administration's (FDA) Rare Disease Innovation Hub,

[1] https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research

[2] https://pubmed.ncbi.nlm.nih.gov/24983031/

[3] https://udnf.org/what-are-ultra-rare-diseases/

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requesting the permanent reauthorization of the FDA's pediatric priority review voucher, releasing guidance on a plausible mechanism pathway for regulatory review, launching the Center for Medicare and Medicaid Innovation's Cell and Gene Therapy Model, and more. Fostering continued adherence to the thoughtfully implemented NIH Guidelines will further enable this groundbreaking and promising research in the US and give hope to patients and their families living with rare and ultra rare diseases.

The NIH Guidelines also align with the Administration's broader efforts to reduce reliance on animal models in biomedical research. hESCs have been instrumental in illuminating our understanding of the disease process, identifying therapeutic approaches in human systems, and serving as treatments. Unlike animal models, hESCs more accurately reflect human physiology, making them a powerful tool for translational research. In March, the NIH announced a $150 million investment in human-based research to reduce the use of animal models[4] and the FDA issued draft guidance on the use of new approach methodologies in drug development as a way to improve human relevance while reducing the use of animal models.[5] Together, these initiatives reflect the position that human-based research tools, which should include hESCs, are more predictive of clinical outcomes than traditional animal studies. Continued investment in and support of hESC research is therefore consistent with, and critical to, achieving the Administration's vision for a more modern and effective biomedical research enterprise.

hESCs Have Enabled New Treatments

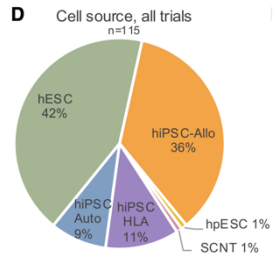
Innovation in rare disease therapies relies on research using hESCs. **Approximately, 42% of all new human stem cell therapies derived from pluripotent sources are enabled by hESC**.[6] For the millions of Americans living with rare diseases, many of whom are children, hESC research represents one of the most promising frontiers in modern medicine. The unique properties of hESCs, including their ability to differentiate into virtually any cell type in the human body, make them particularly valuable for modeling rare diseases that are difficult or impossible to replicate in animal systems. This capability allows researchers to study disease mechanisms at the cellular level, screen potential drug candidates, and develop cell-based therapies tailored to the underlying biology of rare conditions. In many cases, hESC-derived models have provided the first meaningful insight into diseases that affect only a small number of patients, where traditional research approaches are limited by the scarcity of available biological samples and the impracticality of large clinical trials. Furthermore, hESC research serves as a critical foundation for emerging therapeutic strategies such as gene editing and regenerative medicine, both of which hold particular promise for rare genetic disorders. Restricting access to hESC research would not only stifle scientific innovation but could delay or altogether eliminate potential cures for diseases that currently have no approved treatments.

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[4] https://www.nih.gov/news-events/news-releases/nih-invests-150-million-human-based-research-reduce-use-animal-models

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-use-new-approach-methodologies-drug-development

[6] https://www.cell.com/action/showPdf?pii=S1934-5909%2824%2900445-4



Source: Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update

In the context of the broader biomedical innovation landscape, hESC lines have contributed in the following ways:

- **The Foundation for Advanced Therapies**: In 2025, hESCs were the starting point for approximately 42% of clinical trials involving pluripotent stem cell-derived treatments. These clinical trials are treating a variety of conditions including:
    - Spinal cord injury
    - Macular degenerations / blindness
    - Heart failure and cardiac impairment
    - Diabetes
    - Liver disease
    - Cartilage injury
    - Epilepsy seizures
    - Cancers - multiple sites

These trials utilize unique stem cell lines considered optimal for the specific therapeutic product. Given the inherent variability of biological systems, including cell lines, it is likely that opportunities for optimization will continue to emerge over time. It may become apparent that creating a stem cell line utilizing specific methodologies (e.g. laboratory procedures) or from a donor with specific characteristics (e.g. genetic markers) is an essential prerequisite to advancing medical innovation.

- **Understanding the Genetic and Cellular Drivers of Disease**: One area where hESCs are the gold standard for research is the study of inborn disease. The value of these lines is reflected in the fact that a proportion of NIH registered lines are “disease-specific” hESCs.

- **Established Research Tools:** hESCs have been used to create engineered lines designed to provide real-time monitoring of cell behavior. Known as “reporter lines”, these tools have been developed at considerable expense. To highlight one use of these lines, they enable high-throughput screening of thousands of drug candidates simultaneously, allowing researchers to quickly identify which compounds promote or inhibit specific biological processes. This dramatically accelerates the drug discovery pipeline, particularly for rare diseases where time and resources are limited.

- **Creating Model or "Replica" Organs:** hESCs are used to create tissue cultures that replicate the structure and function of human organs, such as the brain, liver, and lung. These model organ systems can then be used to study disease and test the effect of potential treatments. Because these systems are developed with human cells, they may be more predictive than animal models.

- **Understand Human Development**: Studies using hESCs have been used to understand human development and the origins of birth defects. These studies can be conducted in "petri-dishes" and further serve to reduce reliance on animal studies.

- **Unique resource:** While human induced pluripotent stem cells (hiPSC) represent a powerful complementary approach to hESC, they do not replace hESC. hESCs remain the gold standard for human pluripotent stem cell characteristics, and future basic and clinical research with hiPSC depends on benchmarking against hESC. For example, hiPSCs are generated through a reprogramming process that frequently introduces genetic mutations[7]. Additionally, hiPSCs retain an epigenetic "memory" of the adult cell from which they were derived, which can influence their differentiation potential[8]. It remains unknown whether hiPSC will be the optimal choice for all future applications of human pluripotent stem cells, and currently unforeseen new technologies may enable derivation of hESC lines with superior characteristics for certain applications, including clinical products.

Existing Policy has Spurred Medical Innovation and Competitiveness

hESC research is integral to the broader, $11.5 billion in 2025, cell and gene therapy innovation sector and thus, the United States' bioeconomy.[9] Biomedical innovation is among the most dynamic and synergistic sectors of research and development. This dynamism and synergy are evidenced by the fact the sector has been among the earliest adopters of advanced genetic technologies, machine learning and artificial intelligence, and personalized / human-centered health innovation. Further, this innovation is occurring in a global environment with many nations seeking to support commercial success.[10] One study found that there is a strong economic justification for stimulating hESC research and therapeutic development given that it leads to increased economic output, employment, and tax revenues.[11]

Prohibiting new submissions to the NIH Human Embryonic Stem Cell Registry would reestablish restrictions for the creation of new stem cell lines, which have the potential to limit domestic innovation and drive investment outside the United States. This concern is grounded

[7] https://www.nature.com/articles/nature09805

[8] https://www.nature.com/articles/nbt.2052

[9] https://alliancerm.org/wp-content/uploads/2026/01/ARM-SOTI-2026_Presentation.pdf

[10] https://www.mordorintelligence.com/industry-reports/stem-cell-research-market

[11] https://www.cirm.ca.gov/wp-content/uploads/archive/files/about_cirm/CIRM_Economic Impact Report_10_3_19 v.2.pdf

in the observation that in the context of biomedical research, highly specialized needs emerge and adaptive tools and resources are needed. Policy changes that disrupt hESCs research will only make it more difficult for the United States to compete and maintain its position as a leader in biotechnology. This is especially concerning given China's aggressive investment in R&D, which now surpasses the United States in total R&D expenditures.[12] Additionally, **in 2025 the Asia-Pacific region, led by China, surpassed North America in the number of clinical trials conducted**.[13] Further, China is investing heavily in the supporting technologies that enable studying human development and the disease process and tools and technologies. A shift in hESC policy might mean that the United States loses out on making the next great discovery.

Existing Guidelines are Ethically Sound

The current NIH Guidelines provide the certainty necessary to unleash the full force of the United States' research infrastructure and innovations sectors by removing prior restrictions and enabling ethically based and thoughtful approaches to the use of hESC lines. As the NIH Guidelines state, "Although hESCs are derived from embryos, such stem cells are not themselves human embryos."[14] Rather, hESCs are derived from the inner cell mass of blastocysts, an early stage in cell development, using tissue that is not intended for uterine transfer or implantation. Of great importance, the NIH Guidelines include restrictions on federal funding on stem cells not compliant with the policy and outline in detail the requirements for the consent process to ensure sufficient comprehension of the potential use, applications, medical benefit, etc. prior to any donation being made.

In fact, the limited decline in requests to add new hESC lines to the registry may well be an indicator of the research community's adherence to high medical and ethical standards. While no new lines have been added to the registry since 2023,[15] maintaining this appropriate pathway to expand the registry is critical as future, unanticipated research needs evolve.

One of the guiding principles of the National Academies' Guidelines is that there is a compelling scientific rationale for new cell line derivation.

> *4.2 The scientific rationale for the need to generate new hES cell lines, by whatever means, must be clearly presented, and the basis for the numbers of embryos, morulae, and blastocysts needed should be justified.* *https://www.nationalacademies.org/projects/DELS-BLS-19-P-153/publication/12923*

The rationale must be determined to be compelling by an independent oversight committee. Recognizing the value of hESCs in therapeutic development as well as research ethics, the

[12] https://www.oecd.org/en/data/insights/statistical-releases/2026/03/oecd-overall-rd-growth-stable-government-rd-budgets-decline-and-reorient-towards-defence.html

[13] https://www.clinicaltrialsarena.com/news/china-surpasses-us-for-annual-trials/?cf-view

[14] https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research

[15] https://stemcells.nih.gov/registry/eligible-to-use-lines

existing guidelines (NIH and National Academies) strike the right balance in fostering innovation without compromising values and thus, should be maintained.

Recommendation

Established guidelines have contributed to the appropriate use of hESC lines and support the ethical use of cell lines as well as play a foundational role in innovation in cell and gene therapies, particularly for rare and ultra rare diseases. This positions the United States not only in the role of responsible leader of this critical area of medical research, but as a strong competitor globally in the expanding field of cell and gene therapy. Existing guidelines further align with the Administration's priorities in advancing therapies for rare diseases and transitioning away from the use of animal models in research and drug development. For these reasons, we strongly recommend that the NIH maintain the current NIH Guidelines and resume accepting submissions to the registry.

Thank you for your consideration of these comments and if we may be of further assistance, please contact Uta Grieshammer, ugrieshammer@cirm.ca.gov, (510) 944-4017.

Sincerely,

Dr. Jonathan Thomas JD
President and CEO

54. Edward Randle

I am responding: On behalf of myself

Name: Edward Randle

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

55. University of Wisconsin- Madison

I am responding: On behalf of an organization

Name: Dorota A. Grejner-Brzezinska

Name of Organization: University of Wisconsin - Madison

Type of Organization: Academic Institution

Role: Organizational Official

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.

As research tools, hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models. They provide the raw material for cell replacement therapies in many organ systems.

The original five hESC lines derived by researchers at Wisconsin in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (Ludwig et al., PMID: 30388422). Distribution increased with the Bush administration's approval of US federal funding for hESC research in August 2001. In 2005, US government support of stem cell research resulted in the funding of a US National Stem Cell Bank that significantly increased access to high-quality hESC lines and, combined with the European Union (EU) approval of European Commission (EC) funding for hESC research in 2006, resulted in a dramatic increase in hESC distributions. These Wisconsin lines continue to be the most accepted and best characterized hESCs for research.

The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. In addition to the utility of the native Wisconsin lines, hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.

The Wisconsin lines and other hESCs are the foundation of the translational pipeline to generate cell therapies. They are used to generate specialized cells to replace damaged, diseased, or dying tissue in patients, including applications in neurology, cardiology and diabetes. In fact, promising new cell therapies derived from hES cells are currently being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005).

While there has been a decline in the number of cell lines submitted for review to be added to the NIH hESC Registry and NIH support for hESC research has stabilized, these data should not be interpreted as a decline in the need and utility of hESCs in research. As with any new technology, there is often a surge of demand for the novel technology, followed by a plateau or steady-state of demand. The federal NIH registry is less than two decades old, a short timeframe for widespread adoption of a new technology. By studying the examples, of AI, 3D printing and tissue engineering, some argue that 30 to 50 years is the realistic time between novel concept and widespread adoption (https://doi.org/10.1016/j.matt.2019.10.011 and https://www.entrepreneur.com/leadership/the-pace-of-technological-change-is-faster-than-ever/386410).
New hES cell lines are needed to expand and broaden the genetic backgrounds of the current hESC lines. New hES cell lines are needed to study disease where there are no other human models. New hES cell lines are of particular value for fertility research because the beginning of human development is inaccessible. Stem cell research has resulted in important new breakthroughs in the treatment of infertility. hESC technology has led, and will continue to contribute to, a better understanding of human development, and perhaps even new ways to treat infertility and prevent miscarriages. For families who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, hESC-based approaches are promising.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
The large number of genetically engineered hESC tools that are used in research would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
hESCs provide the only reference for the development of alternatives. They provide a unique benchmark for future work and the development of alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable

reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies. The advent and use of induced pluripotent stem cells (iPSCs) does not and should not preclude the need and use of hESCs. hESCs cannot be separated from or replaced by iPSCs in the stem cell research enterprise.

While iPSCs have substantially expanded the field, they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs. iPSCs are more prone to harbor deleterious mutations, introduced either in the reprogramming process or through stress of prolonged passaging, than hESCs. The effects of these mutations in research and more importantly, on future cell therapies, are currently unknown. The replacement of hESCs with iPSCs is premature.

Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development. A responsible strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Comprehensive epigenomics, multiomics, metabolic, and functional comparisons are necessary to fully define the differences between hESCs and iPSCs or other potential alternative technologies. Secondly, methods to engineer iPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research. The feasibility and timeline to meet all these requirements is completely unknown and would require substantial investment of funding.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/2026-04-21-NIH-hESC-RFI.pdf

Description: Response from the University of Wisconsin-Madison

Office of the
Vice Chancellor for Research
UNIVERSITY OF WISCONSIN–MADISON

April 21, 2026

To: National Institutes of Health Office of Science Policy

Re: NOT-OD-26-031, NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

To whom it may concern:

Thank you for the opportunity to provide input on reducing reliance on human embryonic stem cells in NIH-supported research. The University of Wisconsin-Madison, established in 1848, is one of the nation's leading and largest research institutions, well known for its development of human stem cell research. The university's distinction in stem cell research started in 1995 with the first successful culturing of embryonic stem cells from non-human primates. In 1998, developmental biologist James Thomson isolated the first laboratory-derived human embryonic stem cells (hESCs). His lab's accomplishment underpins the new field of regenerative medicine, and the all-purpose cells are used worldwide to test drugs, develop treatments for diseases and further our understanding of basic human biology. Because of this early discovery and the collaborative environment at Wisconsin, many researchers on campus continue to engage in pioneering hESC research advancing tissue specific and disease-specific applications. The research we undertake is making great strides in biomedical science and our ability to treat debilitating diseases, discover new medicines and uncover the fundamental processes that lead to disease. We are committed to ensuring that stem cell research and clinical translation continue in a responsible, merit-based, and ethical manner.

1. **Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed;**

hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.

As research tools, hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models. They provide the raw material for cell replacement therapies in many organ systems.

The original five hESC lines derived by researchers at Wisconsin in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (Ludwig et al., PMID:

30388422). Distribution increased with the Bush administration's approval of US federal funding for hESC research in August 2001. In 2005, US government support of stem cell research resulted in the funding of a US National Stem Cell Bank that significantly increased access to high-quality hESC lines and, combined with the European Union (EU) approval of European Commission (EC) funding for hESC research in 2006, resulted in a dramatic increase in hESC distributions. These Wisconsin lines continue to be the most accepted and best characterized hESCs for research.

The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. In addition to the utility of the native Wisconsin lines, hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.

The Wisconsin lines and other hESCs are the foundation of the translational pipeline to generate cell therapies. They are used to generate specialized cells to replace damaged, diseased, or dying tissue in patients, including applications in neurology, cardiology and diabetes. In fact, promising new cell therapies derived from hES cells are currently being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005).

While there has been a decline in the number of cell lines submitted for review to be added to the NIH hESC Registry and NIH support for hESC research has stabilized, these data should not be interpreted as a decline in the need and utility of hESCs in research. As with any new technology, there is often a surge of demand for the novel technology, followed by a plateau or steady-state of demand. The federal NIH registry is less than two decades old, a short timeframe for widespread adoption of a new technology. By studying the examples, of AI, 3D printing and tissue engineering, some argue that 30 to 50 years is the realistic time between novel concept and widespread adoption (https://doi.org/10.1016/j.matt.2019.10.011 and https://www.entrepreneur.com/leadership/the-pace-of-technological-change-is-faster-than-ever/386410).

New hES cell lines are needed to expand and broaden the genetic backgrounds of the current hESC lines. New hES cell lines are needed to study disease where there are no other human models. New hES cell lines are of particular value for fertility research because the beginning of human development is inaccessible. Stem cell research has resulted in important new breakthroughs in the treatment of infertility. hESC technology has led, and will continue to contribute to, a better understanding of human development, and perhaps even new ways to treat infertility and prevent miscarriages. For families who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, hESC-based approaches are promising.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives.

Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable;

Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.

The large number of genetically engineered hESC tools that are used in research would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.

hESCs provide the only reference for the development of alternatives. They provide a unique benchmark for future work and the development of alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

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hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies. The advent and use of induced pluripotent stem cells (iPSCs) does not and should not preclude the need and use of hESCs. hESCs cannot be separated from or replaced by iPSCs in the stem cell research enterprise.

While iPSCs have substantially expanded the field, they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs. iPSCs are more prone to harbor deleterious mutations, introduced either in the reprogramming process or through stress of prolonged passaging, than hESCs. The effects of these mutations in research and more importantly, on future cell therapies, are currently unknown. The replacement of hESCs with iPSCs is premature.

Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.

A responsible strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Comprehensive epigenomics, multiomics, metabolic, and functional comparisons are necessary to fully define the differences between hESCs and iPSCs or other potential alternative technologies. Secondly, methods to engineer iPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research. The feasibility and timeline to meet all these requirements is completely unknown and would require substantial investment of funding.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

Thank you for your consideration.

Sincerely,

[redacted]

Dorota A. Grejner-Brzezinska, Ph.D.
Vice Chancellor for Research

[redacted]

Anita Bhattacharyya, Ph.D.
Associate Professor, Cell and Regenerative Biology
Chair, UW–Madison's Stem Cell Research Oversight Committee

56. UCLA Broad Stem Cell Research Center

I am responding: On behalf of an organization

Name: Maria Dominguez

Name of Organization: UCLA Broad Stem Cell Research Center

Type of Organization: Academic Institution

Role: Other

Role - Other: BSCRC Director of Operations, Compliance and Regulatory Affairs

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Currently approved hESC lines continue to meet many core needs of the research community due to their extensive characterization, widespread adoption, and foundational role in both basic and translational science. These lines have also enabled the development of promising cell-based therapies, several of which are now being evaluated in clinical trials for conditions including Parkinson's disease, age-related macular degeneration, epilepsy, and type 1 diabetes. However, important gaps remain, particularly in genetic diversity, disease modeling, and reproductive biology, that necessitate the derivation of new hESC lines. While existing lines provide a critical and stable reference standard, expanding the available repertoire is essential to fully capture human variation and enable progress in areas that cannot be addressed with current resources alone.

Areas where currently approved hESC lines are sufficient:

Benchmark for human development, pluripotency and alternative technologies.
• Provide the "ground truth" for early human development and stem cell identity
• Essential reference standard for validating induced pluripotent stem cells (iPSCs) and emerging stem cell models

Widely validated models and established research tools
• Established lines (e.g., H1, H7, H9, H13, H14) are extensively characterized and globally used
• Extensive library of engineered reporter and functional lines enables precise and efficient research

Foundation for translational research infrastructure and cell therapy development
• Long-standing datasets, protocols, and community standards built on existing lines
• Serve as the foundation for generating therapeutic cell types across multiple organ systems
• Already used in clinical trials (e.g., Parkinson's disease, epilepsy, macular degeneration, diabetes)

Areas where new hESC lines are needed:

Genetic variation and disease-specific modeling needs
• Current lines do not capture the full spectrum of human genetic variation
• Needed for studying diseases lacking adequate human models

Fertility and early developmental research
• Critical for studying inaccessible stages of human development and infertility
Improved biological fidelity
• New lines can address limitations in existing lines (e.g., instability, restricted phenotypes)

Advancing translational applications and future technology development
• Support development of more broadly applicable and personalized cell therapies
• Necessary to ensure accurate benchmarking and continued innovation in stem cell-based systems

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs continue to play a foundational role in biomedical research because they provide the most reliable and well-characterized model of human pluripotency and early development. While alternative systems such as induced pluripotent stem cells (iPSCs) have expanded research capabilities, they still depend on hESCs as a reference standard due to variability introduced by reprogramming and differentiation. In addition, decades of public investment have produced extensive tools, engineered lines, and clinical-grade resources based on hESCs, many of which are already being used in translational and clinical applications. As a result, there remain several key research areas where hESCs are indispensable and where progress would be significantly limited or not feasible in their absence. hESCs are not replaceable by iPSCs; instead, they are necessary to interpret, validate, and advance all stem cell-based research and therapies.

Gold standard for pluripotency and development
• hESCs remain the gold standard for defining authentic human pluripotency and early developmental potential
• Essential reference for benchmarking iPSCs, differentiation protocols, and stem cell-based models
• Without hESCs, it is difficult to confirm whether alternative systems accurately reflect true human biology
• iPSCs require comparison to hESCs due to variability in reprogramming and differentiation fidelity

Early human development research
• Indispensable for studying peri-implantation development, lineage specification, and epigenetic resetting
• Critical for building accurate single-cell and multi-omic reference atlases of human development

Clinical and translation importance
• Many hESC lines are FDA-validated, GMP-derived, and already in clinical pipelines
• Ongoing trials (e.g., Bayer Phase 3 exPDite-2 for Parkinson's disease, Neurona NRTX-1001 for epilepsy,

Astellas ASP7317 for Age-related Macular Degeneration) rely on FDA-approved hESC lines, making them essential for advancing therapies
• Restricting hESC use would significantly hinder the development of cell-based therapies

Established tools and engineered lines
• Extensive infrastructure (reporter lines, engineered models) built on hESCs
• These resources are costly, validated, and irreplaceable for ongoing research

Unique advantages in immunotherapy research
• hESCs lack MHC I expression, making them an ideal tool to study immunotherapy
• This property enables platforms like Human Organoid Tumor Transplantation (iHOTT)
• hESCs are critical for cancer therapy screening, without allogenic responses

Genome engineering and functional studies
• Preferred for CRISPR editing due to stability, reproducibility, and extensive datasets
• Important for studying host–pathogen interactions and gene function

Disease modeling requiring developmental accuracy
• Particularly important for modeling early developmental phenotypes and generating isogenic controls
• Provide more consistent baseline than iPSCs

Translational safety and regulatory standards
• hESCs are important for translational applications requiring highly consistent, well-characterized starting material
• Widely used as standardized starting material in safety testing and regulatory frameworks that rely on hESC-derived datasets

Specialized model systems
• Differences observed between hESC- and iPSC-derived cells (e.g., blood-brain barrier models) highlight unique, not fully understood properties
• Due to the robust number of datasets and tools available for hESC lines, hESCs remain necessary to resolve these biological differences

Need for improved and diverse reference hESC lines
• Existing hESC lines lack sufficient genetic diversity to represent human variation and have limitations (e.g., current hESC lines have limitations in modeling X chromosome inactivation and female-specific regulatory mechanisms)
• Derivation of new hESC lines that preserve X chromosome inactivation is essential to establish biologically accurate reference models
• New hESC lines are required to study early human development, human variation, ancestry-specific effects, rare variants, gene regulation, and gene–environment interactions, and to support accurate disease modeling and proper validation of iPSC-based systems
• Generating new hESC lines is not an alternative to iPSCs, but a prerequisite for their accurate interpretation

Limitations of alternative models (iPSCs)
• iPSCs are generated through reprogramming, which introduces variability across labs
• iPSCs may differ in differentiation potential and developmental fidelity
• Observed phenotypes in iPSCs can be confounded by genetic background differences

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
hESCs cannot be replaced by current alternative technologies. Emerging biotechnologies, such as iPSCs and adult stem cells, have significantly expanded research capabilities, particularly for patient-specific disease modeling personalized medicine and drug screening, and tissue-specific studies. These systems also support organoid and in vitro tissue models. However, these systems do not fully replicate the developmental, epigenetic, and functional properties of hESCs. As a result, while they serve as important complementary tools, they cannot fully substitute for hESCs, which remain essential as the benchmark for validating and advancing these approaches. hESCs continue to represent the gold standard for studies of pluripotency and early human development. Eliminating their use would undermine the ability to rigorously validate alternative technologies and could slow both scientific discovery and clinical translation. A complementary strategy is therefore critical, one that advances iPSC and related systems while maintaining access to hESCs to ensure accuracy, reliability, and continued innovation in the field.

Key limitations preventing full replacement of hESCs:

Lack of true developmental equivalence (iPSCs)
• Do not fully recapitulate early embryonic or epigenetic states

Genomic and epigenetic instability (iPSCs)
• Higher risk of mutations from reprogramming and long-term culture

Restricted differentiation potential (adult stem cells)
• Not pluripotent; limited to tissue of origin

Limited self-renewal capacity (adult stem cells)
• Cannot be maintained indefinitely; require continual sourcing

Inability to model earliest human development
• Alternative systems do not capture pre-implantation or early lineage specification stages

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
To reduce reliance on hESCs, substantial additional investment is needed to develop and validate alternative models that can reliably replicate their biological properties. This includes advancing our understanding of the molecular and functional differences between hESCs and current alternatives, improving the fidelity of reprogrammed systems, and rebuilding the extensive infrastructure and toolsets that currently exist for hESCs. However, the feasibility, cost, and timeline of achieving fully equivalent replacement models remain uncertain, and such efforts would require long-term, large-scale investment.

A balanced approach is needed: invest in alternatives while maintaining access to hESCs to ensure continued scientific and translational progress.

Priority areas for additional investment:

Comprehensive comparative analysis and improvement of alternative cell fidelity
• Epigenomic, multi-omic, metabolic, and functional comparisons between hESCs and alternatives (e.g., iPSCs)
• Development of methods to reprogram or engineer iPSCs into a more hESC-like state

Understanding developmental equivalence
• Deeper mechanistic insight into early human development to guide model improvement

Tool development, genomic stability, and quality control
• Enhanced monitoring and standards to ensure safety and reproducibility of alternative systems
• Recreate and expand gene-edited lines, reporter systems, and validated reagents currently available for hESCs

Standardization and scalability of research resources and protocols
• Establish high-quality, accessible repositories of alternative stem cell lines
• Develop standardized methods for differentiation and experimental use

Challenges and considerations:

Significant cost and long timelines
• Rebuilding equivalent infrastructure and knowledge base would require major funding and sustained effort

Uncertain feasibility
• It is currently unclear whether alternative systems can fully replicate hESC properties

Preservation of prior investment
• Limiting hESC use risks undermining decades of public investment in well-established research tools

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/BSCRCs-Response-to-NIH-RFI-on-hESC-260420.pdf

Description: BSCRC's Full Response Letter to NIH RFI on hESC

Thomas A. Rando, MD, PhD
Director
Eli and Edythe Broad Center of
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610 Charles E. Young Drive, East
3000A TLSB, Box 957357
Los Angeles, CA 90095-7357
(t) 310.206.7351
www.stemcell.ucla.edu

April 20, 2026

NIH Office of Science Policy
6705 Rockledge Drive, Suite 630
Bethesda, MD 20892

RE: Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA Response to the Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

To Whom It May Concern:

I write on behalf of the University of California, Los Angeles (UCLA) Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research Center (BSCRC) in response to the Request for Information on Reducing Reliance on Human Embryonic Stem Cells (hESC) in NIH-Supported Research issued on January 23, 2026.

BSCRC is a campus-wide, interdisciplinary research center dedicated to advancing stem cell science and translating discoveries into therapies that improve human health. Bringing together faculty members across diverse scientific, medical, and academic disciplines, the center fosters collaboration, innovation, and rigorous ethical standards to tackle complex biomedical challenges. Since its founding in 2005, BSCRC has served as a hub for pioneering research in regenerative medicine, supporting cutting-edge technologies, training the next generation of scientists, and accelerating the development of personalized cellular therapies from the laboratory to the clinic.

We submit the following comments to provide NIH broader considerations as it reassesses the utility of hESCs in biomedical research. BSCRC's comments are provided below.

Question 1: Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed;

Currently approved hESC lines continue to meet many core needs of the research community due to their extensive characterization, widespread adoption, and foundational role in both basic

and translational science. These lines have also enabled the development of promising cell-based therapies, several of which are now being evaluated in clinical trials for conditions including Parkinson's disease, age-related macular degeneration, epilepsy, and type 1 diabetes. However, important gaps remain, particularly in genetic diversity, disease modeling, and reproductive biology, that necessitate the derivation of new hESC lines. While existing lines provide a critical and stable reference standard, expanding the available repertoire is essential to fully capture human variation and enable progress in areas that cannot be addressed with current resources alone.

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- Support development of more broadly applicable and personalized cell therapies
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Question 2: Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable;

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Question 3: Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs;

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strategy is therefore critical, one that advances iPSC and related systems while maintaining access to hESCs to ensure accuracy, reliability, and continued innovation in the field.

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Question 4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

To reduce reliance on hESCs, substantial additional investment is needed to develop and validate alternative models that can reliably replicate their biological properties. This includes advancing our understanding of the molecular and functional differences between hESCs and current alternatives, improving the fidelity of reprogrammed systems, and rebuilding the extensive infrastructure and toolsets that currently exist for hESCs. However, the feasibility, cost, and timeline of achieving fully equivalent replacement models remain uncertain, and such efforts would require long-term, large-scale investment. A balanced approach is needed: invest in alternatives while maintaining access to hESCs to ensure continued scientific and translational progress.

Priority areas for additional investment:

Comprehensive comparative analysis and improvement of alternative cell fidelity

- Epigenomic, multi-omic, metabolic, and functional comparisons between hESCs and alternatives (e.g., iPSCs)
- Development of methods to reprogram or engineer iPSCs into a more hESC-like state

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- Recreate and expand gene-edited lines, reporter systems, and validated reagents currently available for hESCs

Standardization and scalability of research resources and protocols

- Establish high-quality, accessible repositories of alternative stem cell lines

- Develop standardized methods for differentiation and experimental use

Challenges and considerations:

Significant cost and long timelines

- Rebuilding equivalent infrastructure and knowledge base would require major funding and sustained effort

Uncertain feasibility

- It is currently unclear whether alternative systems can fully replicate hESC properties

Preservation of prior investment

- Limiting hESC use risks undermining decades of public investment in well-established research tools

hESCs remain indispensable across a wide range of research areas due to their unique role as the definitive benchmark for human pluripotency, early development, and translational applications. While existing hESC lines continue to meet many core scientific and clinical needs, important gaps, particularly in genetic diversity and disease modeling, underscore the need to derive new lines. Emerging technologies such as iPSCs and adult stem cells have expanded the research landscape and can complement hESC use in specific contexts, but they do not yet replicate the full biological fidelity, stability, or developmental relevance of hESCs, making full replacement premature. Significant additional investment would be required to develop alternative systems capable of matching hESCs, including advancing multi-omic comparisons, improving reprogramming fidelity, and rebuilding extensive research infrastructure, with uncertain feasibility and timelines. Limiting access to hESCs or discontinuing support would risk undermining decades of public investment and could slow progress by requiring costly and uncertain efforts to recreate equivalent systems using alternative technologies. A balanced and forward-looking strategy that continues to support hESC research while advancing complementary technologies is essential to sustain scientific progress, maximize prior public investment, and ensure continued innovation in understanding human biology and developing effective therapies for patients.

Sincerely,



Thomas A. Rando, M.D., Ph.D.
Director
Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA

57. Wisconsin Alumni Research Foundation

I am responding: On behalf of an organization

Name: Erik Iverson

Name of Organization: Wisconsin Alumni Research Foundation

Type of Organization: Academic Institution

Role: Other

Role - Other: Chief Executive Officer

Date Submitted: 04/21/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/WARF-Response-NIH-hESC-RFI-signed-04212026.pdf

WARF
Wisconsin Alumni Research Foundation

April 23, 2026

RE: NOT-OD-26-031

Via online comment form

Wisconsin Alumni Research Foundation's Response to NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

The Wisconsin Alumni Research Foundation (WARF) greatly appreciates the opportunity to share our perspective on NIH-supported research involving human embryonic stem cells (hESCs). WARF is a supporting organization of the University of Wisconsin-Madison (UW-Madison), our state's flagship public research university, and of the Morgridge Institute for Research (Morgridge), a private medical research foundation on the UW-Madison campus. In the stem cell space, we coordinate closely with the WiCell Research Institute, a non-profit organization founded by WARF in 1999 to advance stem cell technologies and a world leader in stem cell research, cell banking, characterization testing, and the distribution of stem cell lines.

We are aware of responses being prepared by the above organizations. WARF supports and agrees with their perspectives.

WARF states in no uncertain terms that hESCs continue to be an essential and irreplaceable tool for the advancement of emerging technologies in biohealth and, specifically, regenerative medicine and cancer immunotherapy. Now is not the time to scale back federal support for hESC research, nor is it productive to place new restrictions on hESC lines or the NIH hESC registry. **Indeed, America's foundational leadership in hESC lines, and the careful oversight and guidance that NIH currently provides, give the United States a unique advantage over competitors and adversary nations in advancing the next-generation technologies referenced in the solicitation for this Request for Information.** Even as new, advanced technologies emerge, hESCs will continue to be a critical component of the quality control infrastructure needed to ensure that American biohealth meets the highest standards in the world.

Far from being superseded, hESCs are on the brink of realizing their enormous promise of benefiting human health through the approval of new treatments for a host of previously intractable diseases. Treatments for diabetes, Parkinson's, epilepsy, and macular degeneration have advanced into clinical trials, to cite the most current examples. **We are especially concerned that reductions and restrictions could be disruptive to current and planned clinical trials, both ongoing and upcoming, and could lead to the delay of important therapeutic breakthroughs.**

Beyond their direct use in the development of therapeutics, hESCs serve as tools for basic biological and disease-related research, meaning disruptions to federal support could impede the United States' ability to keep pace with competitors like China in the race to develop future generations of pharmaceuticals and biomedical technologies.

hESCs are a uniquely important and powerful technology evaluated and tested according to thorough and exacting oversight and governance structures. These include local review by Stem Cell Research Oversight committees, NIH hESC registry review, and international standards propagated by a variety of relevant organizations including the International Society for Stem Cell Research and the International Society for Cell and Gene Therapy. These standards and safeguards have been broadly agreed upon by researchers, bioethicists, and policymakers, and have been crafted to apply to the specific ethical considerations involved in the use of hESCs.

WARF has supported and facilitated the development of hESC technologies since 1998, when WARF filed for patent protection on UW-Madison researcher James Thomson's invention of the first isolated and cultured hESCs. Our involvement in stem cell science more broadly dates to 1995 when Dr. Thomson first isolated primate embryonic stem cells and extended forward to 2006 with his development of induced pluripotent stem cells (iPSC). WARF continues to be directly involved in stem cells, both hESC and iPSC, through grants in support of UW-Madison research, a strong portfolio of intellectual property, and licensing agreements with leading companies in the stem cell industry.

In 1999, WARF created WiCell to ensure that cells could be provided to researchers at cost, leading to thousands of patents, licenses, jobs, and new businesses. WARF's efforts seeded an industry and laid the foundation for the infrastructure that enabled the rapid expansion of stem cell research and technology development. Today, WARF's hESC lines, particularly H1 and H9, are among the most widely used and published in the world. Throughout, WARF has been guided in our work by rigorous legal and ethical guidelines referenced consistently in every WARF material transfer agreement and license.

The experience of WARF, WiCell, and the UW-Madison researchers we support has demonstrated without a doubt that hESCs are the gold standard in stem cell science because they are extracted, not derived, and are less manipulated compared to other pluripotent stem cells. They serve as critical controls alongside iPSCs, helping researchers validate findings and ensure scientific rigor. While iPSC technology has advanced, hESCs continue to provide unique scientific value that cannot be reasonably replicated by iPSCs alone.

Considering the above, we are concerned that the plateau in support for hESCs since 2019 (as noted in the Request for Information) does not reflect declining relevance of the technology but instead a worrying signal that U.S. science has begun to fall behind as competitors gain ground. Wisconsin scientists provided the fundamental breakthroughs of stem cell science, which has given the United States a decades-long advantage in the biomedical advances built on hESCs. But that advantage is not guaranteed. **Closing off pathways to the continued development of hESCs in the United States will create a vacuum that other countries— especially China— are already moving to fill.**

In summary, human embryonic stem cells remain an indispensable resource for scientific discovery and clinical advancement and, as such, are crucial to maintaining U.S. leadership and competitiveness in biomedical innovation. WARF urges NIH to continue funding hESC research under consistent, ethical, and rigorous standards. Limiting support for hESCs would undermine decades of progress and jeopardize future breakthroughs that promise to transform human health.

Sincerely,



Erik Iverson
eiverson@warf.org
Chief Executive Officer
Wisconsin Alumni Research Foundation

58. Barbara Fellows

I am responding: On behalf of myself

Name: Barbara Fellows

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

59. American Society of Hematology

I am responding: On behalf of an organization

Name: Stephanie Kaplan

Name of Organization: American Society of Hematology

Type of Organization: Professional Organization/Association

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Upon surveying ASH members, there was consensus that currently approved human embryonic stem cell (hESC) lines are sufficient for conducting most regenerative medicine research, as well as studying developmental biology.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Research using hESCs has not only advanced our understanding of human development and cell differentiation and enabled disease modeling and drug screening but also laid the foundation for other pluripotent stem cell approaches, including induced pluripotent stem cells (iPSCs). Given hESCs' unique biological properties and irreplaceable scientific value, continued access to existing hESC lines is essential, particularly where no viable alternatives exist, since their absence could hinder progress in key research areas.

ASH notes that while hESC alternatives like adult stem cells and human iPSCs can be useful in some studies, there are limitations when using these alternatives. For example, hematopoietic stem cells, which are adult stem cells located in bone marrow and umbilical cord blood, can produce all blood cell types and may be appropriate for studying blood cell lineages. However, they are insufficient for studying the full spectrum of cell differentiation and development as they are generally limited to becoming cell types within their specific tissue of origin and there is little evidence showing that these adult stem cells are fully pluripotent.

Below are areas of research that may experience setbacks if hESCs were unavailable:

- Human hematopoietic development: hESCs serve as the gold standard for studying how blood cells develop from the earliest embryonic and developmental stages. hESCs are essential controls that allow researchers to investigate the differences between naïve and primed pluripotency, or accurately map the genetic and chemical changes that occur during early life hematopoiesis in humans.

- Studies that develop and use iPSCs: Without access to hESCs, iPSC research would face major setbacks, as hESCs remain the gold standard for pluripotency. iPSCs retain epigenetic "memory" and somatic variations which may affect the utility and functionality of these cell lines. Researchers often rely on established hESC lines to validate that engineered iPSCs are stable, truly pluripotent and functionally

comparable to hESCs, which strengthens scientific rigor and reproducibility of studies. Widely used, well-characterized hESCs also enable consistent comparisons across studies and laboratories worldwide, making them essential benchmarks for iPSC research.

- CRISPR gene engineering: hESCs are often the preferred cell types to evaluate how gene edits affect long-term cell development. The field of gene engineering is moving toward the next generation gene engineering strategy to target early development in vivo gene correction, and hESCs will be essential in advancing this new frontier in science.

Although hiPSCs share many similarities with hESCs and are quite effective, hESCs are still needed as a reference to determine whether a newly generated iPSC line is indeed pluripotent. iPSCs are much better alternatives to hESCs that show many similarities to hESCs, but as mentioned previously, any research utilizing iPSCs would also need hESCs as comparators to ensure their pluripotency. Furthermore, because iPSCs are reprogrammed from adult somatic cells, they are not always stable and there may be differences in their characteristics (e.g., epigenetic changes) that we do not completely understand yet. Studies show that there are somatic mutations that may be acquired during reprogramming that can cause significant genomic variation, which limits iPSCs' usefulness in some applications.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Despite some of the limitations outlined above, below are a few areas of research where iPSCs can be useful and have already shown significant potential as alternatives to hESCs:

- Personalized drug screening: iPSCs are an attractive alternative to hESCs as they can be derived from individual patients. They can be useful in toxicology studies during drug development, as well as for patient-tailored testing to determine how patient responds to certain treatment and to optimize treatment.

- Creating organ-on-a-chip/organoids: In hematology, human bone marrow organoid models utilizing iPSCs show a lot of promise for studying normal hematopoiesis and hematologic diseases.

- Autologous Regenerative Medicine: iPSCs may serve as an appropriate alternative to hESCs for some regenerative medicine applications. Even though iPSCs' inherited somatic mutations and variations through reprogramming will continue to be a concern, one of the strengths of utilizing iPSCs is that it minimizes risk to immune rejection since they are derived from the patient's own cells.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
ASH recommends that NIH consider supporting more bioethics research in this area to further inform and address the concerns from scientists, clinicians, patients and ethicists on the utilization and utility of hESC. In addition, ASH recommends that the NIH consider the following promising research areas to further invest in:

- Computational models using artificial intelligence (AI): Development of in silico modeling with AI could help predict how a human embryo or cell would react to a drug or genetic mutation

- Organ-on-a-chip technologies and 3D organoids: Robust investment in bone marrow organoid models would help advance the field of hematology, and more advances in organ-on-a-chip technologies and 3D organoids using iPSCs that can accurately simulate complex organs will significantly advance the entire field of medical research

- Further iPSC research: Better understanding of the changes that occur during reprogramming to create iPSCs and studying how to “deprogram” iPSCs would be helpful. iPSCs, tend to maintain epigenetic “memory” making them less ideal as compared to hESCs. Investing in iPSCs research to achieve high-quality, “memory-free” iPSCs would improve their usefulness in research.

- Virtual embryonic stem cells (ESCs): There is increasing evidence for greater validation and utilization of virtual ESCs with the recent rigorous scientific inquiry that has resulted in spatial omics of whole embryos (1 & 2). The published tools and data are open source. These research advances, such as virtual ESCs using archival human tissue, should be further supported so that the scientific community can gain access to virtual ESCs and virtual tissue niches that could be generated by the powerful combination of spatial omics and AI.

1. https://doi.org/10.1126/science.adt3439
2. https://doi.org/10.1016/j.cell.2026.03.006

60. Human stem cell consortium of the NICHD-funded Intellectual and Developmental Disabilities Research Centers (IDDRC) network

I am responding: On behalf of an organization

Name: N/A

Name of Organization: Human stem cell consortium of the NICHD-funded Intellectual and Developmental Disabilities Research Centers (IDDRC) network

Type of Organization: Professional Organization/Association

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.
As research tools, hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models. They provide the raw material for cell replacement therapies in many organ systems.
The original five hESC lines in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (PMID: 30388422). These lines continue to be the most accepted and best characterized hESCs for research.

The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.
hESCs are the foundation of the translational pipeline to generate cell therapies. They are used to generate specialized cells to replace damaged, diseased, or dying tissue in patients, including applications in neurology, cardiology and diabetes. In fact, promising new cell therapies derived from hES cells are currently being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005).

While there has been a decline in the number of cell lines submitted for review to be added to the NIH hESC Registry and NIH support for hESC research has stabilized, these data should not be interpreted as a decline in the need and utility of hESCs in research. As with any new technology, there is often a surge of demand for the novel technology, followed by a plateau or steady-state of demand. The federal NIH registry is less than two decades old, a short timeframe for widespread adoption of a new technology. By studying the examples, of AI, 3D printing and tissue engineering, some argue that 30 to 50 years is the realistic time between novel concept and widespread adoption

(https://doi.org/10.1016/j.matt.2019.10.011 and https://www.entrepreneur.com/leadership/the-pace-of-technological-change-is-faster-than-ever/386410).
New hES cell lines are essential for: (1) expanding and broadening the genetic backgrounds of the current hESC lines (2) studying diseases with no alternate human models, (3) fertility research, since the beginning of human development is otherwise inaccessible. Stem cell research has resulted in important new breakthroughs in the treatment of infertility. hESC technology has led, and will continue to contribute to, a better understanding of human development, and perhaps even new ways to treat infertility and prevent miscarriages. For families who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, hESC-based approaches are promising.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

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Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs exhibit similar properties to hESCs in many respects, they also have distinct biological characteristics.

Human ESCs are critical for research on fertility. Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.The large number of genetically engineered hESC tools that are used in research would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.

hESCs provide the only reference for the development of alternatives. They provide a unique benchmark for future work and the development of alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

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While iPSCs have substantially expanded the field, they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs. iPSCs are more prone

to harbor deleterious mutations, present in the donor cells, introduced in the reprogramming process or through stress of prolonged passaging, than hESCs. The effects of these mutations in research and more importantly, on future cell therapies, are currently unknown. The replacement of hESCs with iPSCs is premature.

Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development. A responsible strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Comprehensive epigenomics, multiomics, metabolic, and functional comparisons are necessary to fully define the differences between hESCs and hiPSCs or other potential alternative technologies. Secondly, methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research. The feasibility and timeline to meet all these requirements is unknown and would require substantial investment of funding.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/NIH-hESC-RFI-IDDRC-hPSC-WG.pdf

Description: We are members of a consortium of leading researchers throughout the United States who use human stem cell models to understand and advance treatments for intellectual and developmental disorders, such as autism spectrum disorder, childhood epilepsies, and Down syndrome. The principal researchers have established working collaborations through the human stem cell consortium of the NICHD-funded Intellectual and Developmental Disabilities Research Centers (IDDRC) network. We are a transdisciplinary group of researchers focused on stem cell modeling of human brain development and function to assess and improve the precision and translatability of these model systems. Our group has taken a particular interest in improving rigor and reproducibility among human stem cell-based studies of the brain through analyses and cross-center projects to assess reproducibility (PMC8190574, PMC11297560). We are thus committed to ensuring that the resulting phenotypes truly reflect and have relevance to the human brain and, in case of disorder, the clinical characteristics of the patient. We are dedicated to ensuring that stem cell research and clinical translation continue in a responsible, merit-based, and ethical manner. The research we undertake is making great strides in biomedical science and

our ability to treat debilitating neurological diseases, discover new medicines and uncover the fundamental processes that lead to disease.

INTRODUCTION

We are members of a consortium of leading researchers throughout the United States who use human stem cell models to understand and advance treatments for intellectual and developmental disorders, such as autism spectrum disorder, childhood epilepsies, and Down syndrome. The principal researchers have established working collaborations through the human stem cell consortium of the NICHD-funded Intellectual and Developmental Disabilities Research Centers (IDDRC) network. We are a transdisciplinary group of researchers focused on stem cell modeling of human brain development and function to assess and improve the precision and translatability of these model systems. Our group has taken a particular interest in improving rigor and reproducibility among human stem cell-based studies of the brain through analyses and cross-center projects to assess reproducibility (PMC8190574, PMC11297560). We are thus committed to ensuring that the resulting phenotypes truly reflect and have relevance to the human brain and, in case of disorder, the clinical characteristics of the patient. We are dedicated to ensuring that stem cell research and clinical translation continue in a responsible, merit-based, and ethical manner. The research we undertake is making great strides in biomedical science and our ability to treat debilitating neurological diseases, discover new medicines and uncover the fundamental processes that lead to disease.

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hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.

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The original five hESC lines in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (PMID: 30388422). These lines continue to be the most accepted and best characterized hESCs for research.

The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.

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61. American Society for Reproductive Medicine

I am responding: On behalf of an organization

Name: Emma Berens

Name of Organization: American Society for Reproductive Medicine

Type of Organization: Professional Organization/Association

Role: Other

Role - Other: Government Affairs Manager

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Dear Dr. Jay Bhattacharya,

On behalf of the American Society for Reproductive Medicine (ASRM), I write in response to the NIH Notice NOT-OD-26-031 and in opposition to the pause in review/approvals for new Human Embryonic Stem Cell (hESC) lines to be added to the NIH Human Embryonic Stem Cell Registry.

Human embryonic stem cells allow scientists to research human development, practice regenerative medicine and model diseases. They are pluripotent, meaning that they can be induced into specialized stem cells (such neurons or heart muscle cells). Human embryonic stem cells can be both therapeutic and research tools. For example, we have seen great progress in treatment of diabetes, spinal conditions, heart disease, and more recently, Parkinson's through the direct use of human embryonic stem cells.

Notably, presidents of both political parties have approved and supported the use of human embryonic stem cells, both for therapeutic and research purposes. There is bipartisan support for the medical advancements this field promises. Nothing scientifically has changed in this field of research that would justify restrictions on new human embryonic stem cell lines.

While promising research efforts are in progress on alternatives to hESCs, these approaches require further development before they can fully replace existing models. Pausing new human embryonic stem cell lines to be added to the NIH Human Embryonic Stem Cell Registry could have detrimental impacts on the US's cutting-edge biotechnology research, development, and exceptional patient care.

If there is anything ASRM or its nearly 8,000 members can do to support the Institute as it conducts this review, please do not hesitate to reach out to me (r-brannigan@northwestern.edu) or ASRM's DC Office of Public Affairs (publicaffairs@asrm.org).

Sincerely,

Robert Brannigan, MD

President
American Society for Reproductive Medicine

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N/A

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Chief Education & Science Officer

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892

April 22, 2026

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Sincerely,

[redacted]

Robert Brannigan, MD
President
American Society for Reproductive Medicine

62. AAMC

I am responding: On behalf of an organization

Name: N/A

Name of Organization: AAMC

Type of Organization: Professional Organization/Association

Role: Other

Role - Other: N/A

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The NIH Human Stem Cell Registry has the vital role of identifying lines available for use in NIH-funded studies and collecting and displaying this information in an organized and accessible location. The AAMC believes it is equally important that the Registry continue to accept submissions for new hESC lines and maintain a resource where scientists can access fully characterized lines which have gone through a quality control process. Leaving a pathway for the development of new resources is a necessary step in scientific progress and in optimizing the applicability of results obtained from using hESCs. Scientists specializing in stem cell research have emphasized the importance of continuing to develop stem cell lines that are reflective of the genetic diversity present in the U.S. population, in accordance with the Dept. of Health and Human Services' goal of enhancing the health and well-being of all Americans.

It is impossible to determine whether the approved lines meet the future needs of the research community, as these needs are constantly evolving, along with our increased understanding of human biology and advances in technology and methodology. The continual improvement of resources, including the development of new cell lines, facilitates inquiry into emerging and cutting-edge fields and the development of novel therapies. To prevent this improvement in resources would be a detriment to the biomedical and clinical research enterprise and prevent researchers from using the best-available and most appropriate materials for their studies. For these reasons, AAMC strongly recommends that the NIH continue to allow use of existing lines in the Registry as well as the derivation and approval of new lines.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human embryonic stem cells are widely recognized as the gold standard across stem cell research and are the benchmark for in vitro models of human pluripotency . Scientific advances in recent years have highlighted the significant increase in the use of iPSCs, which are adult cells reprogrammed into a pluripotent state. The key feedback provided by scientists in academic medicine, many of whom have research programs built around iPSC models, is that hESCs remain a necessity in the laboratory and clinical environment due to their singular role as a control and the standard for defining pluripotency, developmental potential, and lineage competence in stem cell research.

Future research with iPSCs will continue to require hESCs to ensure that the behavior of and results from these cells are indicative of what is seen with hESCs, the most validated and well-characterized cell type for human development. We also note that this role of hESCs makes them essential in fulfilling NIH's ongoing efforts to improve rigor and reproducibility in research and expand the tools necessary to advance the use of human-based technologies and models in biomedicine.

It is worth noting that alternative cell types, including iPSCs and adult stem cells, cannot fully replace hESCs, as hESCs exhibit significant differences in origin, epigenetic memory, and gene expression, regardless of their performance in an experimental setting. For example, the process of reprogramming iPSCs has been shown to lead to issues with differentiation and reproducibility. We also emphasize that hESCs form the foundation of many ongoing clinical trials, often to develop therapeutics for diseases in which treatments are currently limited or unavailable. It is imperative that these promising efforts in translation continue in order to maximize medical progress based on NIH's many years of investment in hESC research.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
AAMC appreciates that NIH is soliciting feedback on improving validated models for hESC research. While we emphasize that other cell types, especially human iPSCs, will not be able to fully replace a hESC model, there are a number of areas NIH might prioritize for investment in order to strengthen the standardization and characterization of these cells.

Scientists who specialize in iPSC research indicate that although these cells are a very promising resource, there is currently substantial variability in how these cells are derived and no unified standard in the technique for generating the cells. We refer to the ISSCR's opportunities for standards development3, which include standards for source materials; process controls; instrument, facility, environment and personnel; analytic methods; and data processing. Consultation with the scientific community working with iPSCs could identify which of these areas would be most appropriately prioritized for targeted funding from NIH, including the development of standards and/or a reagent guide maintained by the agency. Investing in a better understanding of iPSC cells would additionally advance the NIH's overall goal of rigor and reproducibility across all funded research.

There are also significant opportunities for better characterization of iPSCs, including their genetic and epigenetic background, differentiation potential, any biological changes due to reprogramming, and their function in different environments and in response to diverse stimuli.
Additionally, clinical assessment of iPSCs and how they function, as compared to hESCs, is still at a very nascent stage, and we do not fully understand how these two platforms converge or diverge as a therapeutic modality. All these studies, both in clinical and translational phases, would continue to require hESCs as a control and are a potential area of focus for NIH funding.

Finally, as the field of science moves forward and becomes increasingly data-driven and interdisciplinary,

the use of multi -omic panels, synthetic biology, and biomanufacturing all present new opportunities for more precise manipulation of cell identity, reductions in variability, and increases in scalability. NIH should continue to solicit and welcome applications which focus on emerging and cutting-edge research to advance the field of stem cell research and allow the U.S. to continue to be a global leader in scientific discovery and medical innovation.

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Description: AAMC comments: re NIH NOT-OD-26-031

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April 22, 2026

National Institutes of Health
NIH Office of Science Policy
6705 Rockledge Drive, Suite 630,
Bethesda, MD 20892

Re: Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

Submitted online via https://osp.od.nih.gov/comment-form-reducing-reliance-on-human-embryonic-stem-cells-in-nih-supported-research/

The AAMC appreciates the opportunity to provide comments to the National Institutes of Health (NIH) on its request for information (RFI) on the use of human embryonic stem cells (hESCs) in NIH-funded research.

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, clinical care, biomedical research, and community collaborations. Its members are all 163 U.S. medical schools accredited by the Liaison Committee on Medical Education; 13 Canadian medical schools accredited by the Committee on Accreditation of Canadian Medical Schools; nearly 500 academic health systems and teaching hospitals, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools, academic health systems and teaching hospitals, and the millions of individuals across academic medicine, including more than 210,000 full time faculty members, 99,000 medical students, 162,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Through the Alliance of Academic Health Centers International, AAMC membership reaches more than 60 international academic health centers throughout five regional offices across the globe.

AAMC-member medical schools and teaching hospitals are at the forefront of stem cell research, a critical field of study which has provided invaluable insights into human development and reproductive biology as well as facilitating disease modeling and drug discovery. Different stem cell types, including adult stem cells, human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs), possess distinctive characteristics and applications in research and medicine. In particular, hESCs have long been regarded as the gold standard for human

pluripotency within the scientific community and peer-reviewed literature, due to their unique capability for self-renewal and differentiation into multiple specialized cell types.

AAMC strongly supports the responsible use of hESCs in research which is conducted under the ethical and legal oversight provided by the NIH Guidelines for Human Stem Cell Research[1] and supported by the National Academies[2] and International Society for Stem Cell Research (ISSCR)[3]. The critical importance of hESCs has been recognized internationally by leading scientific and medical bodies and the consistent NIH investment in hESC research, along with maintenance of the NIH hESC Registry,[4] has allowed the U.S. to make impactful advancements in the field of stem cell research, contribute to key discoveries, and remain competitive in this transformational area of science and medicine.

In response to NIH's request for information, AAMC would like to make the following topline recommendations, in addition to addressing the specific questions posed in the RFI.

1) **AAMC recommends that NIH continue to allow access to existing lines in the NIH hESC Registry and resume accepting new submissions for cell lines eligible for use in NIH-supported research.**

2) **AAMC strongly urges continued NIH funding for hESC research, as a scientific necessity and critical component of NIH's ongoing initiatives in gold standard science[5], replication and reproducibility[6], and interest in expanding the use of innovative, human-based technologies[7].**

Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed

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[1] NIH Guidelines for Human Stem Cell Research. https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research

[2] Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (2010), https://doi.org/10.17226/12923.

[3] Guidelines for Stem Cell Research and Clinical Translation. https://www.isscr.org/guidelines. August 2025 Update, Version 1.2.

[4] NIH Human Embryonic Stem Cell Registry. https://stemcells.nih.gov/registry/eligible-to-use-lines.

[5] NIH Publishes Plan to Drive Gold Standard Science. https://www.nih.gov/about-nih/nih-director/statements/nih-publishes-plan-drive-gold-standard-science.

[6] Strengthening Replication and Reproducibility of NIH-funded Research. https://www.nih.gov/replicationandreproducibility.

[7] NIH to prioritize human-based research technologies. https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies.

The NIH Human Stem Cell Registry has the vital role of identifying lines available for use in NIH-funded studies and collecting and displaying this information in an organized and accessible location. The AAMC believes it is equally important that the Registry continue to accept submissions for new hESC lines and maintain a resource where scientists can access fully characterized lines which have gone through a quality control process. Leaving a pathway for the development of new resources is a necessary step in scientific progress and in optimizing the applicability of results obtained from using hESCs. Scientists specializing in stem cell research have emphasized the importance of continuing to develop stem cell lines that are reflective of the genetic diversity present in the U.S. population, in accordance with the Dept. of Health and Human Services' goal of enhancing the health and well-being of all Americans.

It is impossible to determine whether the approved lines meet the future needs of the research community, as these needs are constantly evolving, along with our increased understanding of human biology and advances in technology and methodology. The continual improvement of resources, including the development of new cell lines, facilitates inquiry into emerging and cutting-edge fields and the development of novel therapies. To prevent this improvement in resources would be a detriment to the biomedical and clinical research enterprise and prevent researchers from using the best-available and most appropriate materials for their studies. For these reasons, AAMC strongly recommends that the NIH continue to allow use of existing lines in the Registry as well as the derivation and approval of new lines.

Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable/Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

Human embryonic stem cells are widely recognized as the gold standard across stem cell research and are the benchmark for in vitro models of human pluripotency[8]. Scientific advances in recent years have highlighted the significant increase in the use of iPSCs, which are adult cells reprogrammed into a pluripotent state. The key feedback provided by scientists in academic medicine, many of whom have research programs built around iPSC models, is that hESCs remain a necessity in the laboratory and clinical environment due to their singular role as a control and the standard for defining pluripotency, developmental potential, and lineage competence in stem cell research.

Future research with iPSCs will continue to require hESCs to ensure that the behavior of and results from these cells are indicative of what is seen with hESCs, the most validated and well-

[8] James A. Thomson et al., Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 282,1145-1147 (1998). https://www.science.org/doi/10.1126/science.282.5391.1145

characterized cell type for human development. We also note that this role of hESCs makes them essential in fulfilling NIH's ongoing efforts to improve rigor and reproducibility in research and expand the tools necessary to advance the use of human-based technologies and models in biomedicine.

It is worth noting that alternative cell types, including iPSCs and adult stem cells, cannot fully replace hESCs, as hESCs exhibit significant differences in origin, epigenetic memory, and gene expression, regardless of their performance in an experimental setting. For example, the process of reprogramming iPSCs has been shown to lead to issues with differentiation and reproducibility. We also emphasize that hESCs form the foundation of many ongoing clinical trials, often to develop therapeutics for diseases in which treatments are currently limited or unavailable. It is imperative that these promising efforts in translation continue in order to maximize medical progress based on NIH's many years of investment in hESC research.

Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

AAMC appreciates that NIH is soliciting feedback on improving validated models for hESC research. While we emphasize that other cell types, especially human iPSCs, will not be able to fully replace a hESC model, there are a number of areas NIH might prioritize for investment in order to strengthen the standardization and characterization of these cells.

Scientists who specialize in iPSC research indicate that although these cells are a very promising resource, there is currently substantial variability in how these cells are derived and no unified standard in the technique for generating the cells. We refer to the ISSCR's opportunities for standards development[3], which include standards for source materials; process controls; instrument, facility, environment and personnel; analytic methods; and data processing. Consultation with the scientific community working with iPSCs could identify which of these areas would be most appropriately prioritized for targeted funding from NIH, including the development of standards and/or a reagent guide maintained by the agency. Investing in a better understanding of iPSC cells would additionally advance the NIH's overall goal of rigor and reproducibility across all funded research.

There are also significant opportunities for better characterization of iPSCs, including their genetic and epigenetic background, differentiation potential, any biological changes due to reprogramming, and their function in different environments and in response to diverse stimuli. Additionally, clinical assessment of iPSCs and how they function, as compared to hESCs, is still at a very nascent stage, and we do not fully understand how these two platforms converge or

diverge as a therapeutic modality. All these studies, both in clinical and translational phases, would continue to require hESCs as a control and are a potential area of focus for NIH funding.

Finally, as the field of science moves forward and becomes increasingly data-driven and interdisciplinary, the use of multi -omic panels, synthetic biology, and biomanufacturing all present new opportunities for more precise manipulation of cell identity, reductions in variability, and increases in scalability. NIH should continue to solicit and welcome applications which focus on emerging and cutting-edge research to advance the field of stem cell research and allow the U.S. to continue to be a global leader in scientific discovery and medical innovation.

Thank you again for the opportunity to provide feedback on this RFI. Human embryonic stem cell research is a critical tool to advance our understanding of fundamental human biology and also has powerful therapeutic applications and potential in regenerative medicine and personalized treatments, representing hope for patients and families. This research is already highly regulated and conducted in accordance with strict ethical guidelines. The currently available scientific and translational evidence does not provide any scientific justification for NIH to reduce its funding of hESC research and we strongly urge the agency to lift its pause on submissions to the hESC Registry and continue its commitment to funding high-quality hESC research.

The AAMC looks forward to continued engagement with the NIH on the use of human embryonic stem cells in research and would be glad to provide further information, as needed. AAMC also endorses the comments from the ISSCR in response to this RFI, the largest society of stem cell researchers in the world and a leading organization in developing scientific guidelines and standards for stem cell research.

For any questions about these comments, please contact Anu Dev, PhD, Principal Science Policy and Strategy Leader (adev@aamc.org) and Heather Pierce, JD, MPH, Senior Director for Science Policy and Regulatory Counsel (hpierce@aamc.org).

Sincerely,

[redacted]

Elena Fuentes-Afflick, MD, MPH
Chief Scientific Officer

cc: David J. Skorton, MD, AAMC President and Chief Executive Officer

63. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: University of Wisconsin-Madison

Type of Organization: Not Applicable

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.
As research tools, hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models. They provide the raw material for cell replacement therapies in many organ systems.
The original five hESC lines in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (PMID: 30388422). These lines continue to be the most accepted and best characterized hESCs for research.
The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.
hESCs are the foundation of the translational pipeline to generate cell therapies. They are used to generate specialized cells to replace damaged, diseased, or dying tissue in patients, including applications in neurology, cardiology and diabetes. In fact, promising new cell therapies derived from hES cells are currently being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005).
While there has been a decline in the number of cell lines submitted for review to be added to the NIH hESC Registry and NIH support for hESC research has stabilized, these data should not be interpreted as a decline in the need and utility of hESCs in research. As with any new technology, there is often a surge of demand for the novel technology, followed by a plateau or steady-state of demand. The federal NIH registry is less than two decades old, a short timeframe for widespread adoption of a new technology. By studying the examples, of AI, 3D printing and tissue engineering, some argue that 30 to 50 years is the realistic time between novel concept and widespread adoption (https://doi.org/10.1016/j.matt.2019.10.011 and https://www.entrepreneur.com/leadership/the-pace-of-technological-change-is-faster-than-ever/386410).
New hES cell lines are essential for: (1) expanding and broadening the genetic backgrounds of the current hESC linesm (2) studying diseases with no alternate human models, (3) fertility research, since

the beginning of human development is otherwise inaccessible. Stem cell research has resulted in important new breakthroughs in the treatment of infertility. hESC technology has led, and will continue to contribute to, a better understanding of human development, and perhaps even new ways to treat infertility and prevent miscarriages. For families who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, hESC-based approaches are promising.
hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data show that iPSCs exhibit similar properties to hESCs in many respects, they also have distinct biological characteristics.
Human ESCs are critical for research on fertility. Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples. The large number of genetically engineered hESC tools that are used in research would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
hESCs provide the only reference for the development of alternatives. They provide a unique benchmark for future work and the development of alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating technologies that are insufficient to meet the needs for the research or, potentially incorrect. The advent and use of induced pluripotent stem cells (iPSCs) do not and should not preclude the need and use of hESCs. hESCs cannot be separated from or replaced by iPSCs in the stem cell research enterprise.
While iPSCs have substantially expanded the field, they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs. iPSCs are more prone to harbor deleterious mutations, present in the donor cells, introduced in the reprogramming process or through stress of prolonged passaging, than hESCs. The effects of these mutations in research and more importantly, on future cell therapies, are currently unknown. The replacement of hESCs with iPSCs would thus be premature.
Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from

individuals. Adult stem cells do not recapitulate features of the earliest steps in human development. A responsible strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Comprehensive epigenomics, multiomics, metabolic, and functional comparisons are necessary to fully define the differences between hESCs and hiPSCs or other potential alternative technologies. Secondly, methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research. The feasibility and timeline to meet all these requirements is unknown and would require substantial investment of funding.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

64. Aaron Kheriaty

I am responding: On behalf of myself

Name: Aaron Kheriaty

Name of Organization: Ethics and Public Policy Center

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
See attached document

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
See attached document

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See attached document

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See attached document

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HHS Request for Comments regarding Embryonic Stem Cell Research

History of federal funding for embryonic stem cell research

In 1998 scientists at the University of Wisconsin derived human embryonic stem cells from a procedure that results in the death of a living human being at the embryonic stage of development. Since then, public controversy has centered on whether taxpayer dollars should support research that requires the destruction of living human embryos to obtain stem cells. These embryos are typically surplus products of in vitro fertilization (IVF) treatments, but it is also possible that embryos could be created solely for the purpose of embryo-destructive research (though stem cell lines derived from these sources would not be eligible for federal funding).

From the late 1970s until the early 1990s, federal policy was a de facto moratorium. In the late 1970s, the National Commission on Protection of Human Subjects recommended that Congress establish a permanent Ethics Advisory Board (EAB) to review any federally funded research involving in vitro embryos. This requirement became federal regulation. The EAB's 1979 report endorsed such research in principle, but its charter expired before it approved any specific proposals. The board was never reconstituted, yet the legal mandate for EAB approval remained, effectively blocking funding until 1993. That year, Congress—urged by newly elected President Bill Clinton—repealed the EAB requirement.

Clinton then tasked the NIH with developing guidelines. The NIH Human Embryo Research Panel's 1994 report recommended federal funding for embryo research. Clinton accepted most of the Panel's recommendations but rejected funding for embryos made exclusively for research. Preparations to implement funding were underway when Republicans gained control of Congress in 1994. In 1996, lawmakers attached the Dickey Amendment to the annual Labor-HHS appropriations bill. This rider prohibited federal funds for (1) creating human embryos for research or (2) research in which embryos are destroyed, discarded, or subjected to greater risk than allowed under relevant federal guidelines governing research involving human subjects. Reauthorized annually ever since, the amendment appeared to end Clinton-era efforts to open the door to federally funded embryo-destructive research.

The 1998 scientific breakthrough in deriving embryonic stem cells prompted a pivotal "creative" reinterpretation of the law. HHS's General Counsel under Clinton ruled that the Dickey Amendment barred only the use of federal money to *destroy* embryos. Once embryos were destroyed with private or state funds, subsequent research on the resulting stem cell lines was permissible. This narrow reading would have allowed funding to proceed, but the 2000 election intervened.

President George W. Bush, upon taking office in 2001, suspended pending initiatives for review. His August 9, 2001, policy balanced scientific opportunity with a robust ethical commitment. Legally, Bush agreed that the Dickey Amendment permitted funding for research on already-derived lines. His policy therefore authorized federal support only for

(1) non-embryonic ("adult") stem cell research and (2) embryonic stem cell lines derived before August 9, 2001, using nonfederal funds. Initially, more than sixty genetically diverse lines qualified; the number later reached seventy-eight, though only twenty-one proved usable due to scientific and intellectual-property barriers. By July 2007, the administration had allocated over $3.7 billion for eligible stem cell research, including $170 million specifically for embryonic lines, with nearly 1,000 shipments distributed to researchers. Later, the discovery of induced pluripotent stem (iPS) cells—reprogrammed from adult cells without embryos or eggs—prompted Bush to prioritize NIH funding for the most promising research on pluripotent cells, maximizing scientific progress while honoring ethical limits.

Congress twice passed bills to override Bush's restrictions and expand funding to new embryonic lines. He vetoed both. A separate measure supporting alternative (non-embryonic) sources passed the Senate overwhelmingly but stalled in the House. The President's Council on Bioethics issued balanced reports examining the policy and related issues, while the FDA assured stakeholders of its readiness to regulate resulting therapies.

On March 9, 2009, President Barack Obama rescinded Bush's executive actions and directed the NIH to fund embryonic stem cell research "to the extent permitted by law." Within 120 days, NIH guidelines limited eligibility to cell lines derived from IVF embryos originally created for reproduction but later donated because they were no longer needed. The rules excluded funding for embryos created solely for research due to lack of social consensus on this issue. Notably, neither Obama nor the NIH guidelines addressed the moral status of the human embryo.

This history illustrates how divergent presidential visions have produced a legislative stalemate punctuated by executive action, appropriations riders, and administrative reinterpretations. The Dickey Amendment remains in force, but successive administrations have interpreted and implemented it according to fundamentally different normative frameworks. The result is a policy landscape that continues to reflect the nation's debates over the moral standing of the human embryo and the proper limits of government-supported science in a pluralistic democracy.

Ethical Considerations

Drawing on modern embryology, we can say with certainty that an embryo is a complete, living, self-directing human organism—genetically distinct, integrated, and on a developmental trajectory toward maturity. The classical liberal principle of human equality at the heart of America's founding must apply without discrimination based on age, size, developmental stage, degree of dependency, or utility. The intentional destruction of human embryos for research violates this principle; creating embryos solely for destruction (by IVF or cloning) is even more objectionable.

In its policy considerations, the NIH should reject "contingent personhood" theories that would grant or withhold moral status according to others' judgments about capacities or

usefulness. Such an approach subverts equality by empowering the strong to decide the fate of the weak. This undermines our inalienable rights and risks adopting a sliding scale of legal protections based on cognitive ability or societal value. The NIH should also reject utilitarian arguments that would sacrifice embryos for potential therapies, even if personhood were granted, and refused to treat "spare" IVF embryos as mere raw materials simply because others had deemed them unwanted.

Practical Considerations

As of April 2026—28 years after their first derivation and 25 years after federal funding was authorized—there are no fully approved or marketed therapeutic applications derived from human embryonic stem cells (hESCs) anywhere in the world. In contrast, stem-cell based therapies based on sources that do not require the use and destruction of embryos (e.g., "adult" stem cells derived from more differentiated tissues such as bone marrow, placenta, and adipose cells, and "induced pluripotent state cells" derived from "reprogramming" adult cells to behave like embryonic stem cells) have shown great therapeutic promise.

Applications for adult stem cells include, for example, cardiomyocyte sheets/patches for severe heart failure due to ischemic cardiomyopathy[1], dopaminergic neural progenitor cells for Parkinson's disease[2], and ovarian support cells for ex vivo oocyte maturation to treat infertility.[3] Approved stem cell therapies globally are exclusively from adult sources (e.g., hematopoietic stem cells from bone marrow/cord blood for blood cancers, or certain mesenchymal stem cell products), not embryonic cells. Adult stem cells offer several clinical advantages, including easier generation of patient-specific (autologous) or HLA-matched allogeneic lines, reducing immune rejection and immunosuppression problems. Most importantly, they do not require embryo destruction, thereby avoiding the ethical problems that historically plagued research on embryonic stem cells.

In light of this, and given NIH's responsibility to carefully steward its limited resources, respect ethical boundaries, and to protect the consciences of American taxpayers in a pluralistic society, federal funding should focus on the kinds of stem cells that have been proven therapeutically beneficial (e.g., adult stem cells) and ethically acceptable (e.g., iPSCs), and eschew those (embryonic stem cells) that have failed to live up to previous promises and pose serious ethical problems.

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[1] "World's First iPSC-Derived Cardiomyocyte Therapy for Heart Failure Receives Conditional Approval in Japan," *CUORiPS*, March 6, 2026. https://cuorips.co.jp/en/news/2026/03/06/512/

[2] "iPSC Therapies Make History: Japan Authorizes World's First Two iPSC-based Cell Therapies," *BioInformant*, April 3, 2026, https://bioinformant.com/ipsc-therapies-make-history-japan-authorizes-worlds-first-two-ipsc-based-cell-therapies/

[3] "Gameto Presents Data Supporting Manufacturing Process for its In Vitro Maturation Solution for Fertility Care at 2024 International Society for Stem Cell Research Annual Meeting," *Gameto*, July 10, 2024. https://www.gametogen.com/news/gameto-presents-data-supporting-manufacturing-process-for-its-in-vitro-maturation-solution-for-fertility-care-at-2024-international-society-for-stem-cell-research-annual-meeting/

Aaron Kheriaty, MD
Director, Bioethics, Technology, & Human Flourishing Program
Ethics and Public Policy Center

O. Carter Snead, JD
Charles E. Rice Professor of Law
Concurrent Professor of Political Science
University of Notre Dame
Fellow, Ethics & Public Policy Center

65. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.

• hESC lines have been pivotal in a broad array of basic biological research studies including the use of genetically engineered lines, e.g. reporter lines, and expanding the genetic diversity as well as disease relevance with new hESC lines will provide for future advances.
• hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes, and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.
• New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

• hESC lines provide the "ground truth" of the earliest steps in human development because they are derived directly from the pre-implantation human embryo
• hESCs provide the only natural benchmark for defining human stem cells.
• hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
• Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
• The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The

choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
• Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
• hESCs cannot be replaced by current alternative technologies and are needed as a reference standard and a benchmark for future work and the development of these alternatives. Lack of this benchmark may slow technological advancement or create insufficient technologies.
• hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
• hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.
• Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.
• An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
• Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies
• Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.
• Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.
• Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our

ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

66. Anita Bhattacharyya

I am responding: On behalf of myself

Name: Anita Bhattacharyya

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC lines are irreplaceable to understand the "ground truth" of the earliest steps in human development. Because they are derived directly from the pre-implantation human embryo, hESCs provide the only natural benchmark for defining human stem cells.

As research tools, hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models. They provide the raw material for cell replacement therapies in many organ systems.

The original five hESC lines in 1998 (WA01, WA07, WA09, WA13, and WA14, or as they are commonly known, H1, H7, H9, H13, and H14) are the most common hESC lines used by researchers worldwide, clearly illustrating the impact that they have (PMID: 30388422). These lines continue to be the most accepted and best characterized hESCs for research.

The extensive library of well-characterized hESCs that has been built by the many researchers in the field is a demonstration of the necessity to continue federal support for hESC research. hESC lines have been used to generate sophisticated tools through genomic engineering. These lines are used to increase precision and efficiency in basic and disease related research. Demand for these cells will continue to increase as researchers strive to use newer, more advanced biotechnologies.

hESCs are the foundation of the translational pipeline to generate cell therapies. They are used to generate specialized cells to replace damaged, diseased, or dying tissue in patients, including applications in neurology, cardiology and diabetes. In fact, promising new cell therapies derived from hES cells are currently being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005). While there has been a decline in the number of cell lines submitted for review to be added to the NIH hESC Registry and NIH support for hESC research has stabilized, these data should not be interpreted as a decline in the need and utility of hESCs in research. As with any new technology, there is often a surge of demand for the novel technology, followed by a plateau or steady-state of demand. The federal NIH registry is less than two decades old, a short timeframe for widespread adoption of a new technology. By studying the examples, of AI, 3D printing and tissue engineering, some argue that 30 to 50 years is the realistic time between novel concept and widespread adoption

(https://doi.org/10.1016/j.matt.2019.10.011 and https://www.entrepreneur.com/leadership/the-pace-of-technological-change-is-faster-than-ever/386410).

New hES cell lines are essential for: (1) expanding and broadening the genetic backgrounds of the current hESC linesm (2) studying diseases with no alternate human models, (3) fertility research, since the beginning of human development is otherwise inaccessible. Stem cell research has resulted in important new breakthroughs in the treatment of infertility. hESC technology has led, and will continue to contribute to, a better understanding of human development, and perhaps even new ways to treat infertility and prevent miscarriages. For families who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, hESC-based approaches are promising.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs exhibit similar properties to hESCs in many respects, they also have distinct biological characteristics.

Human ESCs are critical for research on fertility. Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.The large number of genetically engineered hESC tools that are used in research would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.

hESCs provide the only reference for the development of alternatives. They provide a unique benchmark for future work and the development of alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating insufficient technologies.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

hESCs cannot be replaced by current alternative technologies. In fact, they provide an invaluable reference standard and a benchmark for future work and the development of these alternatives. Removing the opportunity to benchmark these new technologies with hESCs may have the effect of slowing technological advancement or creating technologies that are insufficient to meet the needs for the research or, potentially incorrect. The advent and use of induced pluripotent stem cells (iPSCs) does not and should not preclude the need and use of hESCs. hESCs cannot be separated from or replaced by iPSCs in the stem cell research enterprise.

While iPSCs have substantially expanded the field, they are reprogrammed derivatives of adult somatic

cells and do not fully replicate all epigenetic and developmental features of hESCs. iPSCs are more prone to harbor deleterious mutations, present in the donor cells, introduced in the reprogramming process or through stress of prolonged passaging, than hESCs. The effects of these mutations in research and more importantly, on future cell therapies, are currently unknown. The replacement of hESCs with iPSCs is premature.

Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development. A responsible strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Comprehensive epigenomics, multiomics, metabolic, and functional comparisons are necessary to fully define the differences between hESCs and hiPSCs or other potential alternative technologies. Secondly, methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research. The feasibility and timeline to meet all these requirements is unknown and would require substantial investment of funding.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

67. University of California system

I am responding: On behalf of an organization

Name: Deborah Motton

Name of Organization: University of California system

Type of Organization: Academic Institution

Role: Organizational Official

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Please see the attached comments from the University of California system.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Please see the attached comments from the University of California system.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Please see the attached comments from the University of California system.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Please see the attached comments from the University of California system.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/UC-Comments-on-NIH-RFI-on-hESC_final_4.20.2026.pdf

Description: Please see the attached comments from the University of California system.

UNIVERSITY OF CALIFORNIA

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OFFICE OF THE VICE PRESIDENT – RESEARCH AND INNOVATION

OFFICE OF THE PRESIDENT
1111 Franklin Street, 11th Floor
Oakland, California 94607-5200

Submitted via: https://osp.od.nih.gov/comment-form-reducing-reliance-on-human-embryonic-stem-cells-in-nih-supported-research/

April 21, 2026

NIH Office of Science Policy
6705 Rockledge Drive, Suite 630
Bethesda, MD 20892

RE: UC Response to NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

To Whom It May Concern:

I write on behalf of the University of California (UC) system in response to the NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells (hESC) in NIH-Supported Research issued on January 23, 2026.

The UC system is comprised of ten campuses, six academic health centers, an Agriculture and Natural Resources division, and three affiliated U.S. Department of Energy national laboratories. Our researchers have been central contributors to the development of stem cell science for more than 40 years, including in the derivation, characterization, banking, and clinical translation of hESC lines, as well as in the training of the next generation of stem cell scientists and physician-investigators.

While UC recognizes that NIH requested input on four specific questions in the RFI, we respectfully submit the following comments to provide NIH broader considerations as it reassesses the utility of hESCs in biomedical research. UC's comments are provided below.

1. **Response to the Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research**

Human embryonic stem cells (hESCs) remain essential to research because they are the most reliable and well-understood type of pluripotent stem cell. They provide a stable and consistent model for studying how human cells grow and specialize. Scientists use them as a reference point to evaluate newer stem cells and biotechnologies, including induced pluripotent stem cells (iPSCs). While these newer approaches are promising, they can vary in quality and stability and are often

compared to established hESC lines to ensure they perform as expected. In research areas such as early human development, reproductive health, and understanding certain diseases, hESCs continue to provide insights that other cell types cannot yet fully replicate.

hESCs have also played a leading role in the clinical advancement of stem cell-based therapies. Many early-stage clinical efforts have relied on hESC-derived products because they are well-characterized and supported by decades of research. This accumulated experience, including manufacturing methods, safety testing, and regulatory pathways, has created a strong foundation for translating stem cell science into patient treatments. Prematurely moving away from hESCs would likely slow this progress by requiring the field to rebuild that foundation using less mature technologies.

In addition, federal investment has supported the development of carefully tested hESC lines, standardized laboratory methods, and shared research infrastructure. These resources underpin ongoing studies and emerging therapies for conditions such as Parkinson's disease and diabetes. Reducing reliance on these established cell lines would not simply shift research to alternatives; it would disrupt active work, delay therapeutic development, and risk losing the knowledge and infrastructure built through decades of public investment.

While we do not support reducing reliance on hESCs in NIH-supported research at this time, if NIH determines that a future transition is warranted, we urge that such a transition be evidence-based and adequately resourced. We recommend that NIH:

- **Invest substantially in improving alternative models**, including research focused on genomic stability, epigenetic resetting, and reproducible differentiation.
- **Develop clear scientific benchmarks for equivalency**, using existing hESC lines as reference standards during any transition period.
- **Create a phased transition plan,** allowing ongoing projects and clinical translation efforts to proceed without disruption.
- **Sustain funding for workforce development and training**, ensuring that expertise in pluripotent stem cell biology is not lost during policy shifts.

Absent these measures, a rapid reduction in hESC use could take important tools away from the research community and diminish the return on decades of NIH-supported research.

2. **Response to the Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry**

The NIH Human Embryonic Stem Cell Registry (Registry) plays a critical role in ensuring that federally funded hESC research uses cell lines that meet established ethical and scientific standards. Over the past two decades, widely adopted differentiation protocols, genomic reference datasets, and validated reagents have been built around Registry-approved lines. By enabling researchers nationwide to use the same well-characterized materials, the Registry strengthens reproducibility, data comparability, and scientific rigor, and advances federal priorities on transparency and gold standard science, such as required in the Executive Order on Restoring Gold Standard Science.

A pause on new submissions would hinder scientific progress and clinical translation. Deriving, characterizing, and banking new lines, particularly those suitable for clinical-grade (GMP) production, is time- and resource-intensive. As stem cell-based therapies advance toward broader clinical use, demand for genetically stable, well-documented lines will increase. Preventing the addition of new hESC lines could constrain future therapeutic options and limit the ability of researchers to improve standards of quality and reproducibility over time.

Accordingly, we respectfully request that NIH continue to permit the submission and inclusion of new hESC lines to the NIH Human Embryonic Stem Cell Registry until a clear, scientifically validated, and adequately resourced pathway for alternative models is established.

Thank you for the opportunity to comment. We appreciate NIH's engagement with the research community on these complex issues and would welcome continued dialogue as the agency considers next steps related to the NIH Human Embryonic Stem Cell Registry and the future of hESC research in NIH-supported programs.

If you have any questions regarding these comments or would like additional information, please contact Agnes.Balla@ucop.edu and Timothy.Miller@ucop.edu.

Sincerely,



Deborah Motton, Ph.D.
Executive Director
Research Policy Analysis & Coordination
University of California, Office of the President

68. Society for Developmental Biology

I am responding: On behalf of an organization

Name: Michael Layden

Name of Organization: Society for Developmental Biology

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The existing lines have historically been understudied due to prior restrictions on research utilizing hESCs. As a result, many researchers focus their efforts on only a few of the hundreds of established and available lines. The lack of research, compared to the amount of work using iPSCs, makes it difficult to fully realize what gaps may require establishing additional hESC lines. Of particular concern is that it is unclear to what degree iPSC lines might have the same potency as hESCs. Similarly, direct comparisons of iPSC to hESC lines identified similarities in gene and protein expression that would be expected given both lines are pluripotent stem cells but also identified several distinct differences in protein levels particularly within critical metabolic pathways. Thus, iPSCs are not interchangeable with hESCs. Given the lack of research on hESCs compared to iPSCs and a full understanding about whether hESCs are replaceable, we strongly suggest avoiding a moratorium on the addition of newly derived hESC lines. We also suggest establishing criteria that outlines justifications for new lines, such as enhancing gene profiles compared to available lines, a new disease model, etc..

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
To date hESCs remain the best stem cells for generating embryoid bodies, in particular embryoids that resemble the earliest stages in development. While iPSCs are rapidly gaining traction for generating embryoid bodies, they have several limitations that make hESCs a superior model. Of particular concern is that the fact that the reprogramming protocol to generate iPSCs from somatic cells creates several irregularities that limit their potential compared to hESCs. iPSCs cells can: contain mutations accumulated during reprograming; retain epigenetic memory of their somatic origin; have chromosomal instabilities, which lead to genetic variability in resulting iPSCs. The variability becomes increasingly problematic when using iPSCs as disease models, as the variability can introduce false positive background signals that are unrelated to the disease causing mutation of interest. As such, hESCs remain the gold standard for creating embryo models.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
iPSCs are superior to hESCs when there are needs for patient specific cell lines, but still require benchmarking against hESCs in many disease models. Tissue specific adult stem cells can, in some cases, be used to generate cultured/synthetic/engineered organs. However, they can be challenging to recover or maintain in culture and because they display limited potential, they are not always capable of

generating organoids in culture. Thus, neither iPSCs or adult stem cells are justifiable replacements for hESCs at this time. In part, the challenge to fully addressing this prompt is the disproportionate amount of support that has been given to research using non-hESCs compared to hESCs. Thus, we lack the detailed comparisons between hESCs and
non-hESCs to determine how to develop alternative technologies as replacements to hESCS.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

To determine if it is possible to replace hESCs with other stem cell models there are several strategic areas of research that are important to invest in. We highlight key areas below.

1. Promote efforts to characterize the underutilized existing hESC lines. Our current understanding about the potential of hESCs is limited to studies in a few cell lines, with scant studies in many other cell lines. Enhanced characterization will allow a more accurate understanding of the potential of hESCs and facilitate efforts to identify which research areas would likely be unaffected by the exclusion of hESCs from further studies.
2. Support efforts to compare the epigenetic landscape, transcriptomes, metabolomes and proteomes of multiple existing hESC lines with iPSC lines to define a clear understanding about how similar hESCs and iPSCs are.
3. Extend the above comparisons to tissue specific adult cells including efforts to compare iPSC and hESC derived tissue specific adult stem cells to lines derived directly from their respective adult tissues.
4. Investments in efforts to determine if iPSCs can be effectively developed to generate early stage embryo models.
5. Support efforts to generate panels of lineage restricted stem cells that better reflect the genetic diversity of humans, which will be important for utilizing these cells to better predict health benefits of novel therapies at a population level.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/SDB-re-NIH-hESC.pdf

Description: The attached document contextualizes our responses to the prompts in a letter addressed to Lyric Jorgenson

SOCIETY FOR DEVELOPMENTAL BIOLOGY

6120 Executive Blvd. Suite 725, Rockville, MD 20852
T: (301) 634-7815 E: sdb@sdbonline.org
http://www.sdbonline.org
EIN: 38-1909157

April 22, 2026

Lyric Jorgenson, PhD
Associate Director for Science Policy
National Institutes of Health
6705 Rockledge Drive
Bethesda, MD 20817

RE: Response to Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

Dear Dr. Jorgenson,

The Society of Developmental Biology (SDB) is writing to provide feedback on your request for information about the use of hESCs in NIH-supported research. We appreciate the opportunity to share with you the importance of hESCs as a tool to better understand human development and disease. SDB is uniquely positioned to provide an important perspective regarding the use of hESCs, as many of our members utilize both hESCs and multiple sources of non-hESC stem cells in their research. Thus, we are able to provide insights on the current value of the various stem cell models and provide context about their shared and unique properties.

Our recommendation is that it is not prudent to replace hESCs with other stem cell sources at this time. Each category of stem cell lines have different strengths and challenges. We urge the NIH to consider prioritizing support that encourages expanding our investigations of existing hESC lines, which will provide the needed data to conclusively determine the extent to which we can rely on non-hESC derived cell lines for impactful biomedical studies. Below we provide specific responses to the provided prompts in the RFI.

Prompt 1: Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.

The existing lines have historically been understudied due to prior restrictions on research utilizing hESCs. As a result, many researchers focus their efforts on only a few of the hundreds of established and available lines. The lack of research, compared to the amount of work using iPSCs, makes it difficult to fully realize what gaps may require establishing additional hESC lines. Of particular concern is that it is unclear to what degree iPSC lines might have the same potency as hESCs. Similarly, direct

comparisons of iPSC to hESC lines identified similarities in gene and protein expression that would be expected given both lines are pluripotent stem cells but also identified several distinct differences in protein levels particularly within critical metabolic pathways. Thus, iPSCs are not interchangeable with hESCs. Given the lack of research on hESCs compared to iPSCs and a full understanding about whether hESCs are replaceable, we strongly suggest avoiding a moratorium on the addition of newly derived hESC lines. We also suggest establishing criteria that outlines justifications for new lines, such as enhancing gene profiles compared to available lines, a new disease model, etc..

Prompt 2: Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable;

To date hESCs remain the best stem cells for generating embryoid bodies, in particular embryoids that resemble the earliest stages in development. While iPSCs are rapidly gaining traction for generating embryoid bodies, they have several limitations that make hESCs a superior model. ***Of particular concern is that the fact that the reprogramming protocol to generate iPSCs from somatic cells creates several irregularities that limit their potential compared to hESCs***. iPSCs cells can: contain mutations accumulated during reprograming; retain epigenetic memory of their somatic origin; have chromosomal instabilities, which lead to genetic variability in resulting iPSCs. The variability becomes increasingly problematic when using iPSCs as disease models, as the variability can introduce false positive background signals that are unrelated to the disease causing mutation of interest. As such, hESCs remain the gold standard for creating embryo models.

Prompt 3: Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs;

iPSCs are superior to hESCs when there are needs for patient specific cell lines, but still require benchmarking against hESCs in many disease models. Tissue specific adult stem cells can, in some cases, be used to generate cultured/synthetic/engineered organs. However, they can be challenging to recover or maintain in culture and because they display limited potential, they are not always capable of generating organoids in culture. ***Thus, neither iPSCs or adult stem cells are justifiable replacements for hESCs at this time.*** In part, the challenge to fully addressing this prompt is the disproportionate amount of support that has been given to research using non-hESCs compared to hESCs. Thus, we lack the detailed comparisons between hESCs and non-hESCs to determine how to develop alternative technologies as replacements to hESCS.

Prompt 4: Research areas in which additional investments should be made to bolster validated models to replace use of hESCs;

To determine if it is possible to replace hESCs with other stem cell models there are several strategic areas of research that are important to invest in. We highlight key areas below.

1. Promote efforts to characterize the underutilized existing hESC lines. Our current understanding about the potential of hESCs is limited to studies in a few cell lines, with scant studies in many other cell lines. Enhanced characterization will allow a more accurate understanding of the potential of hESCs and facilitate efforts to identify which research areas would likely be unaffected by the exclusion of hESCs from further studies.
2. Support efforts to compare the epigenetic landscape, transcriptomes, metabolomes and proteomes of multiple existing hESC lines with iPSC lines to define a clear understanding about how similar hESCs and iPSCs are.
3. Extend the above comparisons to tissue specific adult cells including efforts to compare iPSC and hESC derived tissue specific adult stem cells to lines derived directly from their respective adult tissues.
4. Investments in efforts to determine if iPSCs can be effectively developed to generate early stage embryo models.
5. Support efforts to generate panels of lineage restricted stem cells that better reflect the genetic diversity of humans, which will be important for utilizing these cells to better predict health benefits of novel therapies at a population level.

SDB thanks the NIH for the opportunity to comment on the potential use of hESCs and their alternatives is biomedical research. We hope that we have provided clear advice about when hESCs are essential for discovery, and when alternatives to hESCs are appropriate choices. It would be prudent that any policies moving forward leave in place avenues to develop additional hESCs when scientifically justified.

Please do not hesitate to contact me if you have questions or would like SDB to provide additional information.

Sincerely,



Richard Behringer, PhD
SDB President
rrb@mdanderson.org

69. Shawn MacGregor

I am responding: On behalf of myself

Name: Shawn MacGregor

Name of Organization: University of Wisconsin Madison Waisman Center

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
I agree that research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed. They are already in use and cannot be 'put back'.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
I agree that research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable. While all levels of research are necessary in translational research, stem cell research is the logical step between animal models and clinical trials.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
I agree that research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs in some cases.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
I believe that research areas in which additional investments should be made to bolster the use of hESCs to validate their findings. Their research cannot be replaced.

70. Shelly Klingman

I am responding: On behalf of myself

Name: Shelly Klingman

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/22/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

71. Accelerated Biosciences Corp.

I am responding: On behalf of an organization

Name: Yuta Lee

Name of Organization: Accelerated Biosciences Corp.

Type of Organization: Industry (Biotech/Device/ Pharmaceutical Company)

Role: Organizational Official

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
There is an alternative stem cell line that can fully replace the use of hESCs.

Human trophoblast stem cells (hTSCs) are a uniquely robust, ethically sourced, embryonic-stage stem cell population derived from pre-placental tissue of ectopic pregnancies at 4–8 weeks post-fertilization, under IRB oversight and informed consent. They exhibit pluripotent-like developmental potential, expand to at least 85 population doublings (a single donor line can generate a theoretical cell output equivalent to the biomass of ~2 trillion humans), and express HLA-G, conferring natural immune privilege that makes them an ideal, scalable allogeneic platform.

Unlike induced pluripotent stem cells or adult stem cells, hTSCs sit at a developmental window that closely mirrors the early embryonic context historically modeled with hESCs, yet avoid the creation or destruction of viable embryos. hTSCs have already been manufactured under GMP, demonstrating that they can be banked, standardized, and distributed as a stable, renewable source of early embryonic–stage biology for NIH-supported research and therapeutic development.

In collaboration with the National Institute on Aging, the secretome of hTSCs (including their extracellular vesicles) was recently shown to attenuate senescence-associated traits, directly linking this platform to NIH's priorities in aging, multimorbidity, and longevity science. This work illustrates that hTSC-derived products can recapitulate key functional attributes sought from hESC-based systems while operating within a more acceptable ethical and regulatory framework.

Given their embryonic-stage biology, unlimited scalability, inherent immune privilege, and demonstrated impact on fundamental aging mechanisms, hTSCs are exceptionally well-positioned to replace hESCs in many research domains. Targeted NIH encouragement and support for hTSC-focused programs and

comparative studies would accelerate the transition away from hESC dependence while preserving and enhancing the scientific capabilities available to the research community.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Human trophoblast stem cells (hTSCs) are a validated, GMP-ready, embryonic-stage stem cell platform with demonstrated robustness, genetic stability, and functional impact on senescence and systemic aging biology. Additional NIH investment should focus on four translational research areas where hTSC-based models can both replace hESCs and materially advance human health:

Validated hTSC Platforms for Aging and Multimorbidity Models

Expand mechanistic and interventional studies using hTSC-derived secretome/extracellular vesicles (EVs) to model and modulate hallmarks of aging (senescence, SASP, chronic inflammation, metabolic drift, immune dysfunction).

Fund multi-center, standardized hTSC-EV reference studies (proteome, miRNome, and functional assays) as direct comparators to legacy hESC-based models in geroscience, including cross-tissue and multi-organ readouts.

Develop hTSC-based "systems aging" models (in vitro and in vivo) to evaluate candidate longevity interventions in place of hESC-derived systems.

Immune–Metabolic Disease and Autoimmunity Platforms (e.g., Type 1 Diabetes)

Support hTSC-EV–based models and interventions in type 1 diabetes and other autoimmune/metabolic indications, where functional data already show protection of human beta cells and enhanced survival/proliferation under toxic conditions.

Build standardized hTSC-derived immune/metabolic co-culture models (beta cell–immune cell, adipocyte–macrophage, hepatocyte–lipoprotein) to replace hESC-derived endocrine and immune lineages in early-stage immune–metabolic research.

Invest in comparative studies testing hTSC-EVs versus hESC-derived cells for restoring tissue function and immune tolerance in autoimmune settings.

Neurological and Neurodegenerative Disease Models

Develop hTSC-based neuroprotection and neuroregeneration models, leveraging their secretome's enrichment in neurorelevant proteins and miRNAs to support neuron survival, synaptic plasticity, myelination, and glial function.

Fund head-to-head studies where hTSC-EVs replace or complement hESC-derived neural cells and organoids for modeling neuroinflammation, white matter injury, and age-related neurodegeneration.

Create standardized hTSC-EV toolkits and protocols for academic investigators (dosing, routes of administration, in vitro paradigms) to accelerate adoption as a routine alternative to hESC-based neuro models.

Organ Repair, Fibrosis, and Wound Healing / Tissue Remodeling

Invest in hTSC-based platforms for cardiac, musculoskeletal, and multi-organ repair, focusing on fibrosis resolution, ECM remodeling, angiogenesis, and functional tissue recovery.

Support the use of hTSC-EVs in validated models of osteoarthritis, degenerative disc disease, tendon injury, chronic wounds, and post-ischemic organ damage, with the explicit aim of replacing hESC-derived mesodermal lineages.

Prioritize studies that define dosing, safety margins, and pharmacodynamics of hTSC-EVs across multiple organ systems to establish them as a generalizable, hESC-sparing regenerative tool.

Standards, Repositories, and Comparative Evaluation Frameworks

Establish NIH-supported reference banks of well-characterized hTSC lines and hTSC-derived EV preparations, with open access for qualified investigators, analogous to past investments in hESC and iPSC repositories.

Fund systematic side-by-side comparisons of hTSC-, iPSC-, adult stem cell–, and hESC-based models across key domains (aging, immune–metabolic disease, neurodegeneration, organ repair) to formally validate when hTSCs can replace hESCs without loss of biological fidelity.

Develop consensus guidelines and best practices for hTSC use in NIH-supported research, including ethical sourcing, manufacturing, quality control, and data standards, to de-risk broad adoption.

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The Secretome of Human Trophoblast Stem Cells Attenuates Senescence-Associated Traits

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ABSTRACT

Senescent cells display indefinite growth arrest and a pro-inflammatory, senescence-associated secretory phenotype (SASP). As the accumulation of senescent cells in tissues with age plays detrimental roles in age-related pathologies, there is much interest in finding therapeutic strategies to eliminate them or suppress the SASP. In this study, we investigated the impact of the secretome and extracellular vesicles (EVs) derived from human trophoblast stem cells (hTSCs) on senescent human fibroblasts. We found that the hTSC conditioned medium (hTSC-CM), and in particular the EVs (hTSC-EVs), significantly reduced the levels of mRNAs encoding SASP factors and the secretion of SASP factors including CXCL1, IL8, and GDF15. Proteomic analysis of hTSC-CM and EVs indicated an enrichment in proteins involved in cell adhesion, tissue repair, and remodeling of the extracellular matrix (ECM). Furthermore, incubation of senescent cells with hTSC-EVs attenuated DNA damage and inflammatory signaling, at least in part by suppressing the function of NF-κB, a major transcriptional regulator of the SASP program. Our findings underscore the value of hTSC-CM and EVs therein in therapeutic approaches directed at senescent cells.

1 | Introduction

Cellular senescence is a state of persistent cell cycle arrest in response to various stressors, including DNA damage, oxidative injury, and telomere shortening (Blagosklonny 2023; Kumari and Jat 2021). Key features of senescent cells include aberrant organelle function, morphological changes, and the acquisition of a senescence-associated secretory phenotype (SASP). The SASP is largely orchestrated by signaling pathways that activate the transcription factor NF-κB, in turn initiating a program to synthesize pro-inflammatory molecules, matrix-remodeling metalloproteases, and growth factors (Ohtani 2022; Zhao et al. 2024). While cell senescence and the SASP contribute beneficially to tissue repair, immune surveillance, and tumor suppression at younger ages, they contribute detrimentally to aging and age-related diseases later in life (Ohtani 2022; Zhao et al. 2024). In this regard, the accumulation of senescent cells in aged tissues can aggravate pathologies including neurodegeneration, cancer, and cardiovascular diseases (Shreeya et al. 2024; Baar et al. 2017; Kovacic et al. 2011; Wang et al. 2024). As the SASP is the main damaging component of the senescent cell secretome (Basisty et al. 2020), there is heightened interest in developing therapeutic strategies aimed at selectively eliminating senescent cells and/or modulating the SASP to alleviate its harmful effects (Roger et al. 2021; Rossi and Abdelmohsen 2021; Zhao et al. 2024).

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Extracellular vesicles (EVs) are small particles enclosed by a lipid bilayer and are secreted by most cell types. EVs contain DNA, RNA, lipids, and proteins, and can mediate cell-to-cell communication and influence gene expression patterns in recipient cells (Kumar et al. 2024). Recent studies have highlighted the critical roles of EVs as key mediators of the SASP, with increased production and altered cargoes contributing to both the beneficial and detrimental effects of the SASP (Wallis et al. 2020). For example, EVs secreted from senescent cells promote paracrine senescence in neighboring cells by delivering interferon-induced transmembrane protein 3 (IFITM3) (Borghesan et al. 2019; Estévez-Souto et al. 2023). Additionally, small extracellular vesicles (sEVs) secreted by senescent cells, enriched in reactive oxygen species (ROS)-induced EphA2, can promote cancer cell proliferation (Takasugi et al. 2017).

However, the detrimental effects of the SASP can be counteracted by opposing secretomes from other cells. For example, there is growing evidence that the beneficial effects of stem cells, such as the suppression of senescence-associated inflammation and the promotion of tissue repair, are largely mediated through their secretome, which includes both soluble factors and EVs (Praveen Kumar et al. 2019). In addition, heterochronic parabiosis studies showed that exposure to a young systemic environment rejuvenates old tissues by restoring regenerative signaling through circulating factors (EVs and non-EV particles) without the need for stem cell engraftment (Conboy et al. 2005). Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) can suppress inflammation, accelerate muscle regeneration, and enhance proliferation, providing protection against cellular senescence in mouse models of muscle injury (Sandonà et al. 2021). MSC-EVs reverse senescent cell phenotypes by lowering the production of senescence proteins p16, p21, and p53, by restoring the balance between pro- and anti-inflammatory cytokines, and by reducing oxidative damage and counteracting age-associated mitochondrial dysfunction (Gorgun et al. 2022). The anti-senescence properties of MSC-EVs appear to be elicited through the transfer of specific microRNAs or proteins that modulate senescence-associated pathways (Xiao et al. 2022; Alfonzo et al. 2022; Motlagh et al. 2024). These findings highlight the potential value of MSC-EVs in the development of senotherapeutic strategies aimed at mitigating the effects of aging and age-related diseases (Dorronsoro et al. 2021). Unfortunately, the wide use of MSC-EVs is hindered by several limitations, particularly poor immune tolerance towards MSC-EVs and the difficulty in scaling up their production.

In contrast, human trophoblast stem cells (hTSCs) can be produced at scale, as they divide rapidly. Additionally, TSCs exhibit immune privilege due to the expression of HLA-G, which has important therapeutic value (Contini et al. 2020). However, the secretome of hTSCs and associated EVs has not been studied in the context of senescence. Here, we investigated the impact of the hTSC secretome (conditioned medium, CM) and EVs therein on WI-38 fibroblasts, derived from human lung. After triggering senescence in WI-38 fibroblasts by exposure to ionizing radiation (IR) or etoposide (Eto), incubation with hTSC-CM lowered the expression levels of SASP-associated transcripts (*IL8*, *CXCL1*, *GDF15*, *TGFB1*, *BAFF*, and *ICAM1* mRNAs). A similar reduction was observed following incubation with hTSC-EVs. Proteomic analysis of the senescent WI-38 cell secretome confirmed that the corresponding proteins and other SASP factors were similarly reduced. Proteomic characterization of the hTSC-CM and hTSC-EVs revealed an enrichment of proteins involved in proliferation and extracellular matrix remodeling. Moreover, treatment with hTSC-CM and hTSC-EVs reduced IR-induced DNA damage and phosphorylation of NF-κB, a key regulator of the SASP program. These results highlight the potential of hTSC-CM and EVs as therapeutic agents to mitigate senescence and its associated effects, underscoring their potential value for combating age-associated diseases.

2 | Results

2.1 | hTSC-CM Suppresses SASP mRNAs

Passage 7 hTSCs grew robustly in culture, as assessed on phase-contrast micrographs (Figure 1a), and were a highly pure population, displaying canonical stem cell markers CD90 and CD105 (> 95% positive) and minimal levels of the pan-hematopoietic marker CD45 (1.05% positive), as assessed by flow cytometry (Figure 1a). These features persisted through passages 11 and 19 (Figure S1a). To evaluate the impact of hTSC-CM on senescent cells, we prepared conditioned medium (CM) collected from hTSCs (Methods) and used fresh, non-conditioned medium (NCM) in control incubations. We triggered senescence employing a well-established cell model, human diploid WI-38 fibroblasts, using two different paradigms. In one, WI-38 fibroblasts were exposed to ionizing radiation (IR, 10 Gy) once on Day 1 after plating (Day 0); IR causes single- and double-strand breaks on the DNA that promote senescence and activate NF-κB, which in turn increases the transcription of genes encoding SASP factors. Immediately after exposure to IR, cells were incubated for 5 days with either hTSC-CM or NCM, refreshing the medium on Day 3, as shown (Figure 1c). In the other, etoposide (Eto, 50 μM) was added to the culture medium on Day 1, and refreshed on Day 3; cells were collected on Day 5. The continuous exposure to Eto stabilizes TOP2-DNA cleavage complexes in cells, which generates double-strand DNA breaks that promote senescence, activate NF-κB, and enhance the SASP trait. Along with the addition of Eto, WI-38 fibroblasts also received NCM or hTSC-CM on Days 1 and 3 (Figure 1c).

To evaluate the effect of hTSC-CM relative to the control incubation (NCM) on senescence traits, we performed several measurements. By Day 5, IR-treated fibroblasts incubated with hTSC-CM displayed lower percentages of cells positive for senescence-associated β-galactosidase activity (SA-β-Gal) than fibroblasts incubated with NCM (Figure 1d); likewise, both the density and numbers of IR-treated fibroblasts increased when cultured in hTSC-CM as compared to NCM (Figure S1b). By Day 5, IR-treated fibroblasts cultured in hTSC-CM or NCM were collected, and reverse transcription (RT) followed by quantitative (q)PCR analysis was used to measure the levels of several mRNAs. As shown, fibroblasts cultured with hTSC-CM expressed higher levels of *MKI67* mRNA, encoding the proliferation marker Ki-67 (Mansfield et al. 2024), than fibroblasts cultured in NCM (Figure S2c). Conversely, the levels of

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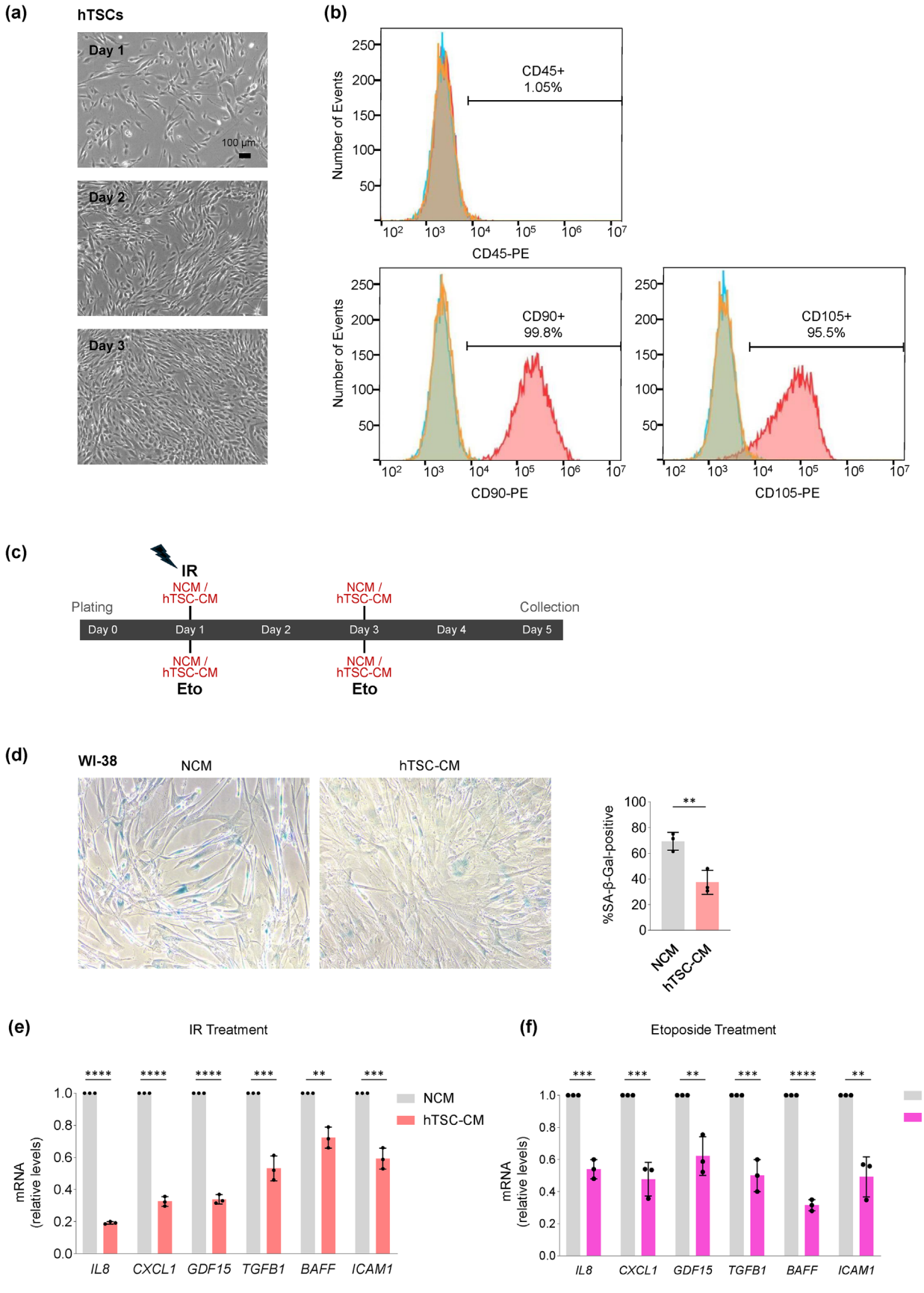


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FIGURE 1 | Incubation with hTSC-CM reduces the levels of SASP mRNAs in senescent WI-38 fibroblasts. (a) Phase-contrast micrographs of hTSCs (passage 7) on three consecutive days of culture (Days 1–3). (b) Flow cytometry analysis of surface markers of hTSCs at passage 7 using antibodies recognizing stem cell markers CD90 and CD105, and the pan-hematopoietic marker CD45 (to identify possible contamination). (c) Experimental timeline and workflow for inducing senescence in WI-38 human lung fibroblasts by a single exposure to ionizing radiation (IR, 10 Gy) or by continuous treatment with etoposide (Eto), incubated in the presence of non-conditioned medium (NCM) or conditioned medium from hTSC (hTSC-CM) from Day 1 to Day 5; on Day 3, NCM or hTSC-CM was refreshed with nothing additional (IR group) or with fresh Eto (Eto group). On Day 5, cells were harvested for analysis. (d) Senescence-associated β-galactosidase (SA-β-Gal) activity in WI-38 cells on Day 5 after IR, comparing the effect of culture in hTSC-CM or NCM as visualized on micrographs (*left*) and quantified (*right*) to represent % SA-β-Gal-positive WI-38 cells relative to total cells per field. (e, f) WI-38 cells were exposed to IR (e) or Eto (f) and then incubated in either NCM or hTSC-CM for 5 days, whereupon the levels of SASP-related mRNAs were measured by RT-qPCR analysis and normalized to the levels of *GAPDH* mRNA. Data in (d-f) represent the means ±SEM. Statistical significance (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$) was assessed using Student's *t*-test.

SASP-related transcripts, including *IL8*, *CXCL1*, *GDF15*, *TGFB1*, *BAFF*, and *ICAM1* mRNAs, were significantly lower in WI-38 cells incubated with hTSC-CM than in cells incubated with NCM (Figure 1e).

We validated the specificity of the effects of hTSC-CM after triggering senescence in WI-38 cells by exposure to Eto following the same timeline as for IR (Figure 1c). Similarly to what was seen after IR, incubation with hTSC-CM markedly decreased the levels of SASP-associated transcripts after Eto-induced senescence, as compared with incubation with NCM (Figure 1f). Collectively, these findings indicate that in cells induced to undergo senescence, incubation with hTSC-CM dampened senescence traits, as it reduced growth arrest, SA-β-Gal activity, and the expression of mRNAs encoding SASP factors.

2.2 | Reduced Expression and Secretion of SASP Factors by Fibroblasts Treated With hTSC-CM

To comprehensively evaluate the effects of hTSC-CM on senescent cells, we conducted high-throughput analysis of the transcriptome and secretome of WI-38 cells after exposing them to senescence-inducing damage and culturing them in hTSC-CM or NCM. Following exposure to IR, WI-38 fibroblasts were incubated with hTSC-CM or NCM; on Day 5, RNA-sequencing (RNA-seq) analysis (GSE282054) revealed a broad reduction in the levels of SASP-associated mRNAs in WI-38 fibroblasts incubated with hTSC-CM relative to those incubated in NCM. Among the reduced mRNAs in fibroblasts incubated with hTSC-CM were those that encode SASP factors (*CXCL1*, *IL8*, and *GDF15* mRNAs), and particularly several matrix metalloproteinases (*MMP1*, *MMP3*, and *MMP9* mRNAs), known mediators of inflammation, extracellular matrix remodeling, and tissue damage (Figure 2a and Table S1). Gene Ontology (GO) analysis of mRNAs showing reduced abundance, performed using ShinyGO, revealed that several biological pathways associated with the SASP were affected by incubation with hTSC-CM, including the CXCR chemokine receptor binding pathway, metalloendopeptidase activity, cytokine activity, and signaling receptor ligand activity (Figure 2b). GO analysis of mRNAs showing increased abundance indicated an enrichment in pathways involved in ECM collagen, plasma membrane signaling, and structural integrity (Figure S1). These findings suggest that culture with hTSC-CM not only suppressed SASP-related inflammation but it also actively promoted ECM integrity, fostering a more regenerative cellular environment.

To further assess the impact of hTSC-CM on the secretion of SASP factors, we performed Olink proteomic analysis to compare the secretory profiles of WI-38 fibroblasts cultured in hTSC-CM relative to those cultured in NCM (Table S2). Several pro-inflammatory cytokines, including IL6, GDF15, and CXCL1, were less abundant in the hTSC-CM-treated group (Figure 2c), mirroring the RNA-seq data, and suggesting a coordinated suppression of both mRNAs encoding SASP factors and the secretion of such SASP factors by senescent WI-38 cells in the presence of hTSC-CM. Several other proteins were more abundantly secreted by WI-38 cells after incubation with hTSC-CM (Figure 2d), suggesting a broad reprogramming of the secretory profile.

The results obtained using the Olink platform were further evaluated by Bio-Plex analysis. In the same paradigm of fibroblasts treated with IR and incubated with hTSC-CM or NCM, Bio-Plex analysis confirmed a reduction in the levels of individual SASP factors (IL6, IL8, GDF15, MMP3, and others) after incubation with hTSC-CM (Figure 2e). Collectively, these findings support the notion that hTSC-CM broadly suppresses the production and secretion of SASP factors by senescent fibroblasts.

2.3 | Characterization of the hTSC-CM

To understand how hTSC-CM might suppress the SASP, we comprehensively analyzed the protein content in hTSC-CM using Olink proteomics, cytokine arrays, and Bio-Plex multiplex assays, as outlined in Figure 3a. Olink proteomic analysis followed by CellMarker analysis revealed that a number of diverse cell types contributed to the proteome present in hTSC-CM, including stem cell cartilage, stem adipose cells, and bone marrow stem cells (Figure 3b). This analysis further highlighted the presence of proteins linked to stemness and regenerative potential across diverse tissue types in hTSC-CM. Olink analysis revealed several proteins that were abundant in NCM and reduced in hTSC-CM (blue), suggesting that they were eliminated or internalized by hTSCs, and several other proteins that were enriched in the hTSC secretome (red), suggesting that they were actively secreted or less internalized by hTSCs (Figure 3c, *left*); the latter group included proteins PTX3, MMP1, COL1A1, COL6A3, IL6, IL8, CXCL3,

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and VEGFA (Figure 3c, *right*; Table S3). Functional analysis of the hTSC secretome identified pathways such as growth factor activity, extracellular matrix, cytokine receptor binding, cytokine activity, signaling, and cell adhesion (Figure 3d). These pathways suggest that the hTSC-CM can potentially play roles in cell growth and ECM remodeling.

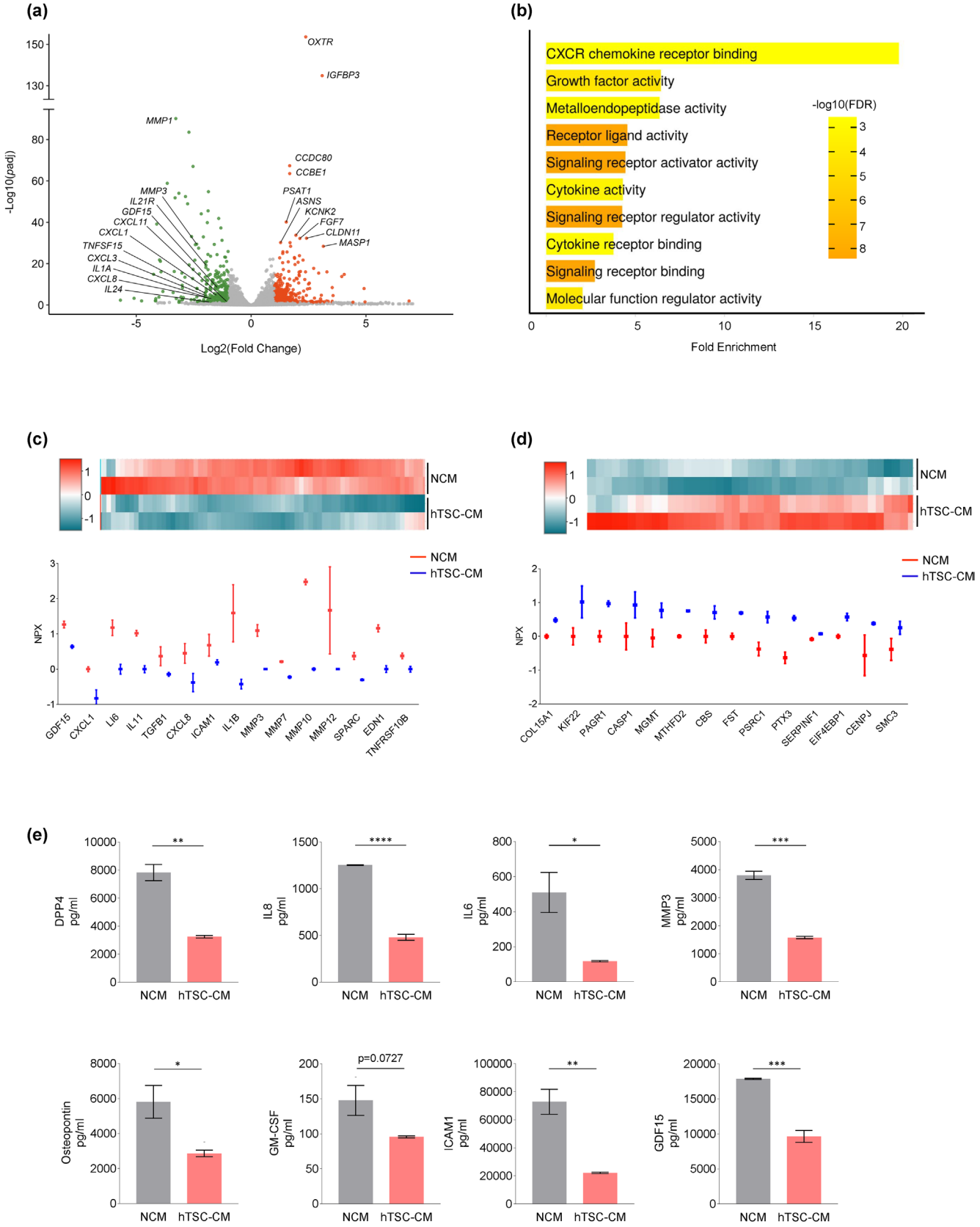


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FIGURE 2 | Broad suppression of production and secretion of SASP factors in IR-treated WI-38 fibroblasts incubated in hTSC-CM. (a) Volcano plot summarizing RNA-seq analysis of the relative abundance of SASP-related mRNAs in WI-38 cells that were exposed to IR and then cultured with either hTSC-CM or NCM. (b) Those mRNAs from panel (a) showing reduced expression in the hTSC-CM relative to NCM were used to identify pathways enriched by Gene Ontology (GO) using ShinyGO. (c, d) Olink normalized proteomic analysis (NPX) of proteins less abundant [shown in green (c)] or more abundant [shown in red (d)] in the secretome of IR-treated WI-38 cells by 5 days following culture with hTSC-CM relative to NCM. *Top*, heatmaps of the analysis; *bottom*, subsets of the secreted factors. (e) Measurement of SASP factors (DPP4, IL8, IL6, MMP3, ICAM1, and GDF15) secreted by irradiated WI-38 cells that were cultured in hTSC-CM or NCM using Bio-Plex. Data in (e) represent the means ±SEM. Statistical significance (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$) was assessed using Student's *t*-test.

To complement the Olink proteomic analysis, we performed protein array and Bio-Plex analyses. The protein array analysis confirmed the enrichment of several key proteins, including PTX3, IL8, SERPINE1, and DKK1, in hTSC-CM (Figure 3e). A longer exposure of the protein array (Figure S2a) indicated additional proteins in hTSC-CM, such as IGFBP2, MCP-1, MIF, BSG, and VEGFA. Interestingly, fibroblast growth factor 2 (FGF2) and platelet-derived growth factor (PDGF) were less abundant in hTSC-CM than in NCM (Figure 3e, Figure S2a), suggesting that these proteins were degraded or taken up by the cells. Bio-Plex analysis (Figure 3f) indicated an enrichment of MMP3, CXCL1, and IL8 in the hTSC-CM, while senescence-associated secreted factors such as DPP4 and GPNMB remained unchanged, indicating selectivity in the protein composition in hTSC-CM. A summary of proteins enriched in hTSC-CM in the protein array and Bio-Plex assays is presented in Figure S2b. Together, these results characterize the protein content of the hTSC-CM secretome, highlighting protein profiles related to stemness and to potential roles in cell growth and tissue repair.

2.4 | hTSC-EVs Suppress SASP mRNAs

As described above, treatment with the hTSC-derived secretome (CM), which includes both EVs and soluble non-EV factors, led fibroblasts undergoing senescence to express reduced levels of SASP-related mRNAs and to secrete lower concentrations of SASP factors. To dissect the specific contribution of hTSC-EVs, we isolated EVs from the hTSC secretome using size exclusion chromatography (SEC). Fractions 7 to 13 were enriched in soluble proteins, as shown by the protein concentration peaks in the SEC chromatogram (Figure 4a), while fractions 2 to 4 were largely devoid of soluble proteins and instead contained EVs, as identified by their distinct elution profile (Figure 4b). These EV-enriched fractions (fractions 2 to 4) were pooled, concentrated using a 3-kDa cutoff filter, and analyzed for size distribution and particle concentration using NanoFCM, which confirmed particle sizes distributing mainly in the range of 50–150 nm, consistent with the sizes of small EVs such as exosomes (Figure 4c). The identity and morphology of the isolated hTSC-EVs were confirmed using transmission electron microscopy (TEM), which identified spherical, membrane-enclosed vesicles with diameters averaging ~80 nm, exhibiting a well-defined lipid bilayer typical of EVs (Figure 4d). Further characterization of the surface markers of EV-associated proteins using an ExoView instrument detected a robust presence of canonical EV markers CD63, CD81, and CD9 (Figure 4e). The negligible mIgG signal confirmed the specificity of the assay, while the low CD41a signal indicated minimal contamination from platelet-derived particles (Figure S3a); individual marker channels revealed the heterogeneity in marker expression (Figure S3b). To assess EV uptake, WI-38 fibroblasts were incubated for 24 h with PKH26-labeled hTSC-EVs; uptake was confirmed by intracellular fluorescence (Figure 4f).

To evaluate the functional impact of hTSC-EVs on the SASP, WI-38 fibroblasts were irradiated with 10 Gy and immediately afterwards they were incubated with hTSC-EVs at a concentration of 10^{10} particles/mL (Day 1). EV treatment was refreshed once 48 h later (Day 3), as outlined in Figure 4g, and cells were harvested on Day 5 after IR to carry out RNA analysis. Phase-contrast micrographs indicated that culture with hTSC-EVs did not significantly alter cell morphology or density compared to untreated, irradiated control cells (Figure 4g *bottom*). However, RT-qPCR analysis revealed a significant reduction in the levels of mRNAs encoding SASP factors, including *IL8*, *GDF15*, and *CXCL1* mRNAs, in hTSC-EV-treated cells compared to controls (Figure 4h). These findings support the notion that hTSC-EVs effectively reduce the levels of SASP-associated mRNAs in recipient cells, suggesting a potential role in mitigating inflammation and tissue remodeling associated with cellular senescence.

2.5 | hTSC-EVs Are Enriched in Proteins Downregulated in Senescence

For a more comprehensive understanding of hTSC-EVs, we performed mass spectrometry (MS) analysis (MassIVE MSV000096320). The enrichment of stem cell-derived proteins in the EVs was evaluated by the cell marker score; as shown in Figure 5a, the proteins present in hTSC-EVs were scored as mesenchymal stem cells, trophoblasts, and placental stem cells, confirming that the hTSC-EVs analyzed maintained their global stem cell features. The cellular components and structural functions of the proteins identified in the hTSC-EVs were then examined. GO analysis revealed that these proteins are associated with extracellular organelles, vesicles, and exosomes (Figure 5b), and they are also associated with focal adhesions, cell-substrate junctions, and anchoring junctions, which are critical for cell adhesion and communication with the surrounding ECM (Figure 5b). Regarding molecular functions, hTSC-EV proteins were enriched in extracellular matrix structural constituents, suggesting roles in ECM maintenance and stability (Figure 5c). MS analysis further identified a range of collagen types and ECM-related proteins, such as Collagen alpha-3(VI) chain, MMP2, Thrombospondin-1 (TSP1), and Agrin (Figure 5d, Table S4).

Next, we integrated data from the Olink and mass spectrometry (MS) analyses to identify proteins present in both the EV and

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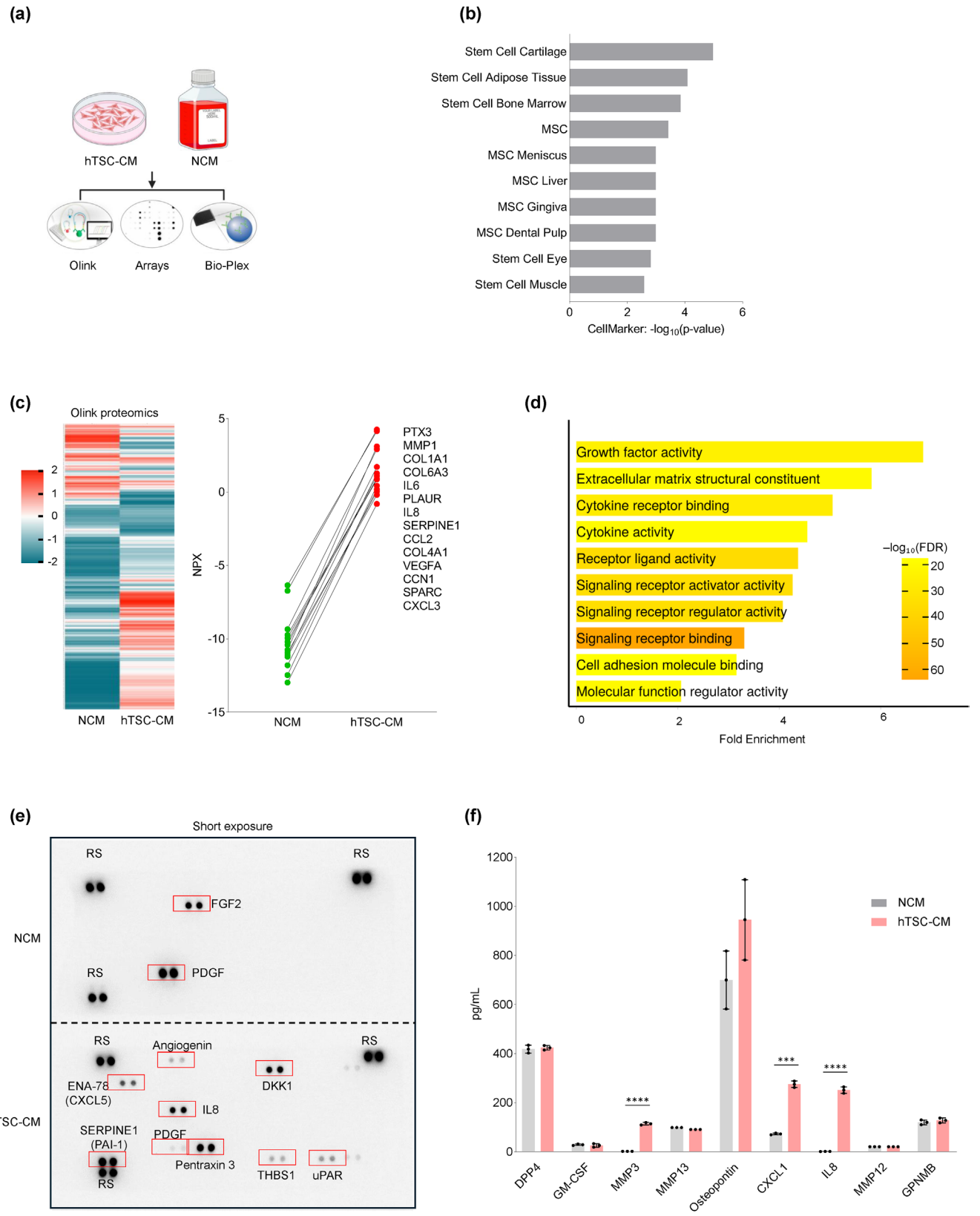


FIGURE 3 | Characterization of the secretome in hTSC-CM. (a) The proteins present in hTSC-CM and NCM were quantified by Olink proteomic, protein array, and Bio-Plex analyses. (b) CellMarker analysis of protein profiles associated with stem cell types identified from Olink proteomic analysis of hTSC-CM compared to NCM. (c) Heatmap of the Olink proteomic datasets in NCM and hTSC-CM (*left*); normalized expression of proteins (NPX) more highly abundant in hTSC-CM compared to NCM in the Olink dataset (*right*); details in Table S3. (d) GO enrichment analysis of hTSC-CM proteins. (e) Protein array (human cytokine antibody array) analysis of hTSC-CM compared to NCM; red rectangles, select differentially abundant proteins (low exposure); see Figure S2a for long exposure. (f) Bio-Plex analysis to quantify secreted proteins enriched in hTSC-CM compared to NCM. Data in (f) represent the means ±SEM. Statistical significance (***$p < 0.001$; ****$p < 0.0001$) was assessed using Student's *t*-test.

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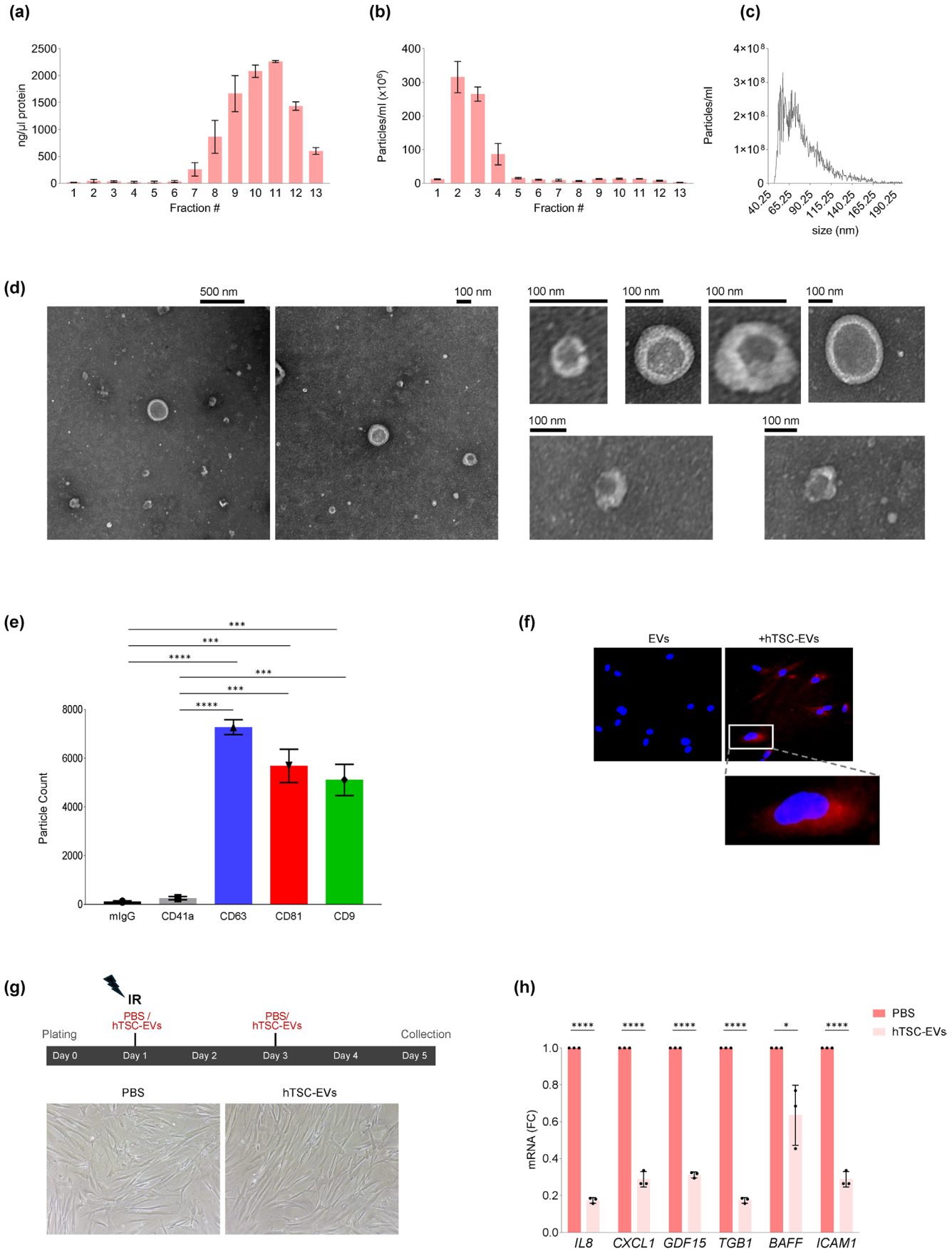


FIGURE 4 | Legend on next page.

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FIGURE 4 | Characterization of EVs in hTSC-CM and impact on the levels of SASP mRNAs in senescent WI-38 fibroblasts. (a) Size exclusion chromatography (SEC) profile of hTSC-CM, showing protein concentration peaks in fractions 7 through 13. (b) SEC elution profile of hTSC-EVs, identifying EV-enriched fractions 2 through 4. (c) Nanoparticle tracking analysis (NanoFCM) of hTSC-EV size distribution and particle concentration, confirming a size range of 40–150 nm. (d) Transmission electron microscopy (TEM) images of hTSC-EVs, displaying spherical, membrane-enclosed vesicles. (e) ExoView analysis of hTSC-EV particle count with surface markers CD63, CD81, and CD9. (f) IR-treated WI-38 cells were incubated for 24 h with PKH26-labeled EVs derived from hTSCs-CM. Red fluorescence, PKH26-labeled hTSC-EVs in WI-38 fibroblasts. White box, magnified view of a single cell. (g) *Top*, experimental timeline and workflow of WI-38 cells irradiated (10 Gy) on Day 1 and immediately cultured with purified hTSC-EVs at 10^{10} particles/mL (or with control vehicle, PBS); fresh hTSC-EVs or PBS were added on Day 3 and cells were harvested on Day 5 after IR for RNA analysis. *Bottom*, representative micrographs of IR-treated WI-38 cells 5 days after incubation with hTSC-EVs or PBS, to ascertain cell morphology and density. (h) Levels of SASP-related mRNAs in IR-treated WI-38 cells incubated with hTSC-EVs or PBS; RT-qPCR analysis was performed on RNA collected on Day 5 after IR, and data were normalized to *GAPDH* mRNA levels. Data in (a, b, e, h) represent the means ±SEM. Statistical significance (*$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$) was assessed using Student's *t*-test.

non-EV fractions of the hTSC secretome, and we examined their relevance to cellular senescence. Interestingly, we found 148 proteins enriched in the hTSC secretome (Figure 5e, Table S5) that were previously reported to be downregulated in senescent cells (Munk et al. 2021), including Lamin B1 (LMNB1) and Heterogeneous nuclear ribonucleoprotein C (HNRNPC), which play roles in nuclear structure and RNA processing, respectively. These findings suggest that hTSC-EVs contain proteomes rich in stem cell- and ECM-related factors and may potentially restore proteins that are lost or reduced in senescent cells.

2.6 | hTSC-CM and EVs Suppress DNA Damage and NF-κB Activity

In senescence, DNA damage (as triggered by IR or Eto) is tightly interconnected with signaling leading to the activation of the transcription factor NF-κB, which in turn amplifies the SASP. We thus hypothesized that hTSC-CM and EVs may broadly impact senescence by interfering with NF-κB activation.

To assess DNA damage in WI-38 cells after IR, we performed the Comet assay, which measures the extent of unrepaired DNA in the form of fast-migrating tails (comets). In IR-treated cells that were incubated with NCM, comets showed longer and brighter tails, indicating higher levels of DNA damage. In contrast, IR-treated cells that were incubated with hTSC-CM showed shorter, less intense tails, suggesting reduced DNA damage (Figure 6a). Following IR treatment of WI-38 cells, incubation with NCM led to higher levels of phospho (γ)H2AX (a marker of DNA damage) and phospho (p)NF-κB (a marker of NF-κB activation) compared to the levels in WI-38 cells incubated with hTSC-CM or EVs, which exhibited lower γH2AX and p-NF-κB signals, suggesting reduced DNA damage and reduced NF-κB activation (Figure 6b). Similarly, treatments with hTSC-EVs revealed decreased γH2AX and p-NF-κB in senescent WI-38 cells (Figure 6c). These findings indicate that hTSC-CM and hTSC-EVs suppress or repair DNA damage and suppress NF-κB activation, culminating in decreased SASP factor production (Figures 2, 4, and 6b,c).

3 | Discussion

Cellular senescence is a double-edged sword in aging and disease (Calcinotto et al. 2019). While it protects against tumorigenesis and facilitates tissue repair after acute damage, the accumulation of senescent cells in organs drives age-related diseases through SASP-associated inflammation, fibrosis, and tissue dysfunction (Kumari and Jat 2021). To alleviate these detrimental effects, several therapeutic strategies have been developed targeting senescent cells, including senolytics, which induce apoptosis of senescent cells, and senomorphics, which suppress the SASP (von Kobbe 2019). Senolytics, such as dasatinib and quercetin, have demonstrated efficacy in reducing the senescent-cell burden and alleviating age-related symptoms in preclinical models (Lelarge et al. 2024). Senomorphics, targeting pathways like NF-κB, JAK/STAT, and mTOR, include compounds like metformin and rapamycin, which reduce inflammation and mitigate SASP-related damage (Salminen et al. 2012). Recent studies suggest that combining senolytics and senomorphics may enhance therapeutic efficacy while minimizing side effects, offering promising avenues to improve health span and combat chronic conditions associated with aging (Luis et al. 2022; Robbins et al. 2021).

Stem cells exhibit significant regenerative and therapeutic potential across a range of diseases, primarily through their paracrine activity, which involves the secretion of bioactive factors such as cytokines, growth factors, and microRNAs. For example, MSCs secrete soluble factors like vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and interleukin-10 (IL10), which regulate inflammation and promote tissue regeneration (Bagno et al. 2022; Fan et al. 2020; Merimi et al. 2021). In addition, MSC-derived EVs, including exosomes, can recapitulate the therapeutic effects of their parent MSCs by delivering genetic materials to target cells, thereby regulating gene expression and cell function. MSC-secreted molecules create a pro-regenerative microenvironment that supports tissue repair, modulates immune responses, and promotes angiogenesis (Bagno et al. 2022; Han et al. 2022). Unfortunately, the broad use of MSCs is hampered by concerns related to proliferation capacity, differentiation, targeting desired cells, and safety; MSC-EVs also present challenges in production scaling and functional efficacy (Kou et al. 2022; Lee 2018; Wang et al. 2020).

Given these limitations, hTSCs and their secretome, including EVs, present promising alternatives and offer advantages for regenerative medicine thanks to their ability to remain proliferative and differentiate into various cell types (Chang and Parast 2017; Dong et al. 2020). In addition, EVs derived from hTSCs exhibit regenerative properties on MSCs, making

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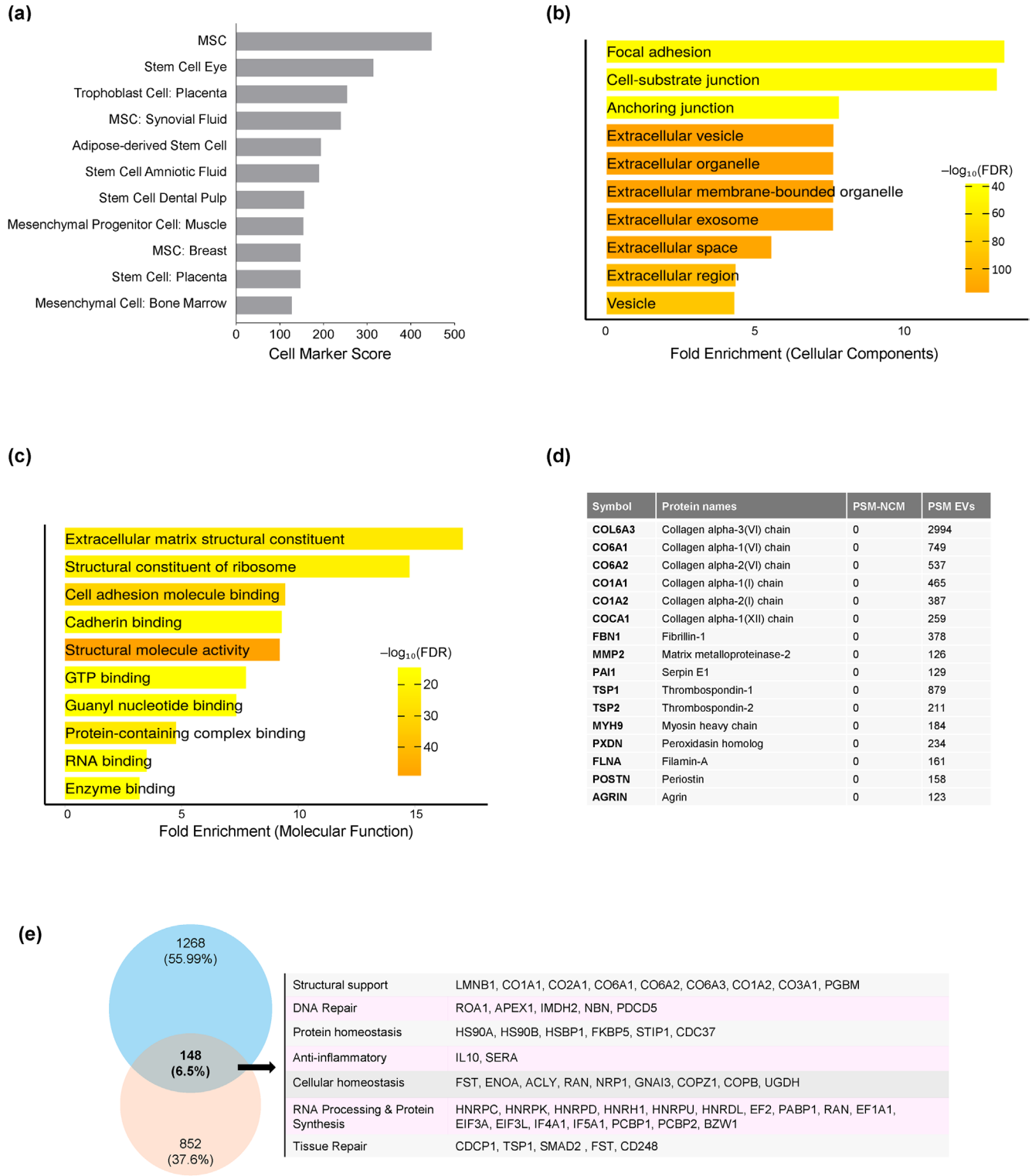


FIGURE 5 | hTSC-CM and EVs are enriched in proteins downregulated in senescence. (a) CellMarker analysis of the proteome of hTSC-EVs, showing general enrichment in stem cells and confirming the stem cell origin of hTSCs. (b) GO enrichment analysis of hTSC-EV cellular components. (c) GO enrichment analysis of hTSC-EV molecular functions. (d) Mass spectrometry analysis of hTSC-EV protein composition, highlighting ECM-related and structural proteins. (e) Venn diagram of protein sets enriched in hTSC-CM and EVs (pink) and reduced in senescent cells (blue) (Munk et al. 2021); the intersection shows 148 shared proteins (Table S5) including the highlighted proteins, grouped by function.

them promising candidates for therapeutic interventions (Go et al. 2023). However, the impact of the hTSC-CM and EVs on senescence, aging, and age-related diseases is unknown.

In this study, we present evidence that the secretome and EVs of hTSCs exert potent anti-senescence effects upon irradiated WI-38 human lung fibroblasts, particularly by suppressing

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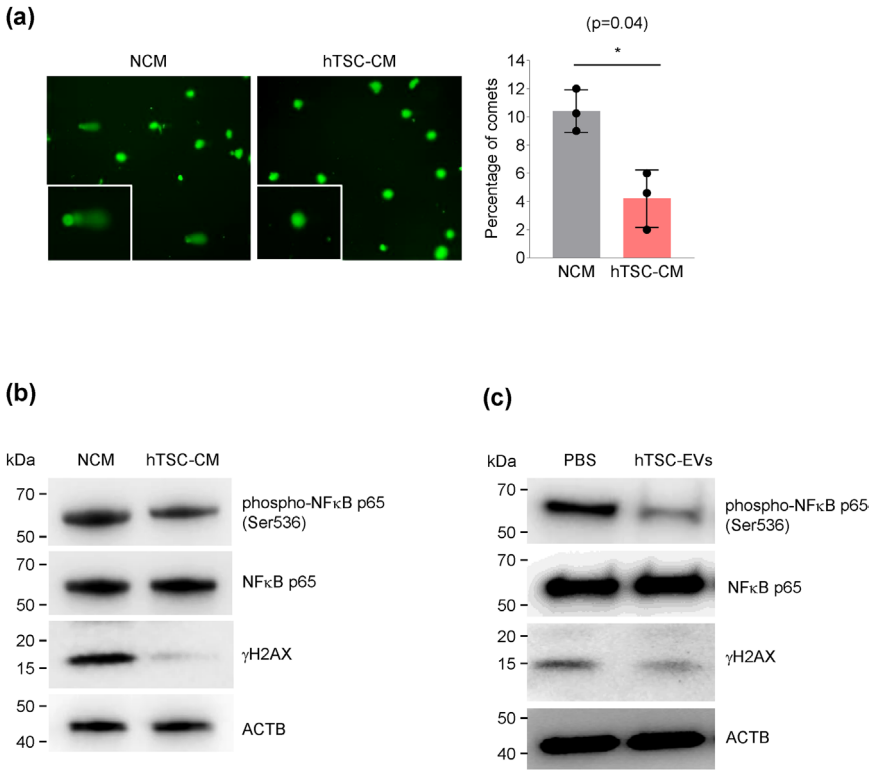


FIGURE 6 | hTSC-CM and EVs suppress DNA damage and NF-κB activity. (a) Comet assay images (left) and quantification of DNA damage (graph) in IR-treated WI-38 cells that were incubated with NCM or hTSC-CM following irradiation (10 Gy) for 5 days. (b) Western blot analysis of the levels of phospho-NF-κB p65 (Ser536), total NF-κB, γH2AX, and ACTB (β-Actin) in IR-treated WI-38 cells that were incubated with NCM or hTSC-CM for 5 days. (c) Western blot analysis of the levels of phospho-NF-κB p65 (Ser536), total NF-κB, γH2AX, and ACTB in IR-treated WI-38 cells that were incubated with hTSC-EVs or PBS for 5 days. Data in (a) represent the means ±SEM. Statistical significance (*$p < 0.05$) was assessed using Student's *t*-test.

the production of SASP-related mRNAs and proteins (e.g., CXCL1, IL8, and GDF15). Analysis of the hTSC-CM and EV proteomes revealed enrichment of proteins involved in ECM remodeling (e.g., COL1A1 and MMP1) and growth factors (e.g., VEGFA); these proteins are implicated in pathways that promote ECM organization, proliferation, and tissue repair, suggesting that hTSC-CM may contribute to a regenerative microenvironment (Williams and Ehrhart 2022). The ECM-modulating and stemness properties observed in MSC-EVs further support this notion (Kou et al. 2022; Patel et al. 2023). The fact that proteins enriched in hTSC-CM and EVs (e.g., VIME, HNRNPC, HSP90, ENO1, ACLY, PABP1, HNRNPK, EF2, IMDH2, RAN, PPIA, ROA1, and TSP1) are often down-regulated in senescent cells (Munk et al. 2021) suggests that hTSC-CM and EVs may elicit their beneficial effect at least in part by restoring these depleted factors in senescent fibroblasts. In this regard, through transfer from hTSC-CM or hTSC-EVs to senescent cells, VIME could restore cytoskeletal integrity (Patteson et al. 2021), HNRNPC may restore RNA processing (Niggl et al. 2023), and HSP90 may mitigate stress and promote homeostasis (Somogyvári et al. 2022). Further studies are needed to validate their cargo specificity and the underlying mechanisms of action.

In line with growing interest in stem cell-derived secretomes and EVs as modulators of senescence and aging, we found that culturing irradiated WI-38 cells with hTSC-CM or EVs reduced the production of many SASP factors (e.g., IL1A, IL6, and MMP3) and the mRNAs that encode them. Furthermore, the presence of ECM structural components and cell adhesion factors in hTSC-EVs may contribute to stabilizing the cellular microenvironment and counteracting SASP-driven matrix degradation (Basisty et al. 2020; Patel et al. 2023). While the exact mediators await identification, proteomic analysis suggests that hTSC-EVs act through mechanisms involving the suppression of SASP-associated inflammation and ECM remodeling.

Functional analysis indicated that both hTSC-CM and EVs reduced DNA damage and NF-κB phosphorylation, two inducers of the SASP (Figure 6), suggesting that hTSC-CM and EVs are promising senomorphic targets. The observed reduction in γH2AX, a robust marker of DNA damage, suggests that hTSC-CM and EVs may enhance DNA repair capabilities or deliver protective factors that mitigate genotoxic stress. In this regard, EVs were previously reported to modulate biological processes relevant to age-related changes in hematopoietic stem cell (HSC) phenotypes, including DNA damage responses (Goldberg 2021); our results (Figure 6c) suggest that hTSC-EVs alone might be sufficient to elicit anti-senescence traits. Furthermore, a recent study found that MSC-derived apoptotic vesicles (apoVs) can modulate DNA damage responses and repair mechanisms in recipient cells, rescuing DNA damage and premature senescence in mice with apoptosis deficiencies. These apoVs were found to contain multiple nuclear DNA repair enzymes, including PARP1, which were transferred to recipient cells to alleviate DNA damage,

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indicating a potential role for EVs as carriers of functional repair proteins, and offering a novel therapeutic path for diseases of genomic instability (Huang et al. 2024). Interestingly, our proteomic analysis identified several proteins directly involved in DNA repair within the hTSC-CM and EVs, including CHEK2, NBN, RAD23B, PARP1, PMS1, and APEX1 (Scheijen and Wilson 2022).

The reduction in phospho-NF-κB p65 (Ser536) in cells treated with hTSC-CM or EVs suggests a suppression of inflammatory signaling, likely through DNA damage, which is known to trigger NF-κB transcriptional activity to increase transcription of pro-inflammatory genes (Giridharan and Srinivasan 2018; Budamagunta et al. 2021; Chien et al. 2011; Vaughan and Jat 2011). Persistent activation of NF-κB leads to chronic inflammation, which promotes biological aging and age-related diseases (Garcia-Garcia et al. 2021). Thus, the ability of hTSC-CM and EVs to attenuate NF-κB activity indicates that these treatments may mitigate the inflammatory responses exacerbated by DNA damage, and aligns with other evidence that EVs can modulate inflammatory pathways in aging, such as those affecting old HSC phenotypes (Goldberg 2021).

Although we found that incubation with hTSC-CM/EVs reduced DNA damage and NF-κB activation in senescent fibroblasts, the molecular mechanisms underlying these effects are unclear. Further research is needed to identify the mechanisms through which hTSC-CM/EVs elicit their anti-senescence effects. The proteomic data in Figure 5c suggest that we focus on mechanisms centered around (i) DNA damage sensing and repair, (ii) proteostasis, (iii) nuclear lamina and RNA processing, and (iv) ECM and focal adhesion signaling. Additionally, it is unclear whether specific proteins within hTSC-CM and EVs (e.g., HNRNPC and HSP90) actively restore function in cells or contribute to a more favorable microenvironment. Future investigation of the RNAs (mRNAs, microRNAs, and long noncoding RNAs) in hTSC-EVs and their roles in recipient cells is also likely to offer valuable insight.

An additional limitation of our study stems from the identity and state of the hTSC lines used as the source of the secretome and EVs. Although these lines were derived from pre-placental chorionic villi and maintained stable morphology and expected marker expression over serial passages, we could not fully exclude the possibility that the culture conditions favored expansion of chorionic mesenchymal stromal cells and/or promoted partial trophoblast differentiation. Because the MesenCult-ACF conditions used here were optimized for MSC-like lineages and not for maintaining canonical hTSC stemness, future work should incorporate trophoblast-specific media (Okae et al. 2018), together with hTSC-defining transcriptomic benchmarks and lineage-specific sorting strategies to more rigorously verify and maintain the trophoblast stem-cell state. These steps will help distinguish trophoblast-specific effects of the secretome and EVs from those potentially mediated by other early-gestation progenitor populations.

Likewise, identifying the receptors and surface proteins on recipient cells that mediate the effects of hTSC-CM and EVs is essential for understanding the specificity of their actions. Our study focused on WI-38 fibroblasts but not other cell types. Given the heterogeneity of senescence across different tissues and pathological contexts, future studies should also assess the effects of hTSC-CM and EVs in other senescent models, including endothelial, immune, and epithelial cells. Furthermore, while our findings in culture suggest a therapeutic potential for hTSC-CM and EVs in mitigating senescence, scaling up the production of hTSC-CM and EVs will allow us to explore their efficacy in animal models. Future studies should investigate the effects of hTSC-CM and EVs on old mice or disease-specific mouse models (e.g., osteoarthritis, pulmonary fibrosis, or Alzheimer's disease) to assess their impact on systemic senescence, SASP factors in circulation, health span, and longevity. Moreover, comparative analyses between hTSC-CM/EVs and other stem cell-derived secretomes/EVs will be crucial to determine whether hTSC-CM/EVs offer distinct or superior benefits in antiaging and regenerative applications. Finally, while the placental origin of trophoblast stem cells may uniquely reduce immune rejection and enhance therapeutic efficacy, it is not known if this advantage is also seen with the secretome or EVs. Thus, the immunogenicity, biodistribution, and long-term safety of hTSC-CM and EVs in preclinical and clinical settings remain to be rigorously evaluated.

In summary, we have found that hTSC-CM and EVs elicit anti-senescence effects by attenuating DNA damage and NF-κB signaling, in turn suppressing the inflammatory cascades that amplify SASP production and secretion. These findings underscore the potential value of hTSC-derived secretomes and EVs as senotherapeutics to improve health span.

4 | Methods

4.1 | Cell Culture, Treatments, and SA-β-Gal Activity

Human WI-38 diploid fibroblasts (Coriell Institute for Medical Research: ID AG06814) were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% non-essential amino acids, and 1% antibiotics (Gibco). Cells were maintained at 37°C in a humidified atmosphere with 5% CO_2 and routinely tested negative for mycoplasma. Proliferating WI-38 fibroblasts (between PDLs 22 and 24) were treated with a single IR dose (10 Gy) on Day 1, and the medium was immediately supplemented with either NCM or hTSC-CM. On Day 3, the medium was replaced and fresh NCM or hTSC-CM was added until harvest on Day 5. Etoposide (Eto) treatment (50 μM) started on Day 1 together with NCM or hTSC-CM, and continued until Day 3, when the medium was replaced with fresh Eto and supplemented with fresh NCM or hTSC-CM. All samples were collected on Day 5 to assess the impact of hTSC-CM (relative to NCM) on cells exposed to a senescence trigger (Figure 1c). Senescence-associated β-galactosidase (SA-β-Gal) activity, a widely used biomarker of senescent cells in culture and in tissues, detects lysosomal β-galactosidase activity at pH 6.0; this activity is specifically elevated in senescent cells due to the increase in lysosomal mass and function that accompanies the senescent phenotype. The pH-dependent detection distinguishes senescent cells from proliferating cells, as normal lysosomal β-galactosidase activity is optimal at pH 4.0.

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SA-β-Gal activity was detected as described (Abdelmohsen et al. 2024), following the manufacturer protocol (Cell Signaling Technology, cat. #9860). Images of SA-β-Gal staining were acquired using a Nikon Digital Sight camera system attached to a Nikon Eclipse TS100 microscope.

4.2 | hTSC Culture, Flow Cytometry, hTSC-CM Concentration, and Treatment of Fibroblasts

Human trophoblast stem cells ABX-001 hTSC 2003 were originally derived from chorionic villi obtained during salpingectomy/salpingotomy procedures for ectopic pregnancy early in gestation. Tissue procurement, derivation, and banking were performed under IRB-approved protocols (KMUHIRB-F(I)-20200184) and ethics review by the Stanford Center for Biomedical Ethics (available upon request). Cells were cultured in conditioned media (MesenCult, Stemcell Technologies, Cat#05446) at Accelerated Bioscience with confirmed mycoplasma-free and pathogen-free status, demonstrating post-thaw viabilities of approximately 97%–98%. The morphology of hTSC cells was documented by imaging in adherent culture using a Keyence (BZ-X710) phase-contrast microscope equipped with a 4× objective.

The presence of surface markers in hTSCs was evaluated by flow cytometry using a CytoFLEX flow cytometer (Beckman Coulter). Cells were harvested, counted, and stained for 30 min with either PE-conjugated primary antibodies recognizing CD45, CD90, and CD105 (R&D Systems) or corresponding isotype controls (R&D Systems; 500,000 cells/sample). Data analysis and measurement of percentages of positive and negative cells was performed using the FlowJo software (BD).

Conditioned medium from passages 1 to 11 was collected from hTSC cultures to test its impact on cellular senescence. Additionally, EVs were isolated from the conditioned media to evaluate their effects on senescence phenotypes. For the control non-conditioned media (NCM), MesenCult was used directly as supplied by the manufacturer, without culture of any cells. All media handling was performed in a sterile cell culture environment, followed by centrifugation to remove cellular components and debris. Cell culture media were concentrated from 200 mL to 10 mL using a 3-kDa molecular weight cutoff filter (Amicon Ultra-15, UFC900308) by centrifugation at 3000 RPM for 1 h at 4°C; after it was concentrated 20×, the medium was stored at −80°C until use. WI-38 cells were incubated with a final 2× secretome immediately following IR treatment or concurrently with Eto treatment; the media were refreshed including Eto at regular intervals as shown in Figure 1c. Similarly, WI-38 cells were incubated with the hTSC-EVs immediately following IR treatment and the media were refreshed with EVs on Day 3 as shown in Figure 4g.

4.3 | Size Exclusion Chromatography (SEC) and Culture With hTSC-EVs

EVs were isolated from the concentrated hTSC-CM (secretome, as explained above) using qEV10, 35-nm SEC columns (IZON Science), according to the manufacturer protocol. Briefly, 10 mL of secretome concentrate was loaded onto the column, after which 13 fractions (5 mL each) were collected to assess EV and protein distribution. Typically, the first 2 to 4 fractions contained EVs, which were then concentrated using a 3-kDa molecular weight cutoff filter. The size and distribution of the concentrated EV sample were subsequently assessed using a NanoFCM instrument. Cells were treated with EVs (~10^9 particles/mL) in 24-well plates.

4.4 | EV Labeling and Uptake

EVs were labeled with the red fluorescent lipid dye PKH26 (Sigma-Aldrich, St. Louis, MO) with modifications to minimize dye micelle formation. Briefly, 100 μL of EVs (10^{10} EVs/mL) were mixed with 0.2 μM PKH26 solution in diluent C (Sigma-Aldrich) and incubated for 1 min at room temperature. As a control, 100 μL of PBS alone were subjected to the same PKH26 staining procedure to assess potential micelle formation. After labeling, 100 μL of PBS were added to the EV solution, and the free dye was removed using a Zeba Spin Desalting Column (7K MWCO, Thermo Fisher Scientific, cat. # 89892). To assess EV uptake, WI-38 cells were incubated with PKH26-labeled hTSC-EVs for 24 h at 37°C and 5% CO_2. Following incubation, cells were washed twice with PBS to remove unbound EVs and fixed with 3% formaldehyde in PBS for 10 min at RT. After fixation, cells were permeabilized with 0.1% Triton X-100 (Sigma-Aldrich) in PBS for 5 min at room temperature, then washed 3× with DPBS to remove residual Triton X-100. To visualize nuclei, cells were stained with DAPI and fluorescent images were captured using a Keyence microscope.

4.5 | Nanoflow Cytometry (NFCM)

The size distribution of the isolated EVs was analyzed using nanoflow cytometry (NFCM) as previously described (Abdelmohsen et al. 2023) with the Flow NanoAnalyzer (NanoFCM Inc.). Briefly, the instrument was calibrated using 250-nm Silica Beads to establish particle concentration and a Silica Nanosphere Cocktail to determine particle size. Particle concentration and size were measured based on the calibration curve, flow rate, and side scatter intensity, with data acquisition performed for 1 min per sample, following the manufacturer guidelines for NanoFCM operation.

4.6 | ExoView Analysis

Surface marker proteins on EVs were analyzed using the ExoView R200 platform (NanoView Biosciences) as described (Abdelmohsen et al. 2023). Briefly, 50 μL of EV samples at equal concentrations were incubated on ExoView Tetraspanin chips in a 24-well plate for 16 h. Following incubation, the chips were washed three times with 1× Solution A before adding 250 μL of detection antibodies in blocking buffer for 1 h. Subsequent washing steps included two washes with Solution A, three washes with Solution B, and a final rinse with deionized water. After drying on absorbent paper, the chips were scanned using the ExoView R200 system and analyzed with ExoScan software (NanoView Biosciences).

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4.7 | Transmission Electron Microscopy

For transmission electron microscopy (TEM) imaging analysis (Johns Hopkins University EM facility), 20 μL of EV samples (approximately 10^{10} particles/mL) were placed onto carbon-coated parlodion copper grids and allowed to adhere for 2 min. The grids were then floated sequentially on two drops of filtered 0.75% uranyl acetate aqueous solution containing 0.03% tylose for 1 min each, followed by blotting with filter paper for adsorption. EVs were immobilized on poly-L-lysine-coated coverslips using a fixation solution of 1% glutaraldehyde in 80 mM phosphate buffer with 5 mM $MgCl_2$. Coverslips were subsequently rinsed with sucrose-containing buffer and post-fixed in osmium tetroxide reduced with potassium ferrocyanide for 1 h on ice.

To improve visualization, *en bloc* staining was applied using a 2% uranyl acetate solution in maleate buffer for 1 h. The EV samples were then dehydrated through a sequence of ethanol solutions (ranging from 30% to 100%), then embedded in Eponate 12 resin, and hardened by heating at 60°C for 48 h. Coverslips were subsequently mounted onto inverted beam capsules and immersed in liquid nitrogen for 10 min, then detached from the capsules. The solidified resin blocks were trimmed and ultrathin sections (50–60 nm) were obtained using a Reichert Ultracut E ultramicrotome equipped with a Diatome diamond knife. Sections were stained with methanolic uranyl acetate, followed by lead citrate incubation. Between staining steps, thorough rinsing was performed with distilled water. Coverslips were fixed in 2% glutaraldehyde in 100 mM sodium cacodylate buffer and stained with 2% uranyl acetate for 20 min and periodically rinsed with distilled water. Finally, imaging was performed on a Hitachi H-7600 TEM operated at 80 kV. Digital images were acquired using an XR50 5-megapixel CCD camera from Advanced Microscopy Techniques Corp.

4.8 | Mass Spectrometry Analysis

For mass spectrometry (MS) analysis, proteins were extracted from the isolated EVs, and protein concentrations were determined using the Pierce MicroBCA kit. Samples were processed by treating with DTT for reduction, subsequently with iodoacetamide for alkylation, and finally digested with trypsin in a 25 mM NH_4HCO_3 solution. The resulting tryptic peptides were purified using a C18 column before being reconstituted in 25 μL of 0.1% formic acid; 12 μL of this mixture was analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at 110-min run time (Thermo Scientific Orbitrap Exploris 240 Mass Spectrometer and a Thermo Dionex UltiMate 3000 RSLCnano System). The Orbitrap Exploris 240 operated in a data-dependent mode, alternating between full-scan MS and MS/MS acquisition. Peptide mixtures were loaded onto a peptide trap cartridge at a flow rate of 5 μL/min before being transferred onto a Thermo Fisher Scientific EasySpray C18 column via a linear gradient of 3%–36% acetonitrile in 0.1% formic acid over 110 min at a flow rate of 0.3 μL/min. Ionization was performed using a Nano-EasySpray Ion Source with a spray voltage of 1.6 kV and a capillary temperature of 275°C. Eluted peptides were ionized and sprayed into the mass spectrometer using a Nano-EasySpray Ion Source (Thermo Fisher Scientific) with spray voltage of 1.6 kV and capillary temperature of 275°C. The instrument was set to isolate and fragment the 15 most intense multiply charged ions ($z \geq 2$) using higher-energy collisional dissociation (HCD) with a normalized collision energy of 30. The AGC target was adjusted to 10^5, with a maximum injection time of 200 ms and a resolution of 17,500. The isolation window was set to 2, and a dynamic exclusion of 20 s was applied to minimize redundant fragmentation. Charge state screening was enabled to exclude unassigned ions and those with a charge state of 1+ or ≥ 7+. To ensure specificity, the same steps were performed using MesenCult (Stemcell Technologies, Cat#05445) as a negative control. Raw data files were processed using Proteome Discoverer (v1.4) and analyzed via the SEQUEST algorithm (Thermo Fisher Scientific). The acquired spectra were searched against protein sequence database from UniProtKB/Swiss-Prot. Peptide filtering criteria included a minimum sequence length of five amino acids and a maximum false discovery rate (FDR) threshold of 0.01. Assembled proteins with peptide spectrum match (PSM) counts were quantified and normalized using the normalized spectral abundance factors (NSAFs) to determine their relative abundance. Raw files are available in MSV000096320 [doi: 10.25345/C5QR4P30R].

4.9 | Protein Extraction and Western Blot Analysis

To extract total protein, cells were rinsed twice in 1× PBS before lysis in a 2% SDS buffer containing 50 mM HEPES and freshly prepared protease/phosphatase inhibitors (Cell Signaling Technology). Protein concentration was quantified with the BCA assay kit (Pierce). The lysates were mixed with 4× SDS Laemmli buffer (Bio-Rad) supplemented with β-mercaptoethanol and heated at 95°C for 5 min to denature proteins. For western blot analysis, protein samples were loaded onto Tris-Glycine gels (Bio-Rad), separated by SDS-PAGE, and transferred to nitrocellulose membranes using the iBlot kit (Invitrogen). Membranes were blocked for 1 h at room temperature with 5% nonfat milk in 1× TBST, followed by overnight incubation at 4°C with primary antibodies. Primary antibodies were used that recognized phospho-Histone H2AX Ser139 (γH2AX) (#9718), phospho-NF-κB p65 Ser536 (#3033), and NF-κB p65 (#8242) (all from Cell Signaling Technology), as well as β-actin (ACTB) (sc-8432, Santa Cruz Biotechnology). The membranes were then washed in 1× TBST and incubated with secondary antibodies in 5% nonfat milk for 1 h at room temperature. After washing, membranes were treated with ECL solution (Kindle Biosciences), and chemiluminescent signals were detected using a ChemiDoc imaging system (Bio-Rad).

4.10 | RNA Isolation, and RT-qPCR and RNA-Sequencing Analyses

Total RNA was extracted from cells using TRIzol reagent (Thermo Fisher Scientific) following the manufacturer's protocol. RNA concentration was assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific). Reverse transcription (RT) was carried out using 500 ng of total RNA with the Maxima Reverse Transcriptase protocol (Thermo Fisher Scientific) and transcript levels analyzed via quantitative real-time PCR (qPCR) using the SYBR Green FAST qPCR master mix kit (Kapa Biosystems) on a QuantStudio 5 Real-Time PCR System (Thermo Fisher Scientific). For qPCR amplification, these specific primer

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pairs were employed: CAACCAGAGCTGGGAAGATTCG and CCCGAGAGATACGCAGGTGCA for *GDF15*, GAAAGAGTGG CAACCTGCCTTC and GCACCAAGTTTTACTACATCTGCC for *MKI67*, GTCTCCGGGAATCTCTGATGC and GTTCAGT GGAGCCCAGCTCT for *BAFF*, AGTGAGGAACAAGCCAGA GC and GTCAGGGGTGGTTATTGCAT for *IL6*, AGCTTGC CTCAATCCTGCATCC and TCCTTCAGGAACAGCCACCAGT for *CXCL1*, TCCTGATTTCTGCAGCTCTGT and AAATTTGG GGTGGAAAGGTT for IL8, and CATGTACGTTGCTATCCA GGC and CTCCTTAATGTCACGCACGAT for *ACTB* mRNA. RNA levels were calculated with the $2^{-\Delta\Delta Ct}$ method and were normalized to *GAPDH* mRNA levels.

RNA-Sequencing (RNA-seq) was conducted on total RNA extracted from WI-38 recipient cells treated as described in Figure 1a. RNA integrity was evaluated using an Agilent Bioanalyzer, and libraries were generated and sequenced by Azenta Life Sciences. Raw sequencing reads were processed, aligned to the human genome (GRCh38), and subjected to differential expression analysis using DESeq2. Raw sequencing data are available under accession GSE282054.

4.11 | Cytokine Arrays and Bio-Plex Analysis

The levels of secreted cytokines in the hTSC conditioned media (CM) or non-conditioned media (NCM) were assessed using the Human Cytokine Antibody Array (R&D Systems) following the manufacturer protocol, and chemiluminescent signals were captured using a ChemiDoc imaging system (Bio-Rad).

For multiplex cytokine analysis, the hTSC-CM or NCM were analyzed using human Luminex Assay kits (R&D Systems) to quantify DPP4, IL8, IL6, GDF15, MMP3, Osteopontin, GM-CSF, and ICAM1, with media diluted 1:10 in Calibrator Diluent RD6-52. Standards, blanks, and diluted media were incubated with the microparticle cocktail for 2 h at 25°C, followed by incubation with the Biotin-Antibody cocktail for 1 h and a final 30-min incubation with Streptavidin-PE under shaking conditions at 25°C. Each incubation step was followed by three washes with Wash Buffer, and the plate was analyzed using the Bio-Rad Bioplex-200 Instrument with the following settings: 50 μL sample volume, Bio-Plex MagPlex Beads (Magnetic), Double Discriminator Gates set at 8000–23,000, low RP1 target value for the CAL2 setting, and a bead count of 50 per region. Results were processed and analyzed using Bio-Plex Manager software (Bio-Rad).

4.12 | Olink Proteomics

For Olink proteomic analysis, we used the media to evaluate the secretome of the hTSCs or WI-38 cells at Indiana University. Briefly, target proteins were detected through a highly specific binding interaction with dual oligonucleotide-labeled antibody probes. The bound probes underwent microfluidic real-time PCR amplification, enabling the quantitative detection of the corresponding DNA sequences. Internal and external controls were utilized for quality control and normalization. Normalized Protein expression (NPX) values were provided as the final assay readout corresponding to protein levels.

Author Contributions

K.A. conceived and supervised the study. K.A., J.L.M., M.R., A.P., M.B., E.M.A., C.H.S., R.M., M.M., C.-Y.C., and C.J.N.-O. performed the experiments and collected data. M.S.-M. and N.D. performed data analysis and statistical evaluations, Y.L., J.-N.L., S.H.P., and J.H. supplied the hTSC secretome and provided experimental support, K.A. and M.G. supervised and wrote the manuscript with input from all authors. All authors contributed critical feedback that shaped the study and manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data used to generate the statistical analyses and figures in this study are available from the corresponding author upon reasonable request. Raw sequencing data are available at GSE282054. Raw MS data are available at MSV000096320 [doi: 10.25345/C5QR4P30R].

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figures S1–S3:** acel70368-sup-0001-FiguresS1-S3.pdf. **Table S1:** acel70368-sup-0002-TableS1.zip. **Table S2:** acel70368-sup-0003-TableS2.zip. **Table S3:** acel70368-sup-0004-TableS3.zip. **Table S4:** acel70368-sup-0005-TableS4.zip. **Table S5:** acel70368-sup-0006-TableS5.zip.

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72. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESC lines have been pivotal in a broad array of basic biological research studies including the use of genetically engineered lines, e.g. reporter lines, and expanding the genetic diversity as well as disease relevance with new hESC lines will provide for future advances.
hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes, and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.
New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESC lines provide the "ground truth" of the earliest steps in human development because they are derived directly from the pre-implantation human embryo
hESCs provide the only natural benchmark for defining human stem cells.
hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

hESCs cannot be replaced by current alternative technologies and are needed as a reference standard and a benchmark for future work and the development of these alternatives. Lack of this benchmark may slow technological advancement or create insufficient technologies.
hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.
Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.
An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies
Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.
Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.
Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

73. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/23/2026

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hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
hESCs cannot be replaced by current alternative technologies and are needed as a reference standard and a benchmark for future work and the development of these alternatives. Lack of this benchmark may slow technological advancement or create insufficient technologies.
hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.

Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development. An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.

Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.

Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

74. Society for Neuroscience

I am responding: On behalf of an organization

Name: N/A

Name of Organization: Society for Neuroscience

Type of Organization: Professional Organization/Association

Role: Organizational Official

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Please see attached file for response.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Please see attached file for response.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Please see attached file for response.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Please see attached file for response.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/SfN-Comments-on-Reducing-Reliance-on-Human-Embryonic-Stem-Cells-in-NIH-Supported-Research.pdf

Description: Please see attached Society for Neuroscience's official comments to the requested research areas as indicated above.

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April 23, 2026

On behalf of the Society for Neuroscience (SfN), thank you for the opportunity to respond to the National Institutes of Health (NIH) Request for Information (RFI) on reducing reliance on human embryonic stem cells (hESCs) in NIH-supported research. As the world's largest organization dedicated to advancing the understanding of the brain and central nervous system, SfN is committed to advancing biomedical research that drives innovation, improves public health, and maintains the United States' global leadership in scientific discovery. SfN appreciates NIH's efforts to assess research areas suitable for modernization and the role of emerging biotechnologies in advancing biomedical research.

Executive Summary

From a neuroscience perspective, hESCs remain an essential and, in some contexts, irreplaceable research tool, especially in cell replacement therapies for Parkinson's Disease and spinal cord injuries. hESCs serve as the gold standard for human pluripotency and provide unparalleled utility for studying human neural development, neurodevelopmental disorders, and neurodegenerative diseases. While alternative platforms such as induced pluripotent stem cells (iPSCs), adult stem cells, organoids, and computational models have expanded the neuroscience toolkit, none are yet biologically equivalent to hESCs or a suitable wholesale replacement.

Additionally, hESCs contribute to the development of new approach methodologies (NAMs), underscoring the continued necessity of maintaining access to hESCs. Prematurely limiting NIH-supported hESC research risks impeding progress in understanding human brain development, modeling complex neurological diseases, and translating discoveries into therapies for conditions such as Alzheimer's Disease, Parkinson's disease, epilepsy, spinal cord injury, and neurodevelopmental disorders.

Based on the current state of the science, the available evidence does not yet support reducing reliance on hESCs, especially in neuroscience research. The study of human brain development and neurological disease continues to require access to well-characterized human pluripotent stem cells, for which hESCs remain the gold standard. Although alternative approaches have expanded the range of experimental tools available, these systems remain complementary and continue to rely on hESCs. The responses below to the specific RFI questions reflect a neuroscience-based assessment of where hESCs remain necessary to ensure scientific rigor, reproducibility, and progress toward effective treatments for neurological disorders.

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1. *Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.*

The hESC lines currently approved by NIH support many types of neuroscience research. Researchers routinely use them to make brain cells for learning and memory, Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), spinal cord injuries, and vision. However, neuroscience research continues to evolve, and new hESC lines may be needed in the future. For example, some studies require cells that remain stable over long periods to model brain aging or slow neurodegenerative diseases, and new lines may better represent genetic diversity, which is important for studying differences in disease risk or treatment response for disorders such as Alzheimer's disease and Parkinson's disease. Because future research needs cannot be fully predicted, it is important to preserve a pathway for adding new hESC lines when scientifically justified.

2. *Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.*

hESCs are the "gold standard" for human pluripotency in all areas of research, including basic, applied, and clinical translation research. If hESCs were unavailable, numerous lines of inquiry in basic and clinical research would be significantly hindered or not possible.

Studying early human brain development
hESCs are uniquely suited to studying how the human brain forms at its earliest stages. These early steps—such as how brain regions are specified and how immature brain cells mature into different types of neurons—are very sensitive to small biological differences. hESCs provide the most reliable model for these questions.

Understanding neurodevelopmental disorders
Conditions such as autism spectrum disorder, some forms of epilepsy, and intellectual disability often begin during early brain development. hESC-based models allow researchers to study these early processes directly, which is difficult to do using adult cells that have been reprogrammed.

Developing treatments for neurological disease
hESC-derived brain cells are being tested in clinical trials for neurological conditions, including Parkinson's disease, ALS, epilepsy, and vision loss. These trials rely on the long history of careful testing and characterization unique to hESCs.

Role of hESCs in Developing and Validating New Approach Methodologies (NAMs) for Neuroscience
SfN supports the development and appropriate use of New Approach Methodologies (NAMs) to improve human relevance, enhance reproducibility, and, where scientifically justified, reduce

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reliance on animal models. As SfN has emphasized in prior comments to NIH, the successful integration of NAMs in neuroscience requires careful validation, realistic expectations, and alignment with the biological complexity of the nervous system.

hESCs play a critical role in this process. hESCs serve as a foundational human reference standard for NAM development, particularly for in vitro models of the nervous system. Many neuroscience-relevant NAMs—including neural cell cultures and brain-region-specific organoids—depend on pluripotent stem cell–derived neural cells. Because hESCs represent naturally occurring, unmodified human pluripotency, they are uniquely suited for validating whether NAMs accurately capture key features of human neural development and function. Importantly, continued access to hESCs supports, rather than conflicts with NIH and FDA goals to advance NAMs. hESC-derived neural models have already contributed to human-relevant platforms that are difficult to assess in animal models. Limiting access to hESCs could undermine efforts to responsibly advance NAMs in neuroscience by removing a key reference point needed for validation and confidence in these approaches.

SfN supports a complementary strategy that emphasizes integration rather than replacement—using hESCs alongside NAMs and animal models, as appropriate, to strengthen scientific rigor and translational relevance. At the present time, hESCs remain essential to ensuring that NAMs used in neuroscience research are reliable, biologically meaningful, and capable of advancing treatments for neurological disease.

3. *Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.*

At present, no alternative technology can replace hESCs as none has been demonstrated to be fully biologically equivalent. A scientifically responsible strategy would be to strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring while maintaining access to hESCs.

Induced pluripotent stem cells (iPSCs)
iPSCs are useful for studying diseases in cells derived from individual patients, such as rare genetic movement disorders or seizure disorders. While iPSCs have substantially expanded the field of stem cell research and provide a cell source for certain applications, they often do not fully replicate the features of hESCs. Consequently, iPSCs cannot yet be considered functionally equivalent to hESCs, particularly for early developmental neuroscience and translational applications.

Organoids and computer models
Brain organoids and computer-based models are promising tools for studying brain organization and activity; however, they lack full cellular and structural complexity, depend on stem cells whose

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behavior has been defined using hESCs and cannot yet fully predict human brain development or disease. Sophisticated models are in their infancy, with computational models of animal development only just emerging. At present, these models have little predictive value because they are not sophisticated enough to model most aspects of cell biology. Computational modeling and AI-assisted methods offer potential for future research directions, but do not represent a replacement for research using hESCs.

4. *Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.*

Rather than replacing hESC research, additional investments should help improve and validate complementary approaches, such as directly comparing brain cells made from hESCs and iPSCs under the same conditions; following clinical trial outcomes to understand when different stem-cell sources perform better or worse; improving ways to measure whether lab-grown neurons truly behave like human brain cells; and using experimental data from hESC-based systems to improve computational brain models. All these efforts require continued access to hESCs as a reference standard.

Conclusion

From a neuroscience standpoint, hESCs remain essential to understanding the human brain and treating neurological disease. Although emerging technologies have expanded research possibilities, none yet provide the biological equivalence or reliability required to replace hESCs. Continued NIH support for hESC research—alongside strategic investment in complementary approaches—is critical to sustaining progress in basic, translational, and clinical neuroscience.

SfN urges NIH to maintain access to approved hESC lines, preserve pathways for the review of new scientifically meritorious lines, and ensure that neuroscience researchers can continue to use the most appropriate and rigorously validated tools available. Thank you in advance for your consideration, and please contact SfN's Director of Advocacy and Training, Adam M. Katz, at akatz@sfn.org, with any questions.

Sincerely,

[redacted]

Diane Lipscombe, PhD
Chair, Government and Public Affairs Committee, SfN

75. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
There are multiple research areas that only the existence of hESC lines will support and to which such hESCs are essential. hESCs are required to develop reporter lines to investigate lineage and tissue/cell type specific expression particularly in developmental disorders. hESCs are required to develop cell replacement therapies in organ systems, for which there are currently multiple clinical trials in progress for treatment of a variety of human diseases including, but not limited to, diabetes and Parkinson's disease. New hESC lines are needed for fertility research models, where hESCs are essential to replace actual, possibly viable embryos that cannot be used for such models.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs are the only available baseline for human pre-implantation embryonic development. hESCs are the only natural standard for the definition of human stem cells. hESCs allow researchers to learn how human organs develop, and possible allow clinicians to create therapies based on hESCs to treat organ injuries or developmental deficiencies that may otherwise be fatal. hESCs cannot be replaced by iPSCs, due to genomic and epigenetic differences, not all known, that exist between the 2 types of human stem cells.
hESCs can be used as stand-ins for studying both healthy development and pathological development without requiring the use of human embryos.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
There are no existing replacements for hESCs, as hiPSCs do not fully replicate all the features of hESCs, nor do any other cells.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
In order to replace hESCs, we must develop replacements with all the features of hESCs. At this time, and with our current knowledge, we can't develop such replacements, although research on this front has been occurring for the last 30 years.

76. Cellino Biotech

I am responding: On behalf of an organization

Name: Scott Luro

Name of Organization: Cellino Biotech

Type of Organization: Industry (Biotech/Device/ Pharmaceutical Company)

Role: Investigator/Researcher

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Description: Cellino Biotech submits this response addressing Topic 3: research areas where emerging biotechnologies can replace hESCs. Human induced pluripotent stem cells (hiPSCs) are molecularly and functionally equivalent to hESCs and are now clinically validated across hundreds of patients worldwide, with Japan granting the first regulatory approvals of iPSC-derived therapies in March 2026. Combined with AI-driven manufacturing that addresses historical scalability challenges, hiPSC technology can serve as a full replacement for hESCs in neurodegeneration, ophthalmology, cardiovascular disease, diabetes, and immuno-oncology. Full response with citations and clinical trial references is provided in the attached PDF.

RESPONSE TO REQUEST FOR INFORMATION

NOT-OD-26-031

Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

Submitted by: Cellino Biotech, Inc.
Date: April 23, 2026
Contact: connect@cellinobio.com
Website: cellinobio.com

Executive Summary

Cellino appreciates the opportunity to respond to NIH's Request for Information on emerging biotechnologies capable of reducing or replacing reliance on human embryonic stem cells (hESCs). As a company scaling personalized cell therapies through artificial intelligence (AI)-driven biomanufacturing of human induced pluripotent stem cells (hiPSCs), we address Topic 3: research areas where emerging biotechnologies can replace the use of hESCs.

Carefully controlled comparisons show that hiPSCs and hESCs are molecularly and functionally equivalent (Choi et al., Nature Biotechnology, 2015; Song et al., Journal of Clinical Investigation, 2020). The clinical safety of pluripotent stem cell-derived therapies is now established across more than 1,200 patients worldwide, and hiPSC-derived products, which require no embryonic source material, are on track to constitute the majority of new programs entering trials (Kirkeby et al., Cell Stem Cell, 2025). In March 2026, Japan became the first country to grant regulatory approval to iPSC-derived therapies for both Parkinson's disease and heart failure (Mullard, Nature, 2026). When combined with AI-powered manufacturing that addresses historical scalability challenges, hiPSC technology can serve as a full replacement for hESCs, offering patient-specific therapeutic advantages that embryonic-derived cells cannot provide.

1. Scientific Equivalence of hiPSCs and hESCs

Rigorous peer-reviewed research demonstrates that hiPSCs and hESCs are functionally indistinguishable when controlled for genetic background and reprogramming methodology.

Equivalence established: Choi et al. (Nature Biotechnology, 2015) compared genetically matched hESC and hiPSC lines, controlling for cellular origin, reprogramming method, clonality, and sex, concluding that "hESCs and hiPSCs are molecularly and functionally equivalent and cannot be distinguished by a consistent gene expression signature." Song et al. (Journal of Clinical Investigation, 2020) confirmed this in a therapeutic context, finding "an identical degree and time course of recovery" between hESC- and hiPSC-derived dopaminergic progenitors in Parkinsonian rat models.

Variability explained: Historical concerns about hiPSC variability were driven largely by early comparisons that failed to control for donor genetic background. Large-scale studies of hundreds of iPSC lines have since demonstrated that individual genetic differences are the dominant source of variation, explaining approximately 50% of genome-wide expression variability

(Carcamo-Orive et al., Cell Stem Cell, 2017) and up to 46% of variation in differentiation capacity, cellular morphology, and other phenotypic assays (Kilpinen et al., Nature, 2017). This variability affects all human cell types, including hESCs, and is not a limitation specific to iPSC technology.

2. Clinical Validation in Patients

Clinical trial data have now demonstrated safety and efficacy for both iPSC-derived therapies and hESC-derived therapies, establishing iPSCs as a clinically validated alternative to hESCs.

Global scale: Kirkeby et al. (Cell Stem Cell, 2025) identified 115 clinical trials testing 83 hPSC-derived products across 19 countries. Of these, approximately 45 products are hiPSC-derived, with over 680 patients dosed and an estimated $>10^{11}$ transplanted cells from hiPSC sources alone, demonstrating that hiPSC manufacturing has achieved clinical scale. No generalizable safety concerns have emerged from either hESC or hiPSC products.

FDA regulatory progress: Multiple hiPSC therapies have advanced through FDA regulatory and clinical milestones, including the NIH National Eye Institute's autologous iPSC-derived RPE patch for age-related macular degeneration (NCT04339764, first patient treated August 2022); Oryon Cell Therapies' autologous iPSC-derived dopaminergic neurons for Parkinson's disease (NCT06422208, six patients treated as of March 2026); Mass General Brigham's autologous iPSC-derived dopaminergic neuron program for Parkinson's disease (NCT06687837, IND cleared 2023, trial initiating, Schweitzer as PI); HeartWorks' autologous iPSC-derived cardiac lineage cells for congenital heart disease (NCT05647213, IND-cleared, enrolling); Aspen Neuroscience's ANPD001, an autologous iPSC-derived dopaminergic neuronal precursor cell therapy for Parkinson's disease (NCT06344026, first patient dosed April 2024); Fate Therapeutics' FT819, an allogeneic off-the-shelf iPSC-derived CAR T-cell therapy for SLE (NCT06308978, RMAT designation, April 2025); and BlueRock Therapeutics' OpCT-001, an allogeneic iPSC-derived photoreceptor cell therapy for primary photoreceptor diseases (Phase 1/2a CLARICO trial initiated, NCT06789445, first patient dosed July 2025).

International regulatory milestone: In March 2026, Japan granted conditional approval to the world’s first two iPSC-derived regenerative medicines: Amchepry (Sumitomo Pharma/Racthera), an allogeneic iPSC-derived dopaminergic progenitor cell therapy for Parkinson’s disease, and ReHeart (Cuorips), an iPSC-derived cardiomyocyte sheet for severe ischemic heart failure (Mullard, Nature, 2026). These approvals represent the first commercialization of iPSC-based therapies worldwide and establish a regulatory precedent for iPSC-derived products.

Long-term safety data: The RIKEN trial of autologous iPSC-derived retinal pigment epithelial (RPE) sheets for macular degeneration, with the first transplant performed in September 2014, has reported no serious adverse events and no tumor formation during multi-year follow-up (Mandai et al., NEJM, 2017). The graft remained intact for over four years (Takagi et al., Ophthalmology Retina, 2019), one of the longest follow-up periods reported for any pluripotent stem cell-derived therapy. More recently, the Kyoto University Phase I/II trial of allogeneic iPSC-derived dopaminergic progenitors for Parkinson's disease reported graft survival, dopamine production, and no tumor formation at 24 months across seven patients (Sawamoto et al., Nature, 2025).

Phase III milestone: Gameto's Fertilo became the first iPSC-derived product to enter Phase III trials in the United States (NCT06858111, IND cleared January 2025).

3. Advantages Unique to hiPSCs

Beyond achieving parity with hESCs, hiPSC technology offers advantages that embryonic-derived cells cannot match:

Autologous transplantation eliminates the need for lifelong immunosuppression: Patient-derived hiPSCs enable self-sourced therapies without the immunosuppression required for allogeneic hESC-derived grafts. This eliminates associated risks of infection, malignancy (including a two- to four-fold increased cancer incidence; reviewed in Engels et al., JAMA, 2011), organ toxicity, and metabolic disorders – risks that are compounded in elderly patients, who face up to a six-fold increase in post-transplant malignancy risk compared to younger recipients (Agraharkar et al., Kidney International, 2004).

Patient-specific disease modeling and drug screening: hiPSCs derived from patients with genetic conditions provide disease-relevant models impossible to generate with hESCs. This enables personalized drug screening, toxicity testing, and therapeutic optimization before treatment.

Simplified ethics and oversight: hiPSCs generated from adult somatic cells eliminate ethical considerations associated with embryo-derived materials, streamlining institutional review and broadening public acceptance of regenerative medicine.

4. Research Areas Ready for Transition

Based on the clinical evidence presented above, the following research domains are positioned to transition from hESCs to hiPSCs:

Neurodegenerative diseases: Parkinson's disease is the most advanced, with multiple FDA-cleared autologous hiPSC trials underway (Aspen Neuroscience ASPIRO, NCT06344026; Oryon/McLean Hospital, NCT06422208; Mass General Brigham, NCT06687837) and 24-month safety and efficacy data published from the Kyoto University trial (Sawamoto et al., Nature, 2025). Japan granted conditional approval to Amchepry for Parkinson’s disease in March 2026 (Mullard, Nature, 2026). iPSC-derived therapies for ALS, Alzheimer's, and spinal cord injury are also in development.

Ophthalmology: iPSC-derived RPE transplants have the longest clinical track record of any iPSC-derived cell therapy (RIKEN, 2014; Mandai et al., NEJM, 2017). Photoreceptor cell replacement is entering clinical testing (BlueRock OpCT-001 CLARICO trial, NCT06789445; first patient dosed July 2025), and corneal epithelial cell sheet transplants are in earlier clinical stages (UMIN000036539; Soma et al., Lancet, 2024), with preliminary efficacy signals.

Cardiovascular disease: Clinical trials of hiPSC-derived cardiomyocytes for heart failure and ischemic cardiomyopathy include the Heartseed LAPiS study of iPSC-derived cardiomyocyte spheroids (NCT04945018) and the Osaka University iPSC-cardiomyocyte sheet trial (jRCT2053190081). Japan granted conditional approval to ReHeart, an iPSC-derived

cardiomyocyte sheet for severe heart failure, in March 2026 – the world's first approved iPSC-derived cardiovascular therapy (Mullard, Nature, 2026).

Diabetes: iPSC-derived islet cell therapies are entering clinical testing for type 1 diabetes. In early 2025, Kyoto University Hospital initiated a clinical trial (jRCT2053240146) of allogeneic iPSC-derived islet-like cell sheets in patients with insulin-deficient type 1 diabetes (Fujikura et al., Journal of Diabetes Investigation, 2025). Separately, Wang et al. (Cell, 2024) reported insulin independence in a type 1 diabetes patient following autologous transplantation of islets derived from chemically induced pluripotent stem cells, a related non-embryonic reprogramming technology. Additional iPSC-derived islet programs incorporating immune-evasion engineering are advancing toward IND submission (e.g., Century Therapeutics' CNTY-813).

Immuno-oncology: hiPSC-derived CAR-NK and CAR-T cells provide a scalable, off-the-shelf manufacturing model for cancer immunotherapy and autoimmune disease, with multiple products now in clinical development. Fate Therapeutics' FT819 (NCT06308978), an iPSC-derived CAR T-cell therapy, has demonstrated durable clinical responses in SLE and received RMAT designation from the FDA.

5. AI-Driven Manufacturing Solves the Scalability Challenge

A historical barrier to hiPSC adoption has been the labor-intensive, inconsistent manufacturing process. Advances in artificial intelligence and automation are now addressing this limitation, making personalized cell therapy increasingly viable at scale.

As noted in recent reviews (Coronnello & Francipane, Stem Cell Reviews and Reports, 2022; Vo et al., PLOS ONE, 2024), AI and machine learning address critical bottlenecks: clone selection, quality control, differentiation optimization, and process standardization. Scalable production of therapeutic cells cannot rely on manual quality control by trained experts – automated, high-throughput validation is essential.

Cellino's contribution: Our Nebula™ platform integrates deep learning with closed-loop optical bioprocessing to deliver biomanufacturing reproducibility that exceeds traditional manual methods. Key capabilities include: AI-driven optimization of culture conditions and clone selection; laser-based cell management for precise density control; and modular cassette-based systems enabling decentralized production close to patients.

Other groups are moving in the same direction. Aspen Neuroscience and Cell X Technologies announced a collaboration in October 2024 to automate iPSC manufacturing for autologous Parkinson's therapy. The European Commission's AiPSC project is developing AI-guided microfluidic devices for standardized, low-cost, autologous iPSC production. Scalable, automated hiPSC manufacturing is no longer theoretical.

Conclusion

The scientific and clinical evidence supports hiPSC technology as a direct alternative to hESCs. Molecular equivalence is established (Choi et al., Nature Biotechnology, 2015); the safety of pluripotent stem cell-derived therapies is demonstrated across more than 1,200 patients; hiPSC-derived products now represent a growing share of new clinical programs (Kirkeby et al., Cell Stem Cell, 2025); and Japan has granted the world's first conditional regulatory approvals

for iPSC-derived medicines (Mullard, Nature, 2026). AI-driven manufacturing is addressing the remaining scalability gap. Federal research investments should shift toward technologies that deliver better patient outcomes without the ethical complexities of embryo-derived materials.

To accelerate this transition, we encourage the NIH to consider: (1) supporting standardized GMP-compliant hiPSC manufacturing protocols and quality guidelines; (2) funding AI/ML applications for hiPSC quality assessment and differentiation optimization; and (3) establishing a national hiPSC biobank with diverse genetic backgrounds to serve research needs currently met by disease-associated hESC lines.

Cellino welcomes the opportunity to discuss how AI-driven biomanufacturing can support this transition.

Respectfully submitted,

Cellino Team

Scott Luro, PhD, Senior R&D Engineer
Marinna Madrid, PhD, Chief Product and Regulatory Officer, Co-Founder
Nabiha Saklayen, PhD, CEO, Co-Founder
Cambridge, Massachusetts

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77. Sahin Naqvi

I am responding: On behalf of myself

Name: Sahin Naqvi

Name of Organization: Boston Children's Hospital

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The 503 currently approved lines, in particular deeply characterized lines like H9 and H1, are sufficient for most ongoing research programs. These lines have decades of published characterization for karyotypic stability, differentiation efficiency, and genomic integrity. They underpin nearly all cell therapies currently in advanced trials in the US. However, new lines remain scientifically necessary for:
- Lines with improved characteristics identified through ongoing research
- Ensuring scientific reproducibility through independent validation across genetically distinct lines

The registry freeze creates a ratchet effect: reduced submissions justify continued freeze, which further depresses the field. The low submission rate cited in NOT-OD-26-031 reflects a mature, well-supplied field in which many of the key reagents have already been generated and are in widespread use/

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Multiple research areas require hESCs and cannot be adequately addressed with iPSCs:

Clinical translation of cell therapies: All hPSC-derived cell therapies currently in advanced clinical trials in the US use hESC-derived products:
- Bemdaneprocel (Parkinson's disease): Phase 1 results demonstrated safety, graft survival, and clinical improvement in off-medication motor function at 18 months; Phase 3 trial (exPDite-2) initiated H1 2025; FDA RMAT designation [2,3]
- VX-880/zimislecel (Type 1 diabetes): Phase 1/2 results published in NEJM showed 10 of 12 patients achieved insulin independence; pivotal trial ongoing; FDA RMAT and Fast Track designations [4]
- NRTX-1001 (epilepsy): Phase 1/2 results showed 89% median seizure reduction; Phase 3 EPIC trial initiated H2 2025; FDA RMAT designation

These programs chose hESCs due to:
- 25+ years of characterization data on genomic stability
- No reprogramming-associated mutations: iPSCs acquire an estimated 6 protein-coding point mutations per exome during reprogramming [6,7]
- No epigenetic memory artifacts affecting differentiation fidelity: iPSCs retain DNA methylation signatures of their tissue of origin that bias differentiation toward donor lineages [8,9]
- Established FDA regulatory pathway for clinical master cell banks

Replacing these programs' source material with iPSCs would require complete re-derivation, re-characterization, and re-validation, effectively restarting clinical development and delaying patient access.

Protocol optimization and standardization: Directed differentiation protocols used across the field were optimized in hESC backgrounds over decades. iPSC lines show substantial line-to-line variability requiring re-optimization for each new line [10]. H9 and H1 serve as de facto reference standards precisely because of this consistency.

Mechanistic studies of early human development: Trophoblast differentiation, X-chromosome inactivation dynamics, and studies of naive-to-primed pluripotency transitions remain more robust and reproducible in hESC systems. The naive pluripotent state is more readily achieved and maintained in hESCs than iPSCs [11,12].

References:
[2] Tabar V, et al. Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease. Nature 2025;641:978-983. doi:10.1038/s41586-025-08845-y
[3] BlueRock Therapeutics press release, April 16, 2025
[4] Reichman T, et al. Stem Cell–Derived, Fully Differentiated Islets for Type 1 Diabetes. NEJM 2025 2025;393:858-868.
[6] Gore A, et al. Somatic coding mutations in human induced pluripotent stem cells. Nature 2011;471:63-67. PMID: 21368825
[7] Ji J, et al. Elevated coding mutation rate during the reprogramming of human somatic cells into induced pluripotent stem cells. Stem Cells 2012;30:435-440. PMID: 22162363
[8] Polo JM, et al. Cell type of origin influences the molecular and functional properties of mouse induced pluripotent stem cells. Nature Biotechnology 2010;28:848-855. PMID: 20644536
[9] Kim K, et al. Epigenetic memory in induced pluripotent stem cells. Nature 2010;467:285-290. PMID: 20644535
[10] Pantazis CB, et al. A reference human induced pluripotent stem cell line for large-scale collaborative studies. Cell Stem Cell 2022;29:1753-1767. PMID: 36459969
[11] Yu L, et al. Blastocyst-like structures generated from human pluripotent stem cells. Nature 2021;591:620-626. PMID: 33731924
[12] Yanagida A, et al. Naive stem cell blastocyst model captures human embryo lineage segregation. Cell Stem Cell 2021;28:1016-1022. PMID: 33915078

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
iPSCs are appropriate and often preferable for:
- Patient-specific disease modeling (where the goal is to capture individual genetic variation)
- Autologous cell therapy development
- Studies specifically examining reprogramming biology
- Applications where the specific genetic background of the donor is scientifically relevant

However, "replacement" implies an equivalence that does not exist scientifically:

- iPSCs are not equivalent to hESCs. They retain epigenetic memory of their tissue of origin [8,9], carry reprogramming-associated mutations [6,7], and show greater line-to-line variability in differentiation [10,13]. For example, the KOLF2.1J iPSC line, which has been adopted by numerous labs, carries copy number variations associated with neurodevelopmental disorder risk [14]. KOLF2.1J may be a suitable model for many developmental processes, but this again highlights the benefit of having a variety of complementary research tools available to the community and supported by NIH.

Adult stem cells cannot replace pluripotent stem cells. The claim that "75 diseases" are treated with adult stem cells refers almost entirely to hematopoietic stem cell transplantation for blood/immune disorders [15]. Adult stem cells cannot generate the cell types needed for Parkinson's disease, Type 1 diabetes, macular degeneration, or Hirschsprung disease.

The framing of Question 3 presupposes that replacement is the goal. Rather, I urge NIH to consider that different stem cell types serve different and complementary research purposes. Restricting hESC research would not accelerate iPSC research but would rather eliminate the reference standard against which iPSC-derived cells are validated.

References:
[13] Koyanagi-Aoi M, et al. Differentiation-defective phenotypes revealed by large-scale analyses of human pluripotent stem cells. PNAS 2013;110:20569-20574. PMID: 24259714
[14] Gracia-Diaz C, et al. KOLF2.1J iPSCs carry CNVs associated with neurodevelopmental disorders. Cell Stem Cell. 2024 Mar 7;31(3):288-289
[15] ISSCR Statement on the Scientific and Therapeutic Value of Human Embryonic Stem Cell Research, April 15, 2025. https://www.isscr.org/isscr-news/isscr-statement-on-the-scientific-and-therapeutic-value-of-human-embryonic-stem-cell-research

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Investment in iPSC technology is warranted for:
- Improving reprogramming efficiency and reducing mutational burden
- Developing robust methods to convert primed iPSCs to naive pluripotency
- Characterizing and banking reference iPSC lines (KOLF2.1J, WTC11) with the depth applied to H9/H1 [10]
- Standardizing differentiation protocols across iPSC lines to reduce variability

However, these investments should complement rather than replace hESC research. I suggest that the most productive path forward is to 1) maintain NIH support for hESC research, 2) support comparative studies rigorously benchmarking iPSC-derived cells against hESC-derived cells for specific applications, 3) Invest in understanding why iPSCs differ from hESCs, which may enable rational improvements to reprogramming.

Forcing an unnecessary transition to iPSCs before scientific validation would harm patients waiting for therapies and waste taxpayer investment in clinical programs approaching approval.

78. American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG)

I am responding: On behalf of an organization

Name: Rebecca Weaver

Name of Organization: American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG)

Type of Organization: Professional Organization/Association

Role: Organizational Official

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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AAPLOG

Comment on NIH Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research
Notice Number: NOT-OD-26-031
April 23, 2026

The American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) is a medical professional organization that represents approximately 8,000 women's healthcare professionals across the country. We are passionate about providing excellent, evidence-based healthcare to ALL our patients. We were founded to represent the vast majority of OB/GYNs who do not perform induced abortion, which intends the death of our fetal patients. We recognize based on the medical evidence that this practice is not healthcare, and we are passionate about providing excellent, evidence-based healthcare to ALL our patients.

AAPLOG appreciates the National Institutes of Health's (NIH) thoughtful reassessment of the scientific utility and ethical implications of human embryonic stem cell (hESC) research. We strongly support NIH's efforts to reduce and ultimately eliminate reliance on human embryonic stem cells in federally funded research.

AAPLOG affirms that human embryos are distinct living human organisms from the earliest stages of development and therefore deserve the dignity and ethical protections owed to all human beings.[i] Scientific evidence demonstrates that each human being begins life as a human embryo and develops continuously from that embryonic stage.
Because hESC research necessarily depends upon the destruction of human embryos, such research raises profound ethical concerns incompatible with the medical profession's longstanding obligation and commitment to "do no harm." Deliberate destruction of embryos by any means is unethical. Experimentation on human embryos that may lead to their death or destruction, and without their consent, violates core principles of medical ethics and human subject protections.

Importantly, NIH itself recognizes that the biomedical research landscape has evolved substantially, with newer technologies such as induced pluripotent stem cells (iPSCs) and adult/somatic stem cells increasingly supplementing or replacing hESC use. These emerging technologies offer robust scientific alternatives without requiring the destruction of embryonic human life.

AAPLOG respectfully urges NIH to:

1) **Require that any proposed research on embryos conform to the international consensus guidelines on human subject research**, including requirements that the study design ensures that human embryos are not the subject of destructive, harmful, or deforming research;

AAPLOG

2) **Permanently discontinue the use of human hESC in federally funded research**, incorporating development of a strategic framework to phase out federal dependence on hESC-based research;
3) **Prioritize funding and expansion of ethically derived alternatives** such as induced pluripotent stem cells and adult stem cells; and
4) **Increase investment in validation studies** that establish non-embryonic stem cell platforms as replacements for hESCs in areas where hESCs have historically been used.

Scientific advancement need not come at the expense of vulnerable human life. Ethical and innovative biomedical research can and should proceed using methods that respect the inherent dignity of every human being, including human embryos.

AAPLOG commends NIH for opening this important review and encourages the agency to modernize its policies in a manner that reflects both current scientific capabilities and enduring ethical obligations.

Respectfully submitted,

Dr. Christina Francis
CEO
American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG)

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[i] "Ethical Treatment of Human Embryos" available at: https://aaplog.org/wp-content/uploads/2024/11/2024.11.19-WEBSITE-CO-12-Ethical-Treatment-of-Human-Embryos-final.pdf

79. N/A

I am responding: On behalf of myself

Name: N/A

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Research areas that heavily rely on approved hESC lines include studies on human development, disease modeling, and regenerative medicine/cell replacement therapy. For example, many groups in the field of type 1 diabetes still use hESC lines to generate pancreatic islets for their studies. In most cases, the currently approved lines meet the needs of the community.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
While many future projects in research areas such as disease modeling and cell replacement therapy could be transitioned to induced pluripotent stem cells instead of hESCs, many experiments still rely on tools that have been built in existing hESC lines. For example, our group is using genetically modified hESC lines that took years to generate to produce hypoimmune stem cell derivatives. It is thus critical to maintain access to currently approved hESCs even if emerging technologies are preferred in the future.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Additional side by side characterization of iPSC and hESC derivatives is still needed to better understand if they can replace fully them.

80. United States Congress

I am responding: On behalf of an organization

Name: US Representatives and US Senators

Name of Organization: United States Congress

Type of Organization: Other

Type of Organization - Other: US House of Representatives and US Senate

Role: Other

Role - Other: Elected Officials

Date Submitted: 04/23/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Congress of the United States
Washington, DC 20515

April 24, 2026

The Honorable Jay Bhattacharya, M.D., Ph.D.
Director
National Institutes of Health
U.S. Department of Health and Human Services
Building One, Room 244
One Center Drive
Bethesda, Maryland 20892

Director Bhattacharya,

We applaud National Institutes of Health's (NIH) Request for Information[1] (RFI) seeking public comment on reducing or ending the use of human embryonic stem cells for research. This is an area with clear and dramatic need for modernization on the part of NIH to reverse previous unethical policies and to bring NIH funding priorities into better alignment with developments in stem cell research. **To this end, we urge the NIH to end permanently all applications for new human embryonic stem cell (hESC) lines, shut down the NIH Human Embryonic Stem Cell Registry (Registry), and completely stop all funding for hESC research.**

This research is unethical, it has not yielded good results, and there are ethical alternatives available that have already provided treatments and cures.

The NIH policy on funding hESC research and maintaining the Registry, which currently lists more than 500 hESC lines, has been a moral blot on NIH. This research relies on the death of human embryos.[2] It is repugnant to treat any human life as disposable for so-called "medical research purposes." There is no such thing as a "spare" human being, and the U.S. government should not be facilitating or funding research that depends on killing and harvesting cells from human beings in their youngest form.

As an additional consideration, despite enormous research investment in hESC, it has not even yielded good results for patients. By way of background, embryonic stem cells are pluripotent, which means that the cells can differentiate to become different organs and tissues. Over twenty years ago, proponents of hESC research argued that this pluripotency could be harnessed to restore damaged organs and tissues.[3] Supporters, like actor Christopher Reeve, predicted "biological miracles," which have never materialized. More than 25 years of research have not yielded any FDA-approved hESC therapies on the market.[4] Yet, year by year, the federal government continues to fund this outdated, unethical research (between Fiscal Years

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[1] NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research. Notice Number: NOT-OD-26-031. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-031.html

[2] Ibid.

[3] Tarne, Eugune. "Human Embryonic Stem Cell Research 25 Years On." October 30, 2023. https://lozierinstitute.org/human-embryonic-stem-cell-research-25-years-on/.

[4] Ibid.

2021-2024 alone, NIH spent over $1.2 billion on hESC research[5]) rather than focusing resources on more promising, less ethically compromised areas of research.

Meanwhile, ethical stem cell research, such as that conducted with adult stem cells, umbilical cord blood, and induced pluripotent stem cells (iPSCs), already offers treatments and cures for millions of patients worldwide with additional studies seeking to unlock future potential.

Adult Stem Cells. Adult stem cell transplants using stem cells found in blood and bone marrow have been used to treat numerous hematopoietic conditions ranging from blood cancers and blood disorders to certain immune and metabolic disorders, and even select solid tumors.[6] Between 2012 to 2016, the number of patients treated with these transplants jumped from 1 million to 1.5 million.[7] By today, well over 2 million patients would have been treated.[8] The University of Notre Dame's Center for Stem Cells and Regenerative Medicine also notes that adult stem cells, including those found in tissues other than bone marrow, may also have the potential to treat still more conditions, including "type 1 diabetes (providing insulin-producing cells), heart attack (repairing cardiac muscle), and neurological disease (regenerating lost neurons in the brain or spinal cord)."[9] In recent years, adult stem cells have shown evidence of effectiveness in treating a range of conditions, including cardiovascular, cerebrovascular, and autoimmune diseases, as well as graft-versus-host disease and the growth of new corneas for sight recovery.[10,11]

Umbilical Cord Blood. Blood from umbilical cords is another promising source of stem cells. This "cord blood," typically discarded after labor and delivery, is rich with stem cells that can be used in research, regenerative medicine, and transplantation.[12] Umbilical cord blood has so far been used to treat over 75 diseases, including leukemia, lymphoma, and sickle cell disease.[13] Patients with a wide range of conditions have seen their lives transformed due to these treatments.[14]

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[5] NIH Categorical Spending Table. Accessed February 26, 2025. https://report.nih.gov/funding/categorical-spending#/, searching on term "embryonic - human"

[6] Snowden, John A. et al. "Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022." *Bone Marrow Transplantation* 57, 1217–1239, 2022. doi: 10.1038/s41409-022-01691-w

[7] Gratwohl A et al; Worldwide Network for Blood and Marrow Transplantation (WBMT). One million haemopoietic stem-cell transplants: a retrospective observational study. *Lancet Haematol*. 2015;2:e91–e100. doi: 10.1016/S2352-3026(15)00028-9. https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.118.313664

[8] Niederwieser D et al., One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of nonidentical family donors. *Haematologica* 107, 1045-1053, 2022. https://haematologica.org/article/view/haematol.2021.279189

[9] Center for Stem Cells and Regenerative Medicine. "Adult Stem Cells." University of Notre Dame. Accessed February 26, 2025. https://stemcell.nd.edu/research/alternative-stem-cell-sources/adult-stem-cells.

[10] Prentice DA, Adult Stem Cells: Successful Standard for Regenerative Medicine, *Circulation Research* 124, 837-839, 2019; doi: 10.1161/CIRCRESAHA.118.313664

[11] Acharya S et al., Stem cell therapies in the clinic, *Bioengineering and Translational Medicine* 10(3) e70000, May 2025, doi: https://doi.org/10.1002/btm2.70000

[12] Sander Lee, Tara, Ph.D. Written Testimony. Subcommittees on Healthcare, Benefits, and Administrative Rules and Government Operations for the Committee on Oversight and Government Reform "Exploring Alternatives to Fetal Tissue Research" December 13, 2018. https://oversight.house.gov/wp-content/uploads/2018/12/Sander-Lee-Testimony-HCBAR-GO-Fetal-Tissue-12.13.18.pdf

[13] National Marrow Donor Program. "The Cord Blood Donation Process and FAQs." Accessed February 26, 2025. https://www.nmdp.org/get-involved/join-the-registry/donate-cord-blood/cord-blood-donation-process

[14] Stem Cell Connect. https://stemcellresearchfacts.org/ success-stories

The federal government has long recognized the life-saving potential of umbilical cord blood. In 2005, Rep. Chris Smith authored the Stem Cell Therapeutic and Research Act of 2005[15] (P.L. 109-129), ground-breaking legislation that connects patients needing treatment with genetically matched cord blood stem cells, providing new opportunities for patients to access cures. It was reauthorized by Congress in 2010, 2015, and 2020.[16,17] In the past, virtually every placenta and umbilical cord was discarded as "medical waste." Today, doctors have turned this "medical waste" into medical miracles, and it holds significant promise for future stem cell research.

Induced Pluripotent Stem Cells (iPSCs). Yet another ethical source of stem cells, iPSCs are "reprogrammed" adult somatic (body) cells, induced to create pluripotent stem cells that resemble embryonic stem cells—without involving human embryos at all.[18] iPSC technology revolutionized biological research and has been used in applications such as disease modeling, regenerative medicine, and drug discovery studies.[19] Dr. Shinya Yamanaka, who received the Nobel Prize in 2012 for his groundbreaking discovery of iPSCs, said his work was inspired by looking down a microscope at a human embryo.[20] He said, "When I saw the embryo, I suddenly realized there was such a small difference between it and my daughters.. .I thought, we can't keep destroying embryos for our research. There must be another way." [21] iPSCs have since become widely used, including in such areas as cardiac disease monitoring, neural disorders like Alzheimer's disease, liver disease, and spinal cord injury, with early results showing marked successes, including restoring movement for paralyzed patients.[22,23]

The proven effectiveness of these ethical sources of stem cells contrasted with the dismal record of hESC research reveals the urgent need for NIH to modernize its funding strategy for stem cell research. The NIH should never have allowed research that relies upon and incentivizes the destruction of human life to be funded with billions of taxpayer dollars. It certainly should refrain from continuing to do so, especially after that great expense has delivered so little benefit for patients.

In conclusion, the NIH should take this opportunity to end permanently all reliance on hESCs for research—including the cessation of all NIH funding for hESC research, maintenance of the Registry, and any applications for new hESC lines—and redirect those resources towards research using ethical alternatives, such as adult stem cells, umbilical cord blood, and iPSCs, that

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[15] Congress.gov. H.R.2520 - Stem Cell Therapeutic and Research Act of 2005. https://www.congress.gov/bill/109th-congress/house-bill/2520/text/statute?statuteId=42387&s=2&r=20

[16] Congress.gov. H.R.2820 - Stem Cell Therapeutic and Research Reauthorization Act of 2015. https://www.congress.gov/bill/114th-congress/house-bill/2820/text?s=2&r=10

[17] Congress.gov. H.R.3520 - Stem Cell Therapeutic and Research Reauthorization Act of 2019 https://www.congress.gov/bill/116th-congress/house-bill/3520

[18] Tarne, Eugene. "Human Embryonic Stem Cell Research 25 Years On." Charlotte Lozier Institute *On Science Series* 15, October 2023. https://lozierinstitute.org/human-embryonic-stem-cell-research-25-years-on/

[19] Sayed, Nazish, MD, PhD and Joseph C Wu, MD, PhD. "Translation of Human-Induced Pluripotent Stem Cells: From Clinical Trial in a Dish to Precision Medicine." Journal of the American College of Cardiology 67, 2161-2176, 2016. https://www.sciencedirect.com/science/article/pii/S0735109716010263

[20] The Nobel Prize. "Shinya Yamanaka: Facts." https://www.nobelprize.org/prizes/medicine/2012/yamanaka/facts/

[21] Fackler, Martin. "Risk Taking Is in His Genes." New York Times. December 11, 2007. https://www.nytimes.com/2007/12/11/science/11prof.html?pagewanted=print

[22] Aboul-Soud, M.A.M.; Alzahrani, A.J.; Mahmoud, A. Induced Pluripotent Stem Cells (iPSCs)—Roles in Regenerative Therapies, Disease Modelling and Drug Screening. Cells 2021, 10, 2319. https://doi.org/10.3390/cells10092319

[23] Mallapaty, Smriti, "Paralysed man stands again after receiving 'reprogrammed' stem cells." *Nature* News 24 March 2025, https://www.nature.com/articles/d41586-025-00863-0

are already providing treatments for millions of patients, and which hold much greater promise for new breakthroughs and cures.

Sincerely,

Roger F. Wicker
United States Senator

Christopher H. Smith
Member of Congress

Steve Daines
United States Senator

Kat Cammack
Member of Congress

Charles E. Grassley
United States Senator

Andy Harris, M.D.
Member of Congress

Ted Budd
United States Senator

Member of Congress

Jim Banks United
States Senator

Sheri Biggs
Member of Congress

Robert B. Aderholt
Member of Congress

Ron Estes
Member of Congress

[redacted]

Michael Guest
Member of Congress

[redacted]

John J. McGuire III
Member of Congress

[redacted]

Andy Biggs
Member of Congress

[redacted]

Ben Cline
Member of Congress

[redacted]

Eric A. "Rick" Crawford
Member of Congress

[redacted]

Mike Kelly
Member of Congress

[redacted]

Warren Davidson
Member of Congress

[redacted]

Robert E. Latta
Member of Congress

[redacted]

Mary E. Miller
Member of Congress

[redacted]

Addison P. McDowell
Member of Congress

[redacted]

Pete Ricketts
United States Senator

81. Takanori TAKEBE

I am responding: On behalf of myself

Name: Takanori TAKEBE

Name of Organization: Cincinnati Children's Hospital Medical Center

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/24/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Approved lines: molecular similarities and dissimilarities between naive/ primed iPSC and ESC, biological response in space or extensive environments, reproductive lineage differentiation
New hESC lines: genetic heterogeneity, advanced NAM differentiation consistency over iPSC

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Molecular state intrinsic to embryonic state
X chromosome inactivation

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Tissue regeneration and aging related biology

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Long term outcomes of cell based therapy research

82. Science Alliance for Life and Technology (SALT)

I am responding: On behalf of an organization

Name: David A. Prentice, PhD

Name of Organization: Science Alliance for Life and Technology (SALT)

Type of Organization: Non-profit Research Organization

Role: Organizational Official

Date Submitted: 04/24/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
There are no areas of research where hESC lines are adequate for researchers, either scientifically or ethically, whereas adult stem cells and iPS cells fully meet all needs for human research.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
There are no areas where hESCs would factually be considered a gold standard or any standard, lacking ethical as well as scientific robustness. All areas of research are fully open to pursuit via adult stem cells and iPS cells, and these sources are better suited for both basic and clinical applications.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Virtually every area of research is amenable to use of iPS cells, adult stem cells, perinatal sources, and other biotechnologies. These research avenues are both pragmatically and ethically superior to hESCs.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Adult stem cells (tissue stem cells including perinatal sources) and iPS cells, both in terms of in vitro models as well as clinical application models, could benefit greatly from increased investment. These investments promote modern medical science and put the patient first.

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/SALT-comment-to-NIH-hESC-in-NOT-OD-26-031.pdf

Description: Extended comments and remarks in response to RFI

Comment on Stem Cells and NIH-Supported Research

Date: 24 April 2026
To: Dr. Jay Bhattacharya, M.D., Ph.D., Director of the National Institutes of Health
In response to: Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research Notice: NOT-OD-26-031

Dear Director Bhattacharya:

This comment is submitted in response to the above-captioned public notice and is being submitted on behalf of the Science Alliance for Life and Technology (SALT), a 501(c)(3) organization committed to education and research regarding nascent human life.

Thank you for the opportunity to submit comments and information regarding this RFI. This document is meant to supplement and extend the brief statements made in the submission form, as well as to provide additional context to the information.

Alongside the pragmatic questions of research utility, there remain significant bioethical and legal questions regarding the derivation and use of human embryonic stem cells. Certainly the foundational question is whether any human being should be used or destroyed for research. The unassailable fact that a human embryo even at the earliest stages is a human being has been demonstrated repeatedly and is accepted as axiomatic. A new human life begins at sperm-egg fusion, i.e., fertilization.[1] The result is an organism, a totipotent one-cell embryo, meaning a cell capable of generating a globally-coordinated developmental sequence.[2] Indeed, Ronan O'Rahilly, highly-respected embryologist who developed the Carnegie Stages, the accepted standard of human embryological development since 1942, has bluntly stated it in this way: "Prenatal age begins at fertilization, postnatal age at birth."[3] Putting this recognition on a more personal level, the journal Nature titled a story on human development "Your destiny, from day one."[4] Thus, this recognition of the earliest stages of a human embryo as a human being puts the very derivation of embryonic stem cells, relying as it does on destruction of an early embryo, at odds with ethical treatment of nascent human life. Given this bioethical concern for nascent human life, it would be prudent to prohibit support for human embryonic stem cell science.

Alongside this is another ethical concern—acceptability of any product arising from human embryonic stem cell research. The NIH Director in his confirmation hearing stated that "In public health, we need to make sure the products of science are ethically acceptable to everybody," and this is a significant recognition that public health research has the goal of helping the public. There is a significant probability that many citizens would foreswear use of

[1] AAPLOG Research Committee. Ethical Treatment of Human Embryos, *Issues in Law & Medicine* 40 (1), 48-76, 2025; doi: 10.70257/MZYZ1423
[2] Condic ML, Totipotency; What it is and what it is not. *Stem Cells and Development* 23, 796-812, 2014; doi: 10.1089/scd.2013.0364
[3] O'Rahilly R, Müller F, Developmental Stages in Human Embryos: Revised and New Measurements, *Cells Tissues Organs* 192, 73–84, 2010; DOI: 10.1159/000289817
[4] Pearson H, Your destiny, from day one, *Nature* 418, 14–15, 2002; https://doi.org/10.1038/418014a

any product based on human embryonic cells, because it involves destruction of nascent human life. This is not a hypothetical; such a public backlash was seen in the rejection of COVID-19 vaccines by a large swath of the American public for ethical reasons, because the vaccines used tissues and cells from elective abortion in production or testing of the vaccines.

There also remain legal and legislative questions about the validity of federal hESC funding. Two lawsuits brought eight years apart challenged federal support of hESC research based on the longstanding Dickey-Wicker amendment, with particular focus on the phrase in the appropriations rider which prohibits funding for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death…"[5] At one point an Appellate Justice called the interpretation that "research in which" separates the act of destruction of the embryo from use of the embryo's cells in the lab "linguistic jujitsu."[6] Eventually, NIH prevailed in the courts because of Chevron deference, meaning the courts defer to a federal agency in interpretation of an ambiguous phrase. However, in recent years the Supreme Court has overturned the practice of Chevron deference, which opens again the question of legal interpretation of hESC federal funding.[7]

The statement has been made that "NIH is assessing research areas ripe for modernization."[8] Human embryonic stem cell research is certainly one area ripe for discarding as antiquated and unfruitful. Since 1998, when hESC were first successfully cultured in the lab, there have been repeated promises that cures are only 5-10 years away. Yet over 25 years later, there are still zero cures, and a paucity of published papers documenting safety or any clinical progress with hESC.[9] Moreover, the Stem Cell Registry should be abolished as medieval. It was supposedly created to hold various hESC lines for different research projects, providing genetically-diverse lines as well as disease-specific lines. But this necessitated destroying thousands of embryos in order to create the several hundred lines on the Registry, and most lines do not contain experimentally useful genetic traits or diseases. Instead, this has been a route for scientists to access NIH grant funding, by creating the hESC lines.

Replacing hESC research with modern science is smart public policy, as it was with fetal tissue from elective abortion.[10] Referring to the ethical concern of using nascent human life for experiments to derive hESC, the National Bioethics Advisory Commission (NBAC) in its September 1999 report on stem cell research opined:

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[5] *Sherley, et al. v. Sebelius, et al.,* Complaint for Declaratory and Injunctive Relief, No. 1:09-cv-01575 (D.D.C. August 19, 2009); and *Nightlight Christian Adoptions, et al. v. Thompson, et al.,* Complaint for Declaratory and Injunctive Relief at 2, Nightlight Christian Adoptions v. Thompson, No. 1.01 CV 00502-RCL (D.D.C. Mar. 8, 2001).

[6] Jocelyn Kaiser, Stem Cell Ruling Brings Relief for Now, But Legal Battle Continues, Science, 29 April 2011, doi: 10.1126/article.28883.

[7] Amy Howe, Supreme Court strikes down Chevron, curtailing power of federal agencies, SCOTUSblog, June 20, 2024, https://www.scotusblog.com/2024/06/supreme-court-strikes-down-chevron-curtailing-power-of-federal-agencies/

[8] NIH, "NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research, NOT-OD-26-031, January 23, 2026; accessed at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-031.html

[9] Tarne EC, Human Embryonic Stem Cell Research 25 Years On, On Science Series 15, October 2023, Charlotte Lozier Institute, accessed at: https://lozierinstitute.org/human-embryonic-stem-cell-research-25-years-on/

[10] David Prentice, "Modern Science Is Smart Public Policy for a Healthy Nation and Economy" The Daily Signal published February 9, 2026

> "In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research.... The claim that there are alternatives to using stem cells derived from embryos is not, at the present time, supported scientifically. We recognize, however, that this is a matter that must be revisited continually as the science advances."

Sadly, NBAC went on to approve the destruction of embryos for hESC harvest, while ignoring the evidence present even at that time for alternatives. [11]

This brings us to the questions about need and alternatives to hESC given in the RFI. The evidence shows that hESCs have never met the needs of researchers seeking patient treatments or accurate models, were never a gold standard for stem cells or occupied a unique niche for research use, and could be replaced with many, scientifically superior alternatives, all of which deserve the focus and investment of federal taxpayer funding. These alternatives have been known and discussed for years, and even decades ago displayed a wealth of published evidence for their potential.[12] In more recent years the contrast between hESC and iPS cells in terms of grants, publications, and applications has become evident.[13] Perhaps one of the most telling aspects pointing to modern alternatives like iPS cells, is the replacement of hESCs with iPSCs in the commercial lab of Dr. James Thomson, the first successfully to culture hESCs.[14] The ease of creation of iPS cells from virtually any tissue makes them an ideal source for pluripotent stem cells, and an obvious replacement for the failed Registry, because iPS cells can be made from genetically-diverse individuals as well as from patients, allowing study of any "disease in a dish." The iPS cells also make excellent models, can be used for drug screening, and have even restored movement to paralyzed patients in early clinical trials.[15,16,17]

Any discussion of a gold standard of stem cells for patients points to adult stem cells, including umbilical cord and cord blood stem cells. These are the cells that have repeatedly shown evidence not just in preclinical research but in actual clinical applications, now having benefited millions of patients around the globe (1.5 million by 2019)[18] for multiple conditions, including numerous blood cancers, multiple sclerosis, chronic stroke, type 1 diabetes, spinal cord injury,

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[11] Prentice, D.A. The Case Against Federal Funding of Human Embryonic Stem Cell Research, *Yale Journal of Health Policy, Law, and Ethics*, Vol. II, Issue 1, pp. 201-210; Autumn

[12] Prentice, D. "Adult Stem Cells." Appendix K in Monitoring Stem Cell Research: A Report of the President's Council on Bioethics, 309-346. Washington, D.C.: Government Printing Office, 2004. Online version, 2004

[13] NIH, Annual NIH-support levels for hESCs and hiPSCs, accessed at: https://osp.od.nih.gov/supplemental-information-for-guide-notice-pause-on-new-submissions-nih-human-embryonic-stem-cell-registry-and-rfi-on-reducing-reliance-on-human-embryonic/

[14] Baker, M. James Thomson: shifts from embryonic stem cells to induced pluripotency. *Nat Rep Stem Cells* (2008). doi: 10.1038/stemcells.2008.118

[15] Sayed N et al., Translation of Human-Induced Pluripotent Stem Cells: From Clinical Trial in a Dish to Precision Medicine, J American College of Cardiology 67, 2161-2176, 2016, doi: 10.1016/j.jacc.2016.01.083

[16] Aboul-Soud MAM et al., Induced Pluripotent Stem Cells (iPSCs)—Roles in Regenerative Therapies, Disease Modelling and Drug Screening. Cells 2021, 10, 2319, doi: 10.3390/cells10092319

[17] Mallapaty, Smriti, "Paralysed man stands again after receiving 'reprogrammed' stem cells." *Nature* News 24 March 2025, https://www.nature.com/articles/d41586-025-00863-0

[18] Niederwieser D et al., One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of nonidentical family donors, *Haematologica* 107, 1045-1053, 2022, doi: haematol.2021.279189

graft-versus-host disease, and epidermolysis bullosa.[19,20,21,22] Other examples of clinical success include with various leukemias, sickle cell anemia, and Krabbe disease.[23] While this recitation could continue at great length, we will finish with one recent publication that showed evidence for decreasing aging frailty.[24]

In summary, there is no valid reason to continue support or funding for human embryonic stem cell research. Superior alternatives including adult stem cells and iPS cells, provide modern science to benefit patients, scientific modelling, and public health.

Sincerely,

David A. Prentice, Ph.D.
President and Founding Board Member
Science Alliance for Life and Technology (SALT)

[19] Prentice DA (2019) Adult Stem Cells: Successful Standard for Regenerative Medicine, *Circulation Research* 124, 837-839, 15 March 2019; DOI: 10.1161/CIRCRESAHA.118.313664
[20] Prentice DA. Remembering Pioneers in Patient Treatments. *J. Tissue Sci. Eng.* 3:e119, 1000e119, 2012; DOI: 10.4172/2157-7552.1000e119
[21] Hirsch T et al., Regeneration of the Entire Human Epidermis Using Transgenic Stem Cells, *Nature* 551, 327-332, November 16, 2017, doi: 10.1038/nature24487
[22] Acharya S et al., Stem cell therapies in the clinic, *Bioengineering and Translational Medicine* 10(3) e70000, May 2025, doi: 10.1002/btm2.70000
[23] Stem Cell Research Facts, https://stemcellresearchfacts.org/
[24] Ruiz JG et al., Randomized phase 2b dose-escalation trial of stem cell therapy with laromestrocel for aging frailty, *Cell Stem Cell* 33, 1–12, 2026, doi: 10.1016/j.stem.2026.01.017

83. Kathleen M. Schmainda

I am responding: On behalf of myself

Name: Kathleen M. Schmainda

Name of Organization: N/A

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/24/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
No need exists to justify the intentional destruction of human life at any stage, including the embryonic stage. hESC research needs to stop. hESC experimentation has yet to yield proof of concept for cellular therapeutics. Human embryonic research has proven wasteful, ineffective, and problematic.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs are often described as "gold standards" for pluripotency, but several documented limitations refute this assumption.
1. They do not fully replicate in-vivo human embryonic development.
2. They exhibit species-specific and culture-induced artifacts. hESCs are grown in artificial environments that alter gene expression, epigenetic states, and differentiation behavior. These culture conditions create in-vitro artifacts that do not exist in natural human embryos, reducing their value as universal biological references.
3. They lack the genetic diversity of real human populations. All widely used hESC lines come from a tiny number of embryos. This means they cannot model the genetic variation that shapes human biology, disease susceptibility, and drug responses. A single cell line cannot serve as a "reference human."
4. They carry risks and abnormalities not representative of normal biology. Documented limitations include:
*Teratoma formation risk, reflecting uncontrolled growth not typical of normal tissues.
*Low and inconsistent differentiation efficiency, meaning they do not reliably produce mature, functional human cell types.
*Immunogenicity, which is not representative of autologous human tissues.
These issues show that hESCs behave differently from the tissues they are supposed to model.

Even though hESCs are pluripotent, they do not naturally recreate the complexity of human biology.
1. They represent only a brief, pre-implantation developmental window. hESCs originate from the inner cell mass of a blastocyst—a very early embryonic stage. They do not capture later developmental processes, tissue maturation, aging, or environmental exposures that shape real human biology.
2. They lack the multicellular, systemic context of a living organism such as as immune interactions, endocrine signaling, mechanical forces, vascularization. hESCs in a dish cannot reproduce these systemic factors.
3. They often fail to generate fully mature, functional human cell types.

Differentiated derivatives of hESCs frequently resemble fetal-like or immature cells, not adult human tissues. This limits their ability to model adult disease or physiology.
4. They do not model disease-relevant genetic backgrounds. Because hESCs come from embryos without known disease mutations, they cannot naturally model patient-specific conditions—unlike induced pluripotent stem cells (iPSCs), which can be derived from affected individuals.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Ethically sourced human induced pluripotent stem cells (hiPSCs) and non-embryonic human stem cell research have vastly surpassed embryonic stem cells in basic research, clinical advancements, and federal funding.

Human induced pluripotent stem cells (hiPSCs) and organoids (3D cell-derived organ models) are a valuable and ethical alternative available to researchers that do not rely on the destruction of human life or bring harm to the donor and mimic the basic biologic properties of embryonic stem cells and structures. iPSCs can model disease, support drug discovery, and generate differentiated cell types without using embryos.

Taken together, these developments mean that no modern research field is blocked or impossible without hESCs

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
Substantial investment into umbilical cord blood banking is needed. The umbilical cord blood is a rich source of embryonic stems cells that is usually discarded at birth. And nobody is harmed in obtaining these tissues. Moreover, there should be more effort in saving the cord blood of each individual - as a potential therapeutic option later in life with disease onset.

84. N/A

I am responding: On behalf of an organization

Name: Michael S

Name of Organization: N/A

Type of Organization: Industry (Biotech/Device/ Pharmaceutical Company)

Role: Other

Role - Other: CEO

Date Submitted: 04/24/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
None. Bad research. Bad science.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
None.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
All.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
All.

85. Tara Sander Lee, PhD

I am responding: On behalf of myself

Name: Tara Sander Lee, PhD

Name of Organization: Science Alliance for Life and Technology (SALT)

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/24/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
None

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
None. Human life begins at fertilization (sperm-egg fusion). Every human being is a precious human life, from the moment of conception. All research that creates, exploits, manipulates, and destroys human beings at any stage of development is controversial and unethical, because it involves the intentional harm and destruction of nascent human life with inalienable rights, inherent dignity, and value. Human embryonic research has proven wasteful, ineffective, and problematic, and has yet to yield proof of concept for cellular therapeutics.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Several ethical alternatives that do not rely on the intentional destruction of human life have yielded much success in research and medicine. Ethically sourced human induced pluripotent stem cells (hiPSCs) and non-embryonic human stem cell research have vastly surpassed embryonic stem cells in basic research, clinical advancements, and federal funding. Induced Pluripotent Stem Cells (iPSCs) are an ethical and valuable alternative to human embryonic stem cells that do not rely on the intentional destruction of human life. Induced PSCs (iPSCs) mimic the basic biologic properties of embryonic stem cells and structures. In 2006, Dr. Shinya Yamanaka reported the first production of induced pluripotent stem cells (iPSCs). Yamanaka led his research team in the discovery of sets of genes that could be introduced into mature somatic mouse cells and induce them to regain properties nearly identical to those of mouse ESCs. It was not very long, thereafter, that the labs of Yamanaka and others showed that the same types of genes could be used to make human iPSCs (hiPSCs) by similar techniques, using mature somatic human cells (e.g., skin cells) obtained ethically from consenting adults. In 2012, Yamanaka was awarded the Nobel Prize in Physiology or Medicine for this scientific advance.

Tissue Stem Cells (adult stem cells) are another ethical alternative, found in nearly all organs and tissues. Tissue stem cells have distinct biological properties from hESCs. First, unlike hESCs, they are naturally occurring and have not been bioengineered or experimentally derived. They are normal human tissue cells. They are not pluripotent, meaning they are able to produce only the distinctive cells of the organ or tissue that they renew. Tissue stem cells have been the focus of biological investigations of their

nature and function in human organs and tissue for more than half a century. A major focus has been elucidating their role in human carcinogenesis when they sustain either spontaneous or induced mutations in cancer-causing genes. Tissue stem cells are a viable alternative to hESCs for developing innovative cellular therapies for diseases and disorders that lack effective medical treatments. Human tissue stem cell experimentation established proof of its therapeutic concept with bone marrow blood (hematopoietic) stem cell and umbilical cord blood stem cell transplantation treatments decades ago. Ethically sourced adult stem cells from living donors and birthing tissues (i.e., cord blood) have treated over 2 million patients worldwide. Current human tissue stem cell medical research is building on this foundation. For more information, see: https://stemcellresearchfacts.org/

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Organoids (3D cell-derived organ models) derived from ethical cell sources are another valuable and alternative available to researchers that do not rely on the destruction of human life or bring harm to the donor and mimic the basic biologic properties of embryonic stem cells and structures. Additional investments are encouraged to bolster these model systems to replace hESCs.

86. Seth Taapken

I am responding: On behalf of myself

Name: Seth Taapken

Name of Organization: N/A

Type of Organization: Non-profit Research Organization

Role: Member of the Public

Date Submitted: 04/25/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
• hESC lines have been pivotal in a broad array of basic biological research studies including the use of genetically engineered lines, e.g. reporter lines, and expanding the genetic diversity as well as disease relevance with new hESC lines will provide for future advances.
• hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes, and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.
• New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
• hESC lines provide the "ground truth" of the earliest steps in human development because they are derived directly from the pre-implantation human embryo
• hESCs provide the only natural benchmark for defining human stem cells.
• hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
• Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
• The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
• Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

• hESCs cannot be replaced by current alternative technologies and are needed as a reference standard and a benchmark for future work and the development of these alternatives. Lack of this benchmark may slow technological advancement or create insufficient technologies.
• hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
• hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.
• Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.
• An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
• Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies
• Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.
• Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.
• Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

87. Lauretta Lacko

I am responding: On behalf of myself

Name: Lauretta Lacko

Name of Organization: Weill Cornell Medicine

Type of Organization: Academic Institution

Role: Other

Role - Other: Core Facility Director, Assistant Professor

Date Submitted: 04/25/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
• hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes, and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.

• New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
• Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

• Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.

• The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
• hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.

• Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not

pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.

• An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

• Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies

• Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.

• Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.

• Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

88. Paul Feeser

I am responding: On behalf of myself

Name: Paul Feeser

Name of Organization: N/A

Type of Organization: Not Applicable

Role: Member of the Public

Date Submitted: 04/26/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
The use of embryonic stem cells should cease on moral grounds, and any alternative should be furthered.
Significantly, their use has reportedly fallen far short of predicted outcomes.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

89. Catharine Krebs

I am responding: On behalf of myself

Name: Catharine Krebs

Name of Organization: Physicians Committee for Responsible Medicine

Type of Organization: Other

Type of Organization - Other: N/A

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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PhysiciansCommittee
for Responsible Medicine
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April 24, 2026

Re: NOT-OD-26-031 NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

Dear Associate Director Jorgenson:

On behalf of the Physicians Committee for Responsible Medicine, a 501(c)(3) nonprofit organization supported by nearly one million members and supporters worldwide working for effective, efficient, and ethical medical research and product testing, thank you for the opportunity to respond to this request for information.

Human induced pluripotent stem cell (iPSC) use has grown rapidly in the last two decades. These cells are easier to derive and more accessible than human embryonic stem cells (hESCs), with far more than 10,000 lines available and many of them specific to diverse human genetic conditions.[1] Like hESCs, iPSCs are pluripotent; they can be derived via multiple methods and from multiple sources, they have no significant differences in gene expression levels, surface-marker expression or morphology when from the same genetic background and can model specific disease phenotypes from patient donors.[2] iPSCs have transformed *in vitro* research, with a variety of applications including disease and developmental modeling, drug discovery and toxicity testing, and cell-based therapeutics.[3]

Still, there is progress to be made in the development, characterization, and validation of iPSC models. For example, because of the reprogramming process from somatic cells to pluripotent stem cells, iPSCs retain some of their somatic identity, such as transcriptional, methylation, and chromatin accessibility signatures, as well as age-related mitochondrial effects and mutational burden, which can be tumorigenic.[4] iPSCs will therefore only fulfill their promise to replace the use of hESCs if supported by funding and investment. Notably, Germany is acknowledged as a

[1] Guhr A, Kobold S, Seltmann S, Seiler Wulczyn AEM, Kurtz A, Löser P. Recent Trends in Research with Human Pluripotent Stem Cells: Impact of Research and Use of Cell Lines in Experimental Research and Clinical Trials. Stem Cell Reports. 2018;11(2):485-496. doi:10.1016/j.stemcr.2018.06.012
[2] Wnorowski A, Yang H, Wu JC. Progress, obstacles, and limitations in the use of stem cells in organ-on-a-chip models. Advanced Drug Delivery Reviews. 2019;140:3-11. doi:10.1016/j.addr.2018.06.001
[3] Cerneckis J, Cai H, Shi Y. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. Sig Transduct Target Ther. 2024;9(1):1-26. doi:10.1038/s41392-024-01809-0
[4] *Ibid*.

global leader in iPSC research, largely as a result of significant investment and financial and political support.[5] The NIH is already taking steps to effectively prioritize human-based research methods, of which iPSC-based models are a large portion, and has acknowledged that funding, training, and infrastructure will be crucial to their broader use.[6]

To ensure iPSC-based models are being prioritized by investigators, we recommend that administering institutes, centers, and offices encourage their use in funding opportunities and highlighted topics, including by explicitly stating that iPSC-based models are a key area of interest.[7] To ensure the workforce is fully supported to use these methods, the NIH should introduce more iPSC-specific training, education, and career development grant opportunities through the use of T-series, F-series, K-series, and R25 grants.

To encourage their broader use, iPSCs and iPSC-based models should be made more accessible through additional investment in infrastructure projects, including increased investment in academic research centers. Examples of NIH-funded infrastructure projects that have already been successfully used to support the development and use of iPSC-based technologies include: the Translational Center for Microphysiological Systems (TraCe MPS) program,[8] which establishes regional hubs for developing human cell-based models for multiple research areas; the recently awarded Complement Animal Research in Experimentation (Complement-ARIE) Technology Development Centers, which will support the development of combinatorial new approach methodologies—cell-based models integrated with AI—and will have built-in training and outreach components to help scale the adoption of these technologies and further facilitate the transition away from hESCs;[9] and the Standard Organoid Modeling Center, which will serve as a national hub for cell-based organoid development.[10] Additional programs and projects such as these should be supported by the Office of Research Infrastructure Programs and funded through P60 and P30 research center funding mechanisms and G20 and C06 construction grants to develop and modernize research facilities to better support iPSC-based research.[11]

Finally, the NIH should invest in bolstering access to human iPSCs through biobanks, increased donation and collection efforts, and improved storage methods and quality standards. The NIH

[5] Guhr A, Kobold S, Seltmann S, Seiler Wulczyn AEM, Kurtz A, Löser P. Recent Trends in Research with Human Pluripotent Stem Cells: Impact of Research and Use of Cell Lines in Experimental Research and Clinical Trials. Stem Cell Reports. 2018;11(2):485-496. doi:10.1016/j.stemcr.2018.06.012

[6] NIH to prioritize human-based research technologies. National Institutes of Health. Published April 13, 2025. Accessed April 13, 2026. https://www.nih.gov/nih-prioritize-human-based-research-technologies

[7] Grants & Funding. Highlighted Topics. National Institutes of Health. Dec. 10, 2025. Accessed April 14, 2026. https://grants.nih.gov/funding/find-a-fit-for-your-research/highlighted-topics

[8] National Institutes of Health. Translational Centers for Microphysiological Systems (TraCe MPS)(U2C Clinical Trials Not Allowed). National Institutes of Health. Dec 27, 2022. Accessed April 13, 2026. https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-23-001.html

[9] Office of Strategic Coordination—The Common Fund. Complement Animal Research in Experimentation (Complement-ARIE) Program. National Institutes of Health. Mar. 31, 2026. Accessed April 14, 2026. https://commonfund.nih.gov/complementarie/highlights/technology-development-centers-and-nams-data-hub-and-coordinating-center

[10] NIH Standard Organoid Modeling (SOM) Center. National Institutes of Health. Mar. 3, 2026. Accessed April 13, 2026. https://www.nih.gov/som

[11] National Institutes of Health. Development of Collaborative Research Facilities of Research-Resource Facilities (CO6 Clinical Trail Not Allowed). National Institutes of Health. Mar. 20, 2026. Accessed April 13, 2026. https://files.simpler.grants.gov/opportunities/6179eb2c-9239-40ad-9a12-7329291f3509/attachments/f1f13568-9784-4a26-938b-5e0133e0c8e2/PAR-26-106-Revised-Full-Announcement.html

has funded many biobanks that offer iPSCs, like the National Institute of Neurodegenerative Diseases and Stroke (NINDS) Human Cell and Data Repository at Rutgers University,[12] the NINDS Repository Human Induced Pluripotent Stem Cells (iPSCs) at Coriell Institute Stem Cell Biobank,[13] and the Jackson Laboratory iPSC collection funded by the NIH's Center for Alzheimer's and Related Dementias.[14] These resources provide scientists with reliable access to iPSCs, including lines derived from specific disease populations. Expanding the number and scope of these biobanked iPSC collections will help bolster iPSC use and iPSC-based model development across NIH-funded research. Promoting rigorous quality control measures and standardized best practices for iPSC collection, storage, and distribution will help improve reproducibility by reducing pre-experimental variability and further drive adoption. Finally, greater investment in tissue collection and donation efforts is essential to broaden the diversity and representation of available samples, ultimately enhancing the relevance and impact of downstream clinical studies.

Thank you for your attention to these comments.

Sincerely,

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Director of Medical Research
Physicians Committee for Responsible Medicine

Catharine E. Krebs, PhD
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Physicians Committee for Responsible Medicine

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Science Policy Specialist
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Jessica Kopew, PhD
Medical Research Specialist
Physicians Committee for Responsible Medicine

[12] National Institute of Neurological Disorders and Stroke. Cell/Tissue/DNA. Accessed April 24, 2026. https://www.ninds.nih.gov/current-research/scientific-resources/celltissuedna
[13] Coriell Institute for Medical Research. Coriell Stem Cell Biobank. Accessed April 24, 2026. https://www.coriell.org/0/sections/collections/cscb/default.aspx
[14] The Jackson Laboratory. Human iPS Cells. Accessed April 24, 2026. https://www.jax.org/jax-mice-and-services/ipsc

90. Regenerative Medicine Foundation and Healthspan Action Coalition

I am responding: On behalf of an organization

Name: Bernard Siegel

Name of Organization: Regenerative Medicine Foundation and Healthspan Action Coalition

Type of Organization: Other

Type of Organization - Other: N/A

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/RMF_HSAC_NOT-OD-26-031_Comment_Letter_20260424.pdf

9314 Forest Hill Blvd Ste 2,
Wellington, FL 33411

April 24, 2026

Office of Science Policy
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

RE: Response to NOT-OD-26-031

Ladies and Gentlemen:

In its January 23, 2026 notice (NOT-OD-26-031; the "031 Notice"), the NIH Office of Science Policy ("OSP") requested information relating to "Reducing or Potentially Replacing Reliance on Human Embryonic Stem Cells in NIH-Supported Research."[1] In response to the 031 Notice, the two undersigned affiliated patient advocacy not-for-profit organizations, the Regenerative Medicine Foundation ("RMF") and Healthspan Action Coalition ("HSAC"), are respectfully submitting this comment letter.

RMF seeks to accelerate regenerative medicine to improve health and deliver cures. For the past quarter of a century,[2] RMF and its predecessors have been connecting the wide range of stakeholders within the field of stem cell-based regenerative medicine through various communications channels. These stakeholders have included patient advocates, researchers at academic medical centers, physicians, surgeons, administrators and other healthcare industry participants, authors, policymakers, and other organizations with aims similar to those of RMF.[3] A principal communications channel spearheaded by RMF has been the World Stem Cell Summit, held annually in different venues across the United States from 2004 through 2023. For the past three years, RMF has actively pursued expanding and enhancing its social media platform and, through shared leadership, staff, and advisors,[4] has actively collaborated with HSAC.

HSAC sprang from RMF in 2022 as a global, cross-sector stakeholder alliance with a common focus on human healthspan, the period of life an individual spends in good health, free of disease and disability.[5] As of the date of this letter, HSAC includes 300-plus members, consisting mostly of companies engaged in healthspan-oriented businesses and other patient advocacy organizations, and also includes several healthspan-oriented meeting and conference sponsoring organizations whose events are included in HSAC's membership list. HSAC seeks to address aging as a treatable medical condition by advancing innovative policymaking, fostering increased research funding, accelerating regulatory pathways, and assisting patient advocates and other organizations focused on healthspan initiatives.

RMF and HSAC believe that at least for the next several years, research with both hESCs and human induced Pluripotent Stem Cells ("hiPSCs") will remain foundational to further development of regenerative medicine and broadscale widening of healthspan, with the benefits of each important not only to public health, but also the long-term financial stability, strength, and growth of the United States.[6] With respect to public health and healthspan,

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[1] NIH Office of Scientific Policy, "NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research", Release Date January 23, 2026, NOT-OD-26-031, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-031.html; as supplemented by OSP in https://osp.od.nih.gov/supplemental-information-for-guide-notice-pause-on-new-submissions-nih-human-embryonic-stem-cell-registry-and-rfi-on-reducing-reliance-on-human-embryonic/.

[2] "Committed to Cures: An Interview with RMF's Bernard Siegel" (courtesy of Future Medicine), published July 11, 2017. https://regmedfoundation.org/2017/07/11/committed-to-cures-an-interview-with-rmfs-bernard-siegel-courtesy-of-future-medicine/

[3] ***See*** https://regmedfoundation.org/advocacy/.

[4] Shared leadership and advisors include Melissa King, Eve Herold, and Alan Jakimo.

[5] ***See*** https://healthspanaction.org/healthspan-action-coalition-unites-300-cross-sector-organizations-in-worlds-largest-healthspan-alliance/

[6] Several authors have argued that increased healthspan on a population-wide scale will lead to macroeconomic

robust NIH-funded hESC and hiPSC research programs are still key for the development of interventions in the aging process, treatments for age-related diseases, and cell and gene therapies for conditions ranging from the toes to the head. We can readily foresee the integration of hESC research with machine intelligence to create digital twins of each hESC line in the NIH hESC Registry (the "Registry"), thereby allowing at least for a reduction in the use of hESCs. Without continued hESC research, this will be next to impossible, if not fully impossible.

Moreover, while hiPSCs may, at some point in the future, totally eclipse hESCs for powering medical applications of pluripotent stem cell technology, and thereby render unnecessary further government funding support of hESC research, we believe for the reasons discussed in this letter that time has not yet come and will only come through further hESC research that benefits our understanding of both hESCs and hiPSCs as treatment modalities. Policies that weaken hESC research will thus directly impede the invention and development of both hESC-based and hiPSC-based medicines, with negative impacts on public health and healthspan.

As OSP's supplement to the 031 Notice (the "031 Supplement") demonstrates, NIH's annual hESC research funding from 2012 through 2019 doubled, growing from approximately $150 million to approximately $300 million, while NIH's annual funding of hiPSC research over the same period grew sixfold from approximately $150 million to almost $900 million. [7]

The 031 Notice, as so supplemented to include NIH's hESC and hiPSC funding data, suggests that because (i) hiPSC funding has been eclipsing hESC funding and (ii) no new hESC lines have been added to the Registry since December 2023,[8] funding for hESC research and Registry operations for new hESC lines can be ended. We believe, however, that this view does not account for two important items:

> ***First,*** hESC funding did not decline during the period covered in the 031 Supplement, but indeed doubled from 2012 through 2019 and held steady through 2024 thereafter[9]; and
>
> ***Second,*** as demonstrated below, from the very start of the hiPSC field 20 years ago, hESC research has served as the "gold standard" for determining whether hiPSC-based[10] regenerative medicine advanced therapies are safe for administration to patients. At some point, we may know everything there is to know about hiPSCs for purposes of regenerative medicine and/or have advanced New Alternative Methodologies ("NAMs"), such as digital twins of hESC cells, that render obsolete further research with hESCs; but that point is not on today's event horizon. (The FDA program on NAMs is described further below.)

OSP's Request for Information

On January 23, 2026, OSP announced a pause on new submissions to the Registry and requested information relating to reducing reliance on hESCs in NIH-supported research (the "Pause").[11] In the 031 Notice, OSP states:

> Given the decline in requests to NIH for new hESC line approvals, NIH is pausing its review and approval of applications for new hESC lines to be added to the NIH Human Embryonic Stem Cell Registry while it undertakes an assessment of the scientific utility of hESCs. Previously approved hESC lines listed on the Registry may continue to be used in NIH-funded research.

We aim, through the numbered points below, to convincingly demonstrate the continuing scientific utility and necessity of hESC research as a foundation for further research and clinical translation of both hESCs and hiPSCs and the consequent need to continue operation of the Registry. Collectively, these points lead to the conclusion that

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benefits. ***See, e.g.,*** Scott, AJ, Ellison, M & Sinclair, DA, *The economic value of targeting aging.* Nature Aging 1, 616–623 (2021). https://doi.org/10.1038/s43587-021-00080-0. (The authors model that expanding healthspan over mere lifespan extension would boost U.S. GDP via increased consumer spending, work hours, and leisure value; with a 1-year healthspan gain yielding a $37.6 trillion willingness-to-pay (WTP), scaling to $366.8 trillion for 10 years.)

[7] ***See*** Note 1, *supra*.

[8] ***See*** Note 1, *supra*.

[9] NIH's published RCDC data is only available through 2024.

[10] We use the term "regenerative medicine advanced therapy(ies)" ("RMAT(s)" in the manner in which it is defined in the 21st Century Cures Act, Public Law No. 114-255, 130 Stat. 1033 (2016).

[11] NIH. *NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research.* NOT-OD-26-031, January 23, 2026. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-031.html

ending funding support of hESC research is neither scientifically nor clinically justified, and would adversely affect the bipartisan support that hESC research has received for the past 30 years. In 2009, the end of about the first 10 or so years of that span, the Registry emerged as a logical extension of the "existing line" policy adopted by President George Bush on August 9, 2001. Under that policy, research with hESC lines existing as of that date would be federally fundable. The "existing line" policy served as President Bush's Solomonic approach to untying the Gordian knot formed by the simultaneity of the ethical issues raised by hESC research and the enormous medical value of that research.[12]

We acknowledge that there may come a day when NIH funding of hESC research is no longer necessary, but that day, we believe, has not yet come and is not within today's event horizon. Thus, to abandon funding support of hESC research in the short term would, we believe:

1. threaten U.S. leadership in (a) stem cell biology generally and (b) hiPSC applications specifically;
2. adversely affect clinical studies of cell therapies developed through not only hESC technology but also through hiPSC technology;
3. adversely affect FDA's New Approach Methodologies (NAMs) program aimed at fulfilling the 2022 Congressional mandate to refine, reduce, and replace the use of animal models in nonclinical studies of new drugs, biologics, cell and gene therapies, and medical devices; and
4. undermine the broad-based, bipartisan support for increasing years of healthy life for all people.

We need to underscore the third of these four points, as we believe that OSP should consider the potentially adverse impacts of ending government-funded hESC research on FDA's NAMs program. The NAMs program has emerged directly from the FDA Modernization Act 2.0, enacted by the U.S. Congress in December 2022, and discussed in detail below.[13] If hESC research is indeed vital for the development of NAMs as a Congressionally mandated regulatory science matter, this point needs to be carefully understood by policymakers and regulators in any debate or discussion regarding discontinuing government funding of hESC research.

In presenting each of the four points enumerated above, we provide below observations in the literature, in some cases 15 or so years old and in other cases less than three years old, each of which speaks to differences between hESCs and hiPSCs that need to be understood in order to determine that hiPSCs are sufficiently safe for use as, or in the manufacture of, interventions and treatments based on those hiPSCs. The more current literature suggests that several of the differences, first identified 15 or so years ago, may still need to be addressed. As a general principle in assessing the potential elimination or decreased NIH funding of hESC research and closing of the Registry to new cell lines, we believe that the questions posed by these differences needs to be fully addressed before any such actions are taken. This alone seems to justify maintaining the Registry and its operation.

Stem Cell Research – Background

Before engaging in discussion of the points outlined above, we need to review the background history of stem cell research. We do this not to provide an exhaustive text book type description of that history, but to suggest that the discussion and debate engendered by the 031 Notice can be enhanced by participants in that discussion and debate sharing a common understanding of that history.

Stem cell research as reported in the scientific literature begins with the research on "stammzellen" ("stem cells" in English) performed by German scientist Ernst Haeckel at the University of Jena, with his first paper containing that term published in 1868,[14] and research on formation of the different cells comprising blood (which by 1931 came to be called "hematopoiesis"[15]) performed by Russian-American Vera Danchnakoff at The Rockefeller University in

[12] Bush, *G. W. Address to the nation on stem cell research.* (August 9, 2001. Selected Speeches of President George W. Bush 2001-2008. https://georgewbush-whitehouse.archives.gov/infocus/bushrecord/documents/Selected_Speeches_George_W_Bush.pdf

[13] S. 5002, passed unanimously by the U.S. Senate on September 29, 2022, and by the House on December 23, 2022, as part of the Consolidated Appropriations Act, 2023 (Public Law 117-328)

[14] Haeckel, Ernst. *Natürliche Schöpfungsgeschichte: Gemeinverständliche wissenschaftliche Vorträge über die Entwickelungslehre im Allgemeinen und diejenige von Darwin, Goethe und Lamarck im Besonderen*. Berlin: Ernst Günther, 1868. (First edition; based on lectures; 15 plates, 19 woodcuts, 18 stem trees; later editions up to 9th by 1899, translated into 12 languages).

[15] Marmorston-Gottesman J, Perla D. Studies on Bartonella Muris Anemia : V. Compensatory Phenomena

New York City in the mid-1910s,[16] before she moved to Columbia University's College of Physicians and Surgeons. For the next 30 years following Danchnakoff's 1916 publication and except for the work of Sabin, Doan, and Forkner, also at the Rockefeller, in the 1920s and early 1930s,[17] the stem cell field remained quiescent.

This changed in the late 1940s, when physicians in Japan began encountering an unnerving number of leukemias suffered by the survivors of Hiroshima and Nagasaki. These cases, together with radiation studies, revealed the need for hematopoietic (i.e., blood-forming) stem cells to regenerate tissues damaged by radiation or otherwise suffering from radiation-induced cell death, thereby preventing regeneration of blood and other tissues. [18]

This revelation prompted investigations into the role of bone marrow in the recovery of these patients and led to radiation experiments on animals in the late 1940s and 1950s demonstrating that bone marrow transplants could rescue irradiated mice, leading to the hypothesis of self-renewing stem cells. At that time, radiation biology research to address nuclear weapon effects and protecting personnel from radiation was performed at U.S. national labs and universities with funding provided primarily by the U.S. government and military through the U.S. Atomic Energy Commission.[19]

During the 1950s this biomedical radiation research evolved into NIH-supported hematology medical research programs, culminating in James Till and Ernest McCulloch's definitive experiments in the early 1960s confirming the existence of hematopoietic stem cells.[20] And so was born NIH's funding of stem cell-based medical research.

Turning the clock forward, from FY2008 through FY2024 (the most recent period covered by NIH in its web-posted Research, Condition, and Disease Categorization ("RCDC") funding table[21]), NIH funding for stem cell research in aggregate has totaled $27.8 billion, growing at a compound annual growth rate ("CAGR") of 5.9%, from $938 million in FY2008 to $2.35 million in FY2024. The time plot illustrating these funding amounts is presented below in Figure 1. (Figure 1 excludes incremental funding in 2009 and 2010 under the American Recovery and Reinvestment Act of 2009.)

The aggregate funding for hESC research during the same period was $3.7 billion, with the annual amount growing from $88 million in 2008 to $306 million in 2019 (reflecting a CAGR of 12.0%), and rising to $322 million in 2024 (reflecting a CAGR of 1.0% from 2019 through 2024). As a percentage of NIH's annual total stem cell spending , hESC has held relatively steady, growing from 9.4% in 2008 to a high of 15.3% in 2017, and decreasing to 13.7% in 2024. This data is not the sign of a moribund area of scientific research; rather it provides evidence of continued federal funding for hESC research.

In comparison, the aggregate funding for hiPSC research from 2012 (when such spending is first registered in NIH's RCDC data) through 2024 was $6.98 million, almost twice the amount of aggregate hESC research funding during

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Following Splenectomy in the Adult Albino Rat. J Exp Med. 1931 May 31;53(6):877-83. doi: 10.1084/jem.53.6.877. PMID: 19869890; PMCID: PMC2132037.

[16] Danchakoff V. *The Differentiation of Cells as a Criterion for Cell Identification, Considered in Relation to the Small Cortical Cells of The Thymus.* J Exp Med. 1916 Jul 1;24(1):87-105. doi: 10.1084/jem.24.1.87. PMID: 19868031; PMCID: PMC2125411.

[17] Sabin FR, Doan CA, Forkner CE. *The Production of Osteogenic Sarcomata and the Effects on Lymph Nodes and Bone Marrow of Intravenous Injections of Radium Chloride and Mesothorium in Rabbits.* J Exp Med. 1932 Jul 31;56(2):267-89. doi: 10.1084/jem.56.2.267. PMID: 19870065; PMCID: PMC2132174.

[18] Another research project arising from the need to address the leukemias presented by the survivors of Hiroshima and Nagaski, and their offspring, was the Human Genome Project. ***See*** Cook-Deegan R. *The Alta Summi*t. Human Genome Project, U.S. Department of Energy, https://doe-humangenomeproject.ornl.gov/the-alta-summit-december-1984/.

[19] U.S. Department of Energy. *The Atomic Energy Commission and Postwar Biomedical Radiation Research.* ACHRE Report. https://ehss.energy.gov/ohre/roadmap/achre/intro_4.html#:~:text=35%5D%20In%20the%20fall%20of,first%20chief%20of%20the%20DBM.

[20] Lasker Foundation, *Stem cells and their dual properties: self-renewal and differentiation -2005 Albert Lasker Basic Medical Research Award*, https://laskerfoundation.org/winners/stem-cells-and-their-dual-properties-self-renewal-and-differentiation/. (Discusses Till and McCulloch's late 1950s work on ionizing radiation effects, Cold War military concerns, and their foundational stem cell discoveries.)

[21] https://report.nih.gov/funding/categorical-spending#/

the 2008 through 2024 period. As a percentage of NIH's annual total stem cell spending , hiPSC grew steadily from 15.0% in 2008 to 39.4% in 2024.

The figures described above for NIH funding of hESC and hiPSC research are consistent with the chart provided for 2012 through 2024 in the 031 Supplement.[22] Using the number of peer-reviewed articles appearing in the literature as a proxy for leadership, the level of NIH funding for hESC research, supplemented by funds from non-U.S. government sources (e.g., state funding agencies such as those in California, Maryland, Massachusetts, and New York), philanthropists, and private capital, allowed the U.S. to attain the position as the world leader in hESC research. We will return to this point below.

Figure 1*

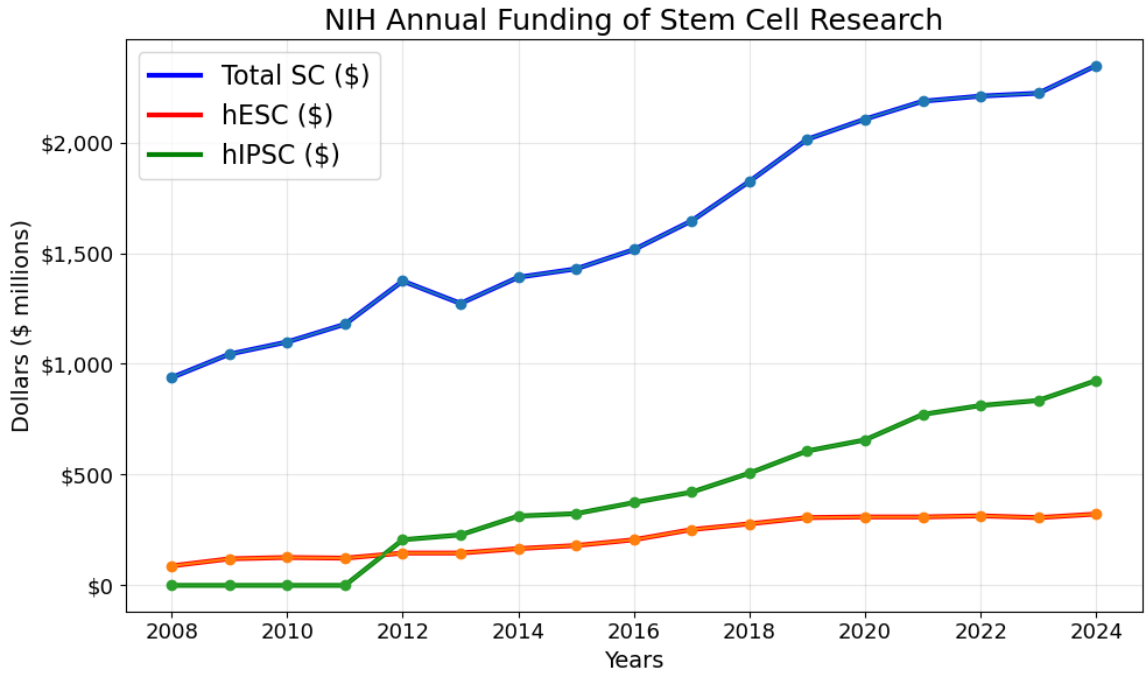


*Figure 1 excludes incremental funding in 2009 and 2010 under the American Recovery and Reinvestment Act of 2009. The first NIH funding year for hiPSC was 2012.

Discussion

We have set forth below five discussion points that we believe are implicated by the suggestion in the 031 Notice that the scientific utility of hESC research may not warrant continuing funding by NIH.

Point 1: Curtailing hESC Research Funding Would Threaten the Benefits of U.S. Leadership in Stem Cell Research Generally.

Axiomatically, any field of scientific research with the promise of transformative medical breakthroughs having U.S. population-wide public health ramifications, with stem cell-based medicine as an example, serves as a key success factor for:

- sustaining U.S. national economic growth and competitiveness;
- ensuring U.S. national security; and

[22] ***See*** Note 1, *supra*.

- propelling the U.S. as a global leader in science and innovation with the attendant benefits thereof.[23]

(a) The Threat to Economic Growth and Competitiveness

A wide-ranging body of economic research describes the "public-private investment multiplier" effect in various fields, including science and technology. According to this effect as a general matter, public spending by government agencies acts as a lever for increased spending in those and adjacent fields by non-government entities.[24] In the case of NIH spending on hESC and hiPSC research, the public-private investment multiplier effect has been described as: driving investment by philanthropists, industry and the states; [25] achieving scientific breakthroughs; expanding new technologies; and supporting job growth[26] and economic growth.[27] Exemplifying the public-private investment multiplier, a report from the University of Southern California states that "[a] $1 public investment in basic research (core to pluripotent stem cells) leverages $8.38 in U.S. industry R&D over eight years, while clinical-stage investments yield $2.35 in private R&D over three years.[28]

Just as public spending on pluripotency stem cell research can positively lever private investment in any given field, so too can it act a negative lever. This means that, acting in reverse, withdrawing a $1 from public investment in pluripotency stem cell research can cause a multiple of that amount to be drawn out of private investment. Thus, before any decision by NIH to eliminate or decrease spending on hESC research, that action needs to be well understood.

(b) The Adverse Impact on National Security

Generally, the U.S. research enterprise serves to protect national security by enhancing warfighter capabilities, securing supply chains, countering biological threats, and preventing adversaries from gaining advantages. In its April 2025 final report, the National Security Commission on Emerging Biotechnology ("NSCEB") underscores this general point by emphasizing biotechnology research aimed at battlefield innovation, supply chain security, readiness, and out-innovating competitors (citing China specifically).[29]

Fifteen years ago, in a blogpost in *The Niche* (a CIRM-sponsored blog),[30] Paul Knoepfler, a CIRM grantee, described several examples of the impact of stem cell technology on regenerative medicine relevant to national security: advances relevant to battlefield injuries (e.g., use of embryonic stem cells to generate different types of blood cells for transfusion); differentiation of hESCs into skin stem cells as a means of healing life-threatening

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[23] ***See, e.g.,*** "Dzau, VJ. *Government-Funded Health and Biomedical Research Is Irreplaceable.* U.S. National Academy of Medicine. August 18, 2025. https://nam.edu/wp-content/uploads/2025/08/Government-Funded-Health-and-Biomedical-Research-Is-Irreplaceable.pdf; and National Academies, *Strengthening the U.S. Research Enterprise.* https://www.nationalacademies.org/strengthening-the-us-research-enterprise (National Academies).

[24] See, e.g., de Janvry A. and Sadoulet E. *Maximising the public-private multiplier*. OECD Development matters. 21 February 2018. https://oecd-development-matters.org/2018/02/21/maximising-the-public-private-investment-multiplier/

[25] The New York Stem Cell Foundation ("NYSCF") exemplifies philanthropic funding of pluripotent stem cell research; and the California Institute for Regenerative Medicine ("CIRM") and the New York Empire State Stem Cell Program ("NYSTEM") serve as examples of state-funded research and development stem cell research programs.

[26] California's $3 billion CIRM initiative created over 56,000 full-time equivalent jobs—half with salaries above the state average in medical and health research—and added $10-10.7 billion to the state's economy via grants, operations, and leveraged funding through 2023.[1] These impacts included $641 million in state/local tax revenue and $727 million federally, while spurring venture capital, licenses, and biotech clusters.

[27] ***See, e.g.,*** Goldman DP et al. *The Economic Case for Public Investment in Stem Cell Research.* USC Shaeffer Center White Paper Series, June 2020. ("California's $3 billion investment in [CIRM]…resulted in over 56,000 jobs created and added approximately $10 billion to the state's economy. Further therapeutic advances, such as in the areas of diabetes, stroke or cancer made as a result of this investment could lead to enormous economic returns. California's experience with stem cell research demonstrates the importance of public investment in this field."

[28] ***See*** Note 27, *supra*.

[29] National Security Commission on Emerging Biotechnology. *Charting the Future of Biotechnology – An action plan for American security and prosperity*. April 2025. https://www.biotech.senate.gov/wp-content/uploads/2025/10/NSCEB-%E2%80%93-Full-Report-%E2%80%93-Sep-30-.25.pdf

[30] Knoepfler, Paul. *Stem cell research a national security issue*. The Niche. California Institute of Regenerative Medicine. March 8, 2011. https://blog.cirm.ca.gov/2011/03/08/stem-cell-research-national-security/

burns; and use of stem cells derived from hESCs for repair of broken bones and cartilage injuries. (Knoepfler also included repair of spinal cord injuries with a reference to an applicable clinical study then underway, but which was not successful.) In each case, Knoepfler pointed out that the scalability of cells derived from hESCs addresses supply chain security, reducing reliance on vulnerable donations amid conflicts. Before eliminating hESC research funded by NIH relevant to these battlefield injury applications in favor of hiPSCs, OSP would need to assure that hiPSCs can stand in for hESCs as matter of scalability and safety described by Knoepfler.

(c) The Diminution of U.S. Leadership in Stem Cell Research Generally Science and Innovation

The significance of the federal government's role in the centuries long achievement by the U.S. of broad-scale leadership in science and innovation, including U.S. leadership in stem cell research generally and pluripotent stem cell research specifically, tracks back at least as far as President Lincoln's 1863 signing into law of the Act of Congress incorporating the National Academy of Sciences ("NAS").[31] The impacts of that long-term achievement of U.S. leadership in science includes overall economic growth, quality of life, and national security through attracting and retaining capital investment, supporting job growth, and deployment from coast to coast of an endlessly expanding universe of novel and useful discoveries and inventions.

The national security element in these benefits was reflected during World War II, when Vannevar Bush, as the Director of the Office of Scientific Research and Development, established a partnership between and among government, universities, and industry focused on innovations important to the war effort. These innovations included the development of breakthroughs such as radar and mass production of penicillin, both of which were credited with helping to end the war in Europe. Bush's innovation was funding civilian scientists without direct government control.

In his 1945 *Science: The Endless Frontier* report, [32] Bush declared that "basic research is the pacemaker of technological progress", posited that scientific progress was essential for national health, public welfare, and defense,[33] and recommended the formation of a National Research Foundation, which in 1950 became the National Science Foundation ("NSF"). In 1980, Congress propelled the potential for this R&D model in the Bayh-Dole Act, allowing universities, subject to various regulations, to license to industry inventions and discoveries arising from their federally funded research and to retain the royalties and fees received by the universities under those licenses.[34] The Bayh-Dole Act has been cited for fostering the growth of the biotechnology industry.[35]

Of concern here is the fact that while aggregate NIH funding of hESC research is just a fraction of the aggregate NIH funding of hiPSC research and an even smaller fraction of aggregate NIH funding of stem cell research generally, these comparisons fail to consider how much both hiPSC research and stem cell research generally rely on the output of hESC research. This is reflected in the following statement by the International Society for Stem Cell Research: [36]

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[31] "An Act to Incorporate the National Academy of Sciences," Chapter 111 of the Statutes at Large, Volume 12, page 806 (12 Stat. 806), enacted March 3, 1863. Section 3 of that Act states in relevant part that NAS "shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science or art, the actual expense of such investigations, examinations, experiments, and reports to be paid from appropriations which may be made for the purpose."

[32] Bush, Vannevar. Science – the Endless Frontier: A Report to the President. U.S. Government Printing Office, 1945.

[33] Bush, *supra* Note 32. ("Science, by itself, provides no panacea for individual, social, and economic ills. It can be effective in the national welfare only as a member of a team, whether the conditions be peace or war. But without scientific progress no amount of achievement in other directions can insure our health, prosperity, and security as a nation in the modern world.")

[34] 35 U.S.C. §§ 200–212 (Title 35, United States Code, Chapter 18: Patent Rights in Inventions Made with Federal Assistance), enacted in Section 6(a) of Pub. L. 96-517, 94 Stat. 3015–3021.

[35] See, e.g., *Pharmaceutical Research and Manufacturing Association, "The Bayh-Dole Act: Spurring American Biopharmaceutical Innovation.* Fact Sheet. October 20, 2022. https://phrma.org/resources/the-bayh-dole-act-spurring-american-biopharmaceutical-innovation).

[36] International Society for Stem Cell Research (ISSCR). *ISSCR Statement on the Scientific and Therapeutic Value of Human Embryonic Stem Cell Research.* April 15, 2025. ISSCR.org. https://www.isscr.org/isscr-news/isscr-statement-on-the-scientific-and-therapeutic-value-of-human-embryonic-stem-cell-research.

> "[hESCs] have enabled foundational advances in regenerative medicine and clinical translation. Research using [hESCs] has informed our understanding of cell differentiation and human development, supported disease modeling and drug screening platforms, and contributed to the development of other pluripotent stem cell–based approaches, such as those using [hiPSCs]. Without [hESC] research, there would be no iPS cells.
>
> Continued federal support for [hESC] research is essential. Eliminating federal funding for[hESC] research… would only delay or prevent the discovery of therapies urgently needed by patients with serious medical conditions. We must leverage every available tool to advance responsible, innovative treatment strategies that improve patient outcomes."

Point 2: Curtailing hESC Research Funding Would Threaten U.S. Leadership in hESC and hiPSC R&D.

(a) The U.S. Leadership Position in hESC Research

The premise of this second point is the leadership position of the U.S. in hESC research. To assess this premise, we performed a preliminary indicative analysis of the peer-reviewed literature posted in pubmed.gov captured by the following search string: "human embryonic stem cell"[Title/Abstract]

We limited the search for this quoted string to the Title and/or Abstract fields in PubMed in order to tighten the gauge of the search filter. The country for each author (without regard for the status of such author as first author, last author, corresponding author, or co-author) in each posted article is set forth in the "Author information" field in the "Abstracts" download format for PubMed listings of articles, reviews, papers, and the like.[37]

Our preliminary work with this method suggests that in terms of the number of papers on hESC research, at least for the period 1996 through 2020, the U.S. was the leading source of peer-reviewed literature relating to that research, but possibly not for the period 2021 through April 2026. We emphasize the preliminary nature of this observation, and that it needs to be treated indicatively, with the attendant need to be reviewed further for accuracy, absence of programming errors, and completeness.

(b) The Continuing Dependency of hiPSC R&D on hESC Research

We believe efforts to refine, reduce, and replace hESC use where scientifically and clinically appropriate are important and should continue. This notwithstanding, hESC research remains scientifically and clinically necessary for important questions arising in hiPSC science.

Consider recent comparative studies showing hiPSCs and hESCs to be broadly similar but not fully equivalent. For example, a proteomic and functional comparison published in 2024 found that notwithstanding the "great potential" of hiPSCs as an alternative to hESCs for applications in regenerative medicine and disease modelling based on near-identical proteomes characterizing hESCs and corresponding hiPSCs, the hiPSCs exhibited "increased total protein content, with increased abundance of cytoplasmic and mitochondrial proteins required to sustain high growth rates, including nutrient transporters and metabolic proteins."[38] This led to "[p]rominent changes detected in proteins involved in mitochondrial metabolism correlated with enhanced mitochondrial potential." In addition, hiPSCs "also produced higher levels of secreted proteins, including growth factors and proteins involved in the inhibition of the immune system. The data indicate that reprogramming of fibroblasts to hiPSCs produces important differences in cytoplasmic and mitochondrial proteins compared to hESCs, with consequences affecting growth and metabolism. This study improves our understanding of the molecular differences between hiPSCs and hESCs, with implications for potential risks and benefits for their use in future disease modelling and therapeutic applications."

These observations in 2024, as well as similar observations reported by others, suggest the existence of open questions as to whether reprogramming yields a distinct pluripotent state with persistent effects on lineage bias, metabolic behavior, and downstream function.

hESCs are also critical for validating hiPSC-based differentiation systems, organoids, and potency assays, especially where direct benchmarking, developmental validation, and safety comparison are required.[39] Reviews and

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[37] The country location in which the institution with which each author is affiliated can be fished out of each such PubMed listing using, among other tools, Python's "regular expression" function.

[38] Brenes AJ, et al. *Proteomic and functional comparison between human induced and embryonic stem cells.* Elife. 2024 Nov 14;13:RP92025. doi: 10.7554/eLife.92025. PMID: 39540879; PMCID: PMC11563575.

[39] ***See, e.g.,*** International Society for Stem Cell Research. *The ISSCR Releases Global Standards to Enhance Rigor*

standardization efforts published after 2020 emphasize persistent challenges in maturation, inter-line variability, and assay reproducibility across human pluripotent stem cell platforms, leaving open the possibility that the process of reprogramming human somatic cells into hiPSCs results in a distinct pluripotent state with persistent effects on lineage bias, metabolic behavior, or downstream function. When hESC and iPSC lines are studied in parallel, investigators can better distinguish limitations of the differentiation protocol from effects attributable to reprogramming history or donor-specific variation. Without hESC comparators, it is more difficult to determine whether an iPSC-derived model faithfully captures human developmental biology or instead reflects a reprogramming-conditioned surrogate state.[40]

Consequently, hESC research may remain required as the only direct human benchmark for defining and evaluating the molecular and functional features of hiPSC states.[41] For so long as such benchmarking is required for determining the safety, efficacy, quality, and labeling ("SEQL") of hiPSC-based interventions and treatments, hESC research will be critical for validating hiPSC-based differentiation systems, organoids, and potency assays. Without hESC comparators, it is exceedingly difficult to determine for SEQL considerations as to whether an hiPSC-derived model faithfully captures human developmental biology or instead reflects a reprogramming-conditioned surrogate state that will result in serious adverse reactions when used for clinical and medical purposes.

To address these concerns as to the comparability of hESCs and hiPSCs, OSP may want to explore a balanced hESC/hiPSC policy aimed at reducing unnecessary hESC research without eliminating NIH funding of continued hESC research on the use of hESC reference standards that may still be needed to answer open questions in pluripotent stem cell biology and to qualify newer, ethically preferred hiPSC models for widespread adoption.[42] Accordingly, reducing or eliminating NIH funding of hESC research aimed at addressing these open questions arising from observed differences between hESCs and hiPSCs, and remaining as challenges to the development of hiPSCs for regenerative medicine, would materially and adversely affect not only such hESC research, but also the research necessary to achieve requisite levels of the safety, efficacy, and quality of interventions and treatments based on the use of hiPSCs.

Point 3. Curtailing NIH Funding of hESC Research Would Adversely Affect On-going Clinical Studies of Stem Cell-based Regenerative Medicine Therapies

The table in Figure 2 below sets forth, as of the date of this comment letter, data relating to clinical studies of stem cell-based interventions and treatments posted in clinicaltrials.gov. This data illustrates that clinical studies of both hESC-based and hiPSC-based interventions and treatments comprise an active area of clinical research.

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and reproducibility of stem cell research. Press Release, June 5,2023. https://www.isscr.org/isscr-news/the-isscr-releases-global-standards-to-enhance-rigor-and-reproducibility-of-stem-cell-research

[40] Brenes Alejandro J., et al. (2024) *Proteomic and functional comparison between human induced and embryonic stem cells*. eLife 13:RP92025. https://doi.org/10.7554/eLife.92025.1 (eLife assessment: "This valuable study uses semi-quantitative proteomics to compare both types of cells, finding interesting differences. The value of the study lies in demonstrating that ESCs and iPSCs cannot be used interchangeably. The conclusions are backed by solid data even if a greater number and diversity in ESC and iPSC clones would help in generalizing the observations.")

[41] Toivonen S, et al. *Comparative analysis of targeted differentiation of human induced pluripotent stem cells (hiPSCs) and human embryonic stem cells reveals variability associated with incomplete transgene silencing in retrovirally derived hiPSC lines.* Stem Cells Transl Med. 2013 Feb;2(2):83-93. doi: 10.5966/sctm.2012-0047. Epub 2013 Jan 22. PMID: 23341440; PMCID: PMC3659749.

[42] EuroStemCell. *Ethics and reprogramming: ethical questions after the discovery of iPS cells.* https://www.eurostemcell.org/ethics-and-reprogramming-ethical-questions-after-discovery-ips-cells

Figure 2: Clinical Studies of Stem Cells Posted in clinialtrials.gov

Search String in Intervention/treatment Field	Total Number of Studies	Number of Recruiting Studies	Number of Active, Not Recruiting Studies	Number of Completed Studies
stem cells	9,126	1,132	449	3,924
pluripotent stem cells	136	45	7	29
induced pluripotent stem cells	134	45	5	30
human induced pluripotent stem cells	59	23	4	7
embryonic stem cells	74	9	8	22
human embryonic stem cells	56	8	7	16

NOTE: The rows in this table are not mutually exclusive. For example, the number of studies in the hESC row is included in the number of studies in the embryonic stem cells row, which tracks back to the number of studies in the stem cells row.

As a matter of first principle, for the reasons described above in Point 2 above, any challenge to clinical translation of hESCs will also, until fully addressed, be an issue for the clinical translation of hiPSCs. Thus, as much as continued hESC research is needed to support clinical translation of hESCs, so too is it needed to support clinical translation of hiPSCs.

For example, for both hESCs and hiPSCs, continued research is needed to address the dependence of clinical translation of each type on: (i) improving clinical-scale manufacturing consistency in compliance with FDA's current Good Manufacturing Practices; (ii) defining potency, and (iv) monitoring long-term safety in differentiated products.

With respect to safety, a November 2025 article describes the "the challenges of immunogenicity, heterogeneity and tumorigenicity" associated with hESCs.[43] This is exacerbated in the case of hiPSCs, where, as the differences described above between hESCs and hiPSCs in terms of their proteomes and mitochondrial metabolism may result in serious adverse effects in clinical studies of hiPSC-based interventions and treatments. In this regard, reviews of hiPSC clinical translation emphasize the existence of unresolved challenges in safety, manufacturing, reproducibility, and regulatory oversight.[44]

With respect to the challenge of heterogeneity, single-cell analyses have revealed increased heterogeneity, slower growth, and impaired differentiation of hiPSCs when compared to hESCs. This less stable state of hiPSCs can have substantial clinical implications, making comparisons with hESCs imperative, which in turn makes cutting edge hESC research imperative.

Emphasizing this point: *As long as clinical translation of hiPSC-based therapies need to be assessed against hESC "gold standard" benchmarks for pluripotency, differentiation fidelity (in contrast to heterogeneity), clinical grade manufacturing consistency and scale-up, and safety-related matters, NIH needs to fund hESC research.*

[43] Xia L, Qin J, Ye S. *Addressing the challenges of immunogenicity, heterogeneity and tumorigenicity in the clinical translation of human embryonic stem cells.* Stem Cell Res Ther. 2025 Nov 25;16(1):694. doi: 10.1186/s13287-025-04826-0. PMID: 41291912; PMCID: PMC12751827.

[44] Dhaiban S, et al. (2025) *Clinical translation of human iPSC technologies: advances, safety concerns, and future directions*. Front. Cell Dev. Biol. 13:1627149. doi: 10.3389/fcell.2025.1627149

Point 4. Curtailing NIH Funding of hESC Research Would Adversely Affect the Use of hESCs and hiPSCs for Drug Discovery and Nonclinical Studies in New Approach Methodologies Required for IND Dossiers

We begin our discussion of this point by taking note of (i) Congress's December 2022 amendment of the Food, Drug and Cosmetic Act of 1938 (as amended) in the FDA Modernization Act 2.0 ("FDAMA 2.0") and (ii) FDA's New Approach Methodologies ("NAMs") program resulting from application of FDAMA 2.0.

In FDAMA 2.0, Congress replaced the term "preclinical tests" with "nonclinical tests" and defined the latter term to include human-cell based "*in vitro*, *in silico*, and *in chemico* studies.[45] We believe that the science of hESCs that is already known combined with the science of hESCs still to come should and can play a vital role in the development and validation of NAMs over the coming years.

As an example of the well-documented use of hESCs and hiPSCs in drug discovery and development, consider the NIH review published in December 2025 titled *Advancements in the in vitro culture of human pluripotent stem cells: progress, challenges, and future directions: comprehensive review*.[46] At the outset of this review, the authors define the term "human pluripotent stem cells" to include hESCs and hiPSCs. The first and last sentences in the abstract of this review read as follows:

> "The advancement of human pluripotent stem cell (hPSC) culture systems has revolutionized the landscape of preclinical drug discovery and toxicological evaluation. …The ongoing evolution of hPSC technologies promises to accelerate the development of safer, more effective therapeutic agents and to reshape the future of human disease modeling and pharmacological research."

Between these two upbeat sentences the following cautionary sentences appear:

> "Despite these advances [of hPSCs], barriers such as cellular immaturity, inter-batch variability, and limited regulatory acceptance persist, *underscoring the need for further protocol standardization and technological refinement*. This review provides a comprehensive analysis of current animal-free hPSC culture platforms, critically examines their strengths and limitations, and discusses future directions for advancing their application in drug discovery and predictive toxicology. *[emphasis added here]*

Given all that is said above about the use of hESCs in their own right as a source of regenerative medicine advanced therapies and as a "gold standard" for assessing the safety, efficacy, quality, and manufacturability of hiPSCs, we believe that we are not at the point at which hESC research funding can be reduced or eliminated. But rather, given the potential value of integrating hPSC science and technology (including both hESCs and hiPSCs) with each of the three principal NAMs components – "*in vitro*, *in silico*, and *in chemico*" – we believe that hESC research funding should be increased to cover this new potential facet of hPSC science and technology.

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[45] FDA over the coming years will be shifting the regulatory science underpinning the collection and analysis of safety and toxicity data for inclusion in Investigational New Drug Applications (INDs) from animal studies to New Approach Methodologies ("NAMs"), with the intent of (i) refining, reducing, and replacing the use of animal testing and (ii) increasing the use of human-derived cells. This safety and toxicology data is required by law for FDA to clear INDs proposing the administration to human subjects of new interventions and treatments. The FDA's NAMs program follows in large part from Congress's amendment of the Food, Drug and Cosmetic Act of 1938 ("FDCA") in its 2022 FDA Modernization Act 2.0. In FDAMA 2.0, Congress (a) replaced the term "preclinical tests" with "nonclinical tests" in the two places in the FDCA relating to the need for FDA to receive safety/toxicology data in order to clear INDs and (b) defined "nonclinical tests" to mean "*in vitro*, *in silico*, or *in chemico*, [and] non-human in vivo test[s]…before or during the clinical trial phase [that] may include animal tests, or non-animal or human biology-based test methods, such as cell-based assays, microphysiological systems, or bioprinted or computer models." The reference to "*in silico*" and "computer models" includes artificial intelligence (perhaps better referred to as "machine intelligence"). FDA relies on this definition of nonclinical tests in both its 2025 Roadmap to reduce preclinical animal studies, and its March 2026 Draft Guidance on validating NAMs. ***See*** FDA. Roadmap to Reducing Animal Testing in Preclinical Safety Studies. April 10, 2025. https://www.fda.gov/files/newsroom/published/roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf; and FDA. *General Considerations for the Use of New Approach Methodologies in Drug Development Guidance for Industry.* Draft Guidance. https://www.fda.gov/media/191589/download

[46] Chaudhary N, Villa-Diaz LG. *Advancements in the in vitro culture of human pluripotent stem cells: progress, challenges, and future directions: comprehensive review*. Front Toxicol. 2025 Dec 2;7:1667573. doi: 10.3389/ftox.2025.1667573. PMID: 41409779; PMCID: PMC12705378.

The use of organoids as a NAM provides an initial example of an integrated NAM/hPSC application, more precisely an integrated NAM/hiPSC application. Beyond this simple example, we foresee a role of the hESC Registry in a program for developing digital twins of existing Registry-approved hESC lines and any future Registry-approved hESC lines. Indeed, in a peer-reviewed article published in November 2025 the authors present "a computational framework that builds digital twins of human induced pluripotent stem cell derived cardiomyocytes from a single optimized voltage clamp experiment [and] unites computational modeling, data simulation, and learning to enable scalable, precise, individualized cardiac electrophysiology modeling and can be readily extended to any electrically active cell type.[47] It is easy to envision extension of this intersection of pluripotent stem cell and machine intelligence technology to the digital twinning of hESC cell lines in the Registry.

Point 5: Elimination of NIH funding of hESC research will undermine the broad-based, bipartisan support for healthspan care for all people through several modalities arising from the development and use of stem cell-based regenerative medicine.

We believe that reducing or eliminating NIH funding of hESC research would severely undermine broad-based, bipartisan support for extending healthspan care to all people through hESC-based and hiPSC-based regenerative medicine therapies.

For example, hESC-based interventions/treatments remain uniquely vital to developing therapies for retinal disease. As of the date of this letter, based on the data in clinicaltrials.gov, nine clinical studies with such interventions/treatments have been completed and three clinical studies with such interventions/treatments are active. These studies demonstrate tangible progress toward the goal of restoring sight to patients, particularly older patients, facing blindness due to retinal diseases.[48]

In addition, as of the date of this letter, based on the data in clinicaltrials.gov, there are 42 clinical studies in various stages of progress and completion with hESC-based interventions/treatments in subjects who are at least 65 years of age.[49] These studies, as well as the 48 such studies with hiPSC-based interventions/treatments in subjects who are at 65 years of age, highlight hESCs' irreplaceable role in translating healthspan discoveries to the bedside, including disease-specific cell lines that accelerate personalized medicine. The indispensable role of hESCs here encompasses both the use of hESC-based interventions and treatments and hiPSC-based interventions and treatments benchmarked against corresponding hESCs for addressing the challenges posed by hiPSC-based interventions and treatments described in the above points.

Bipartisan consensus on healthspan research and development of interventions and treatments aimed at extending healthspan extension for the constitutionally mandated general welfare of the public relies on robust federal support. Without such funding, regenerative medicine's promise for equitable, healthspan-extending therapies may falter, thereby eroding public trust and, echoing Point 1 above, national competitiveness. Stable, continuous NIH funding of hESC research supporting the invention and clinical translation of hESC-based interventions and treatments is thus imperative.

Recommendations

In light of the substantial progress in hESC science and technology achieved during the past 30 years and the need to continue to rely on hESC research to resolve open questions relating to hiPSC clinical and medical applications, we urge NIH to continue funding and regulatory support for hESC research, thereby expediting discovery, development, regulatory approval, and commercialization of regenerative medicine advanced therapies. Toward that end, we urge NIH to adopt the following policies:

1. recognize the importance of hESC research to the success of hiPSC-based regenerative medicine;
2. maintain robust funding for hESC research consistent with the discussion presented above;

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[47] Yang PC, et al. *Large-scale synthetic data enable digital twins of human excitable cells.* bioRxiv [Preprint]. 2025 Nov 17:2025.09.03.674034. doi: 10.1101/2025.09.03.674034. PMID: 40950065; PMCID: PMC12424819.

[48] ***See*** the search of the clinicaltrials.gov database given by https://clinicaltrials.gov/search?intr=human%20embryonic%20stem%20cell&viewType=Card&aggFilters=ages:older&cond=retinal

[49] ***See*** the search of the clinicaltrials.gov database given by https://clinicaltrials.gov/search?intr=human%20embryonic%20stem%20cell&viewType=Card&aggFilters=ages:older

3. resume NIH hESC Registry review and approval operations; and
4. support translational, medical and healthspan widening applications of hESC-based and hiPSC-based regenerative medicine.

Conclusion

Human embryonic stem cells have formed a cornerstone of biomedical research for the past 30 years, enabling transformative discoveries in developmental biology, disease modeling, drug discovery, and regenerative medicine. While hiPSCs represent a major advance, particularly in addressing ethical concerns regarding the derivation of hESCs, they do not and cannot fully replace hESCs across the spectrum of their clinical and medical applications.

We respectfully note that shifting away at this time from hESC research is not scientifically justified and strategically problematic for clinical and medical applications of hiPSCs. This follows from the points discussed in this letter to the effect that a reduction or elimination of NIH-funded hESC research has the potential to:

- threaten U.S. leadership in (a) stem cell biology generally and (b) stem cell-based regenerative medicine applications specifically;
- adversely affect clinical studies of hESC-based and hiPSC-based treatments and therapies;
- adversely affect FDA's program aimed at refining, reducing, and replacing the use of animal models in nonclinical studies of new drugs, biologics, cell and gene therapies, and medical devices by shifting to the use of human cell-based technologies encompassed by New Approach Methodologies described in Point 4 in the above Discussion; and
- undermine the broad-based, bipartisan support for increasing years of healthy life for all people through several modalities, including stem cell-based regenerative medicine.

* * *

On behalf of the Regenerative Medicine Foundation and the Healthspan Action Coalition, we are grateful for the opportunity to comment on the 031 Notice, and we hope that our comments will be helpful to OSP in its consideration of the matters presented in the 031 Notice. Please contact Bernard Siegel, Executive Director of RMF and HSAC, at bernard@healthspanaction.org or 1-888-238-1423, with any questions or comments regarding this letter.

Very truly yours,

/s/ Bernard Siegel
Bernard Siegel
Executive Director
Regenerative Medicine Foundation
Healthspan Action Coalition

91. Charlotte Lozier Institute

I am responding: On behalf of an organization

Name: Cameron Louttit

Name of Organization: Charlotte Lozier Institute

Type of Organization: Other

Type of Organization - Other: N/A

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/Charlotte-Lozier-Institute-Submission-NOT-OD-26-031.pdf

To Whom it May Concern:

The Charlotte Lozier Institute applauds the decision to re-evaluate federal funding for human embryonic stem cell (hESC) research and respectfully urges the NIH to prohibit its further funding, allocating this support instead to promising endeavors that do not put Americans in moral conflict.

The history of hESC research is one of remarkable promises and pressures. Since its earliest days, assertions of "miracle cures" have been routinely used to pave over public and private concerns about this work. Of course, those "miracle cures" have not materialized as proposed, and the reality of over-promising both to secure funding[1] and to appease political and social demands[2] has been well detailed. But over 25 years' worth of attributing unique, curative, and indeed miraculous potential to these cells has, inevitably, left a lasting imprint. External and internal pressures abound to subjugate ethical concerns to scientific potential, both at an individual and a public level.

But this is not an effective strategy to resolve such matters.[3] The reality is that the substantial public and private discomfort with hESCs, evident from the earliest public discussions on their use, has not gone away. Such discomfort is, of course, entirely sensible: it cannot be seriously denied that it is of great consequence to obtain cells, even those with purported therapeutic potential, via the destruction of a human being. As hESC pioneer James Thomson famously put it: "If human embryonic stem cell research does not make you at least a little bit uncomfortable, you have not thought about it enough."[4]

Recent events have provided an opportunity to consider the ramifications of that discomfort. The thoroughly discussed hesitancy of many Americans to receive COVID-19 vaccines (among others) given their links to abortion-derived cell lines[5] has brought into full focus the public health consequences of conducting research and developing therapies that put Americans in moral conflict. Speaking on this topic, NIH Director Dr. Jay Bhattacharya stated in his confirmation hearing that "we need to make sure the products of the science are ethically acceptable to everybody,"[6] subsequently noting that this is "not just an ethical issue, but it's a

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[1] Antonio Regalado, "After 25 Years of Hype, Embryonic Stem Cells Are Still Waiting for Their Moment," MIT Technology Review, August 9, 2023, https://www.technologyreview.com/2023/08/09/1077580/embryonic-stem-cells-25-years-treatments/.
[2] J. Benjamin Hurlbut and Jason Scott Robert, "Stem Cells, Science, and Public Reasoning," *Journal of Policy Analysis and Management* 31, no. 3 (2012): 707–14, https://doi.org/10.1002/pam.21611.
[3] Hurlbut and Robert, "Stem Cells, Science, and Public Reasoning."
[4] Gina Kolata, "Man Who Helped Start Stem Cell War May End It," *The New York Times*, November 22, 2007, https://www.nytimes.com/2007/11/22/science/22stem.html.
[5] Meredith Wadman, "Vaccines That Use Human Fetal Cells Draw Fire," *Science* 368, no. 6496 (2020): 1170–71, https://doi.org/10.1126/science.368.6496.1170.
[6] *Nomination of Jayanta Bhattacharya to serve as Director of the National Institutes of Health: Hearing before the U.S. Senate Committee on Health, Education, Labor & Pensions* (2025), https://www.c-span.org/program/senate-committee/nih-director-nominee-testifies-at-confirmation-hearing/656402.

public health issue." We agree. But further, beyond merely being a public health issue, it foreshadows a public health crisis (or multiple) if we continue along the path of developing therapies that we know many of our citizens may not take.

It need not be so, for two reasons.

Firstly, the pragmatic reason: there is another way. Clinically, substantial impact has already been achieved by adult stem cells (ASCs),[7] to this day the only stem cell therapies with FDA approval. While these cells do not share the pluripotency of hESCs, this in fact contributes to their clinical translatability, as some of the challenges associated with hESCs trace to this very property.[8] The ethical acceptability and demonstrated successes of ASCs certainly merit further support as more such candidates[9] progress through trials. At the same time, the development of induced pluripotent stem cells (iPSCs) has provided an ethically acceptable cell source with the benefits of pluripotency, both for therapeutic candidates and for benchtop research. A recent clinical trial roundup has found iPSC and hESC candidates intermingled amongst a wide array of indications, with hESC trials tapering overall and iPSC trials expanding since 2019.[10] This trend is mirrored in the NIH's data presented in this Request for Information, which shows federal support for iPSCs vastly outpacing that for hESCs in recent years.[11]

The reasons for this preference of iPSCs are multifaceted. There are scientific and clinical advantages, including the availability and diversity of cells, the availability of funding, and the ability to develop therapies that avoid the common hESC challenge of immune rejection.[12] But there are also, importantly, ethical reasons: echoing Director Bhattacharya's remarks, researchers routinely reference the value of creating research outputs that are not ethically problematic.[13] In

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[7] David A. Prentice, "Adult Stem Cells: Successful Standard for Regenerative Medicine," *Circulation Research* 124, no. 6 (2019): 837–39, https://doi.org/10.1161/CIRCRESAHA.118.313664.
[8] *See* Manon Desgres and Philippe Menasché, "Clinical Translation of Pluripotent Stem Cell Therapies: Challenges and Considerations," *Cell Stem Cell* 25, no. 5 (2019): 594–606, https://doi.org/10.1016/j.stem.2019.10.001.
[9] *See, e.g.*, Dragomirka Jovic et al., "A Brief Overview of Global Trends in MSC-Based Cell Therapy," *Stem Cell Reviews and Reports* 18, no. 5 (2022): 1525–45, https://doi.org/10.1007/s12015-022-10369-1; Pingping Han et al., "Engineered Adult Stem Cells: Current Clinical Trials Status of Disease Treatment," in *Progress in Molecular Biology and Translational Science*, vol. 199 (Elsevier, 2023), https://doi.org/10.1016/bs.pmbts.2023.02.007.
[10] Agnete Kirkeby et al., "Pluripotent Stem-Cell-Derived Therapies in Clinical Trial: A 2025 Update," *Cell Stem Cell* 32, no. 1 (2025): 10–37, https://doi.org/10.1016/j.stem.2024.12.005.
[11] National Institutes of Health Office of Science Policy, "Supplemental Information for Guide Notice NOT-OD-26-031: NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research," https://osp.od.nih.gov/supplemental-information-for-guide-notice-pause-on-new-submissions-nih-human-embryonic-stem-cell-registry-and-rfi-on-reducing-reliance-on-human-embryonic/.
[12] Maureen L. Condic and Mahendra Rao, "Alternative Sources of Pluripotent Stem Cells: Ethical and Scientific Issues Revisited," *Stem Cells and Development* 19, no. 8 (2010): 1121–29, https://doi.org/10.1089/scd.2009.0482.
[13] *E.g.*, Samaneh Dehghan et al., "Human-Induced Pluripotent Stem Cells-Derived Retinal Pigmented Epithelium, a New Horizon for Cells-Based Therapies for Age-Related Macular Degeneration," *Stem Cell Research & Therapy* 13, no. 1 (2022): 217, https://doi.org/10.1186/s13287-022-02894-0; Daniela Gois Beghini et al., "Induced Pluripotent Stem Cells: Hope in the Treatment of Diseases, Including Muscular Dystrophies," *International Journal of Molecular Sciences* 21, no. 15 (2020): 5467, https://doi.org/10.3390/ijms21155467; David A. Yefroyev and Sha Jin, "Induced Pluripotent Stem Cells for Treatment of Alzheimer's and Parkinson's Diseases," *Biomedicines* 10, no.

fact, the origin story of iPSCs attests specifically to these ethical considerations. Shinya Yamanaka, awarded the 2012 Nobel Prize in Physiology or Medicine for his work in developing iPSCs, has stated, "[w]hen I saw the embryo, I suddenly realized there was such a small difference between it and my daughters … I thought, we can't keep destroying embryos for our research. There must be another way."[14] And so he found one.

The presence of this "other way" casts new light on the historical discussions of hESCs and, in particular, the pressures regarding their public support. In an influential 2001 *New York Times* editorial, Stephen Jay Gould offered the following:

> Speaking personally, I do not grant the status of a human life to a clump of cells in a dish, produced by fertilization in vitro and explicitly destined for discard by the free decision of the man and woman who contributed the components. But I also have no desire to offend the sensibilities of those who disagree. Thus, if I could derive cells of similar flexibility in a different way, I would gladly do so, even at considerable extra time and expense.[15]

We take profound issue with Gould's characterization of the embryonic human, and we are not alone in that objection; indeed, biology itself testifies against the author.[16] Yet in this article, even the most strident public advancement of hESCs is provided with a caveat—that an alternative, if available, should be pursued instead, if not for the sake of the author, then for the sake of the many who disagree with him.

The presence of these alternatives, and their demonstrated uptake by the scientific and clinical communities, is certainly noteworthy in a discussion of the current status and future of stem cell research. Indeed, it fits squarely within the scope of this Request for Information insofar as this Request seeks public input on "emerging biotechnologies" that can "replace the use of hESCs." Yet this Request additionally invites more input beyond alternatives, asking the scientific community to also justify its current (and future planned) use of hESCs. And here we encounter the second reason why we need not set ourselves on course for a future public health crisis: because it is necessary—and precedented—to set ethical limits on what science can do, even as it pursues noble ends.

While studies have indicated that some hESC researchers encounter moral discomfort in their work,[17] it is perhaps unsurprising given the dynamics of self-selection that many do not, even to

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2 (2022): 208, https://doi.org/10.3390/biomedicines10020208; Condic and Rao, "Alternative Sources of Pluripotent Stem Cells."

[14] Martin Fackler, "Risk Taking Is in His Genes," Science, *The New York Times*, December 11, 2007, https://www.nytimes.com/2007/12/11/science/11prof.html.

[15] Stephen Jay Gould, "What Only the Embryo Knows," *The New York Times*, August 27, 2001.

[16] Emile Scarpelli, "The Earliest Cells: Who Are They?," *The Journal of Maternal-Fetal & Neonatal Medicine* 12, no. 4 (2002): 219–21, https://doi.org/10.1080/jmf.12.4.219.221.

[17] Steven P. Wainwright et al., "Ethical Boundary-work in the Embryonic Stem Cell Laboratory," *Sociology of Health & Illness* 28, no. 6 (2006): 732–48, https://doi.org/10.1111/j.1467-9566.2006.00539.x.

the extent of associating ethics merely with "distracting controversies and poorly designed policies that impede scientific progress."[18] But scientific progress is not a universal good to be pursued always, everywhere, and by any means; in fact, we already have restrictions in place recognizing this. In their discussion of the manifold breakdowns in public deliberations surrounding hESC research, J. Benjamin Hurlbut and Jason Scott Robert note:

> …the observation that the policy environment has had a "chilling effect" on research is not sufficient grounds for criticizing funding limitations as such. Human subjects research protections have a definitive chilling effect on lots of forms of research; that is precisely their purpose. They are intended to prevent (well-intentioned) researchers from violating ethical norms that they may not themselves recognize or agree with.[19]

Across the history of hESC research communications, it is not uncommon to find mention of those ethical perspectives with which researchers disagree. But it is often the case that they are mentioned only to subsequently be ignored in practice, with the "ethical considerations" deemed pertinent to hESC work reduced simply to matters of informed consent, oversight, and appropriate "scientific justification."[20] This latter phrase recalls the Warnock Report's assertion that the embryo has a "special status" that affords him or her protection from being used "frivolously or unnecessarily" in research, but little more.[21] It is thus proposed that an adequate scientific rationale is sufficiently protective against abuses of this "high value" or "sensitive resource"[22] and, therefore, may signify to the public that the experiments proposed are reasonable—or, indeed, even ethically sound. Furthermore, as we have seen, the presentation of the scientific rationale for such studies—often taking the form of lofty promises of these cells' potential—has subsequently dominated the public discussion, sustaining pressure to support and adopt these pursuits regardless of the ethical concerns about their means.

It is through this lens that we offer a cautionary remark on some of the likely responses to this Request for Information, as its call for hESC researchers to justify their work mirrors these long-standing trends in both academic and popular spheres. Surely, scientific rationales will be submitted in response to this Request describing why a particular research endeavor should use hESCs. But this alone is not sufficient. Again, Hurlbut and Robert provide keen insight:

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[18] Holly Longstaff et al., "Scientists' Perspectives on the Ethical Issues of Stem Cell Research," *Stem Cell Reviews and Reports* 5, no. 2 (2009): 89–95, https://doi.org/10.1007/s12015-009-9068-y.
[19] Hurlbut and Robert, "Stem Cells, Science, and Public Reasoning," 709.
[20] *See, e.g.*, Bernard Lo and Lindsay Parham, "Ethical Issues in Stem Cell Research," *Endocrine Reviews* 30, no. 3 (2009): 204–13, https://doi.org/10.1210/er.2008-0031.
[21] Mary Warnock, *Report of the Committee of Inquiry into Human Fertilisation and Embryology* (London, 1984), 63–64, https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf.
[22] Erica C. Jonlin et al., "What Does 'Appropriate Scientific Justification' Mean for the Review of Human Pluripotent Stem Cell, Embryo, and Related Research?," *Stem Cell Reports* 20, no. 5 (2025): 102479, https://doi.org/10.1016/j.stemcr.2025.102479.

> Asking only about the (predicted) instrumental utility of research distracts from the deeper question of what makes for scientific projects that reflect the values, needs, and aspirations of the society in which they are undertaken. These are questions about science itself and about the social contract with science—about how society's aspirations can and should be reflected in the forms of science it supports and upon which it relies.[23]

The questions at hand are indeed beyond mere scientific justification; instead, they ask to what extent—if at all—public support should be enmeshed with research that is objectionable to many Americans and whose fruits may well be on course to yield a public health crisis of our own making. Or, put alternatively, they propose an opportunity: what role can the policies of scientific funding play in establishing, developing, and making widely available that research which is, in the words of the NIH Director, "ethically acceptable to everybody"?

The reality is that science is a resilient field, one that operates within constraints as a matter of course. These constraints are not always technical in nature, nor are they always agreed upon by those whom they regulate. But that can be precisely why they are necessary. To achieve research outputs that do not place Americans in moral conflict, we must place guardrails on the research done by those who may not perceive such conflict. In doing so, we will not only advance the use of existing ethical alternatives, but we will also open wide the path for the development of novel technologies from which all can benefit in sound conscience.

Submitted on behalf of the Charlotte Lozier Institute.

Cameron Louttit, Ph.D.
Director of Life Sciences
Charlotte Lozier Institute
Arlington, VA 22206
202-223-8073

[23] Hurlbut and Robert, "Stem Cells, Science, and Public Reasoning," 710, citing Sheila Jasanoff, ed., *Designs on Nature: Science and Democracy in Europe and the United States* (Princeton University Press, 2007).

92. Tim Kamp

I am responding: On behalf of myself

Name: Tim Kamp

Name of Organization: University of Wisconsin-Madison

Type of Organization: Academic Institution

Role: Investigator/Researcher

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.

- hESC lines have been pivotal in a broad array of basic biological research studies including the use of genetically engineered lines, e.g. reporter lines, and expanding the genetic diversity as well as disease relevance that the available lines can provide for future advances.
- hESCs are being used for cell replacement therapies in many organ systems and are being tested in clinical trials for the treatment of Parkinson's disease, age-related macular degeneration, epilepsy, and Type 1 diabetes (https://doi.org/10.1016/j.stem.2024.12.005), and access to additional genetically diverse hESC lines will provide new opportunities for therapies by reducing immune recognition as well as potentially beneficial biological responses, e.g lines carrying a favorable disease response genetic variant.
- New hESC lines are needed to study disease in which there are no other human models such as fertility research because the beginning of human development is inaccessible or embryonic lethal mutations where iPSC and other models are not possible.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

- hESC lines provide the "ground truth" of the earliest steps in human development because they are derived directly from the pre-implantation human embryo
- hESCs provide the only natural benchmark for defining human stem cells.
- hESCs are required to inform our understanding of how human organs develop, often in species-specific ways that are not recapitulated by animal models.
- Human ESCs remain the gold standard for human pluripotency and cannot be fully replaced by induced pluripotent stem cells (iPSCs). Although data shows that iPSCs are highly comparable and exhibit similar properties to hESCs in many respects, potentially important differences remain.
- The large number of genetically engineered hESC tools that are used in research and therapies would need to be rebuilt with other cell lines. The choice of the replacement cell line is not obvious, as many iPSCs have genomic or epigenomic variations.
- Pregnancy and fetal development are critical stages of life that have a large impact on the subsequent health of both mother and offspring. However, many aspects of both healthy development and pathology during this period remain poorly understood due to the logistical difficulties in obtaining samples.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

- hESCs cannot be replaced by current alternative technologies and are needed as a reference standard and a benchmark for future work and the development of these alternatives. Without this benchmark, new technologies with hESCs may slow technological advancement or create insufficient technologies.
- hiPSCs have substantially expanded the field, but they are reprogrammed derivatives of adult somatic cells and do not fully replicate all epigenetic and developmental features of hESCs
- hIPSCs are more prone to harbor deleterious mutations, either from the somatic cell source or in the reprogramming process with the stress of prolonged passaging.
- Adult stem cells have limited utility as potential replacements for hESCs. Adult stem cells are not pluripotent (cannot differentiate into all cell types) and so their utility is restricted to the organ system from which they were derived (e.g. cord blood stem cells and blood). Adult stem cells cannot be maintained indefinitely in culture (not continuously self-renewing), requiring constant sourcing from individuals. Adult stem cells do not recapitulate features of the earliest steps in human development.
- An effective strategy should strengthen complementary technologies such as iPSCs, organoid systems, and genomic stability monitoring, while maintaining access to hESCs that serve as essential biological reference standards.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

- Comprehensive epigenomics, multiomics, metabolic, and functional comparisons to fully define the differences between hESCs and hiPSCs or other potential alternative technologies
- Methods to engineer hiPSCs to an hESC-like state would be needed but we do not have sufficient knowledge to do so.
- Rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed to provide accessibility to high quality research reagents and enable researchers to carry out their research and therapeutic products.
- Public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

93. Thor Theunissen

I am responding: On behalf of myself

Name: Thor Theunissen

Name of Organization: Washington University in St. Louis

Type of Organization: Academic Institution

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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Response to NIH RFI NOT-OD-26-031 (Theunissen) 04/24/2026

In my research and experience, human embryonic stem cell (hESC) research underpins a broad and mature scientific ecosystem spanning human development, disease modeling, genome engineering, and regenerative medicine. I am concerned that the current NIH pause on new submissions to the Human Embryonic Stem Cell Registry could evolve into broader restrictions that would significantly impair scientifically meritorious research. Such a shift would not represent scientific modernization, but rather a premature and counterproductive policy change that risks slowing discovery, weakening translational momentum, and undermining prior federal investment.

Human embryonic stem cells (hESCs) remain the gold-standard reference because they can give rise to all cell types in the body and therefore provide the most reliable model for studying human development. They are widely used as a benchmark to evaluate other cell systems, including induced pluripotent stem cells (iPSCs). While newer approaches have expanded the range of available methods, they have not been shown to fully match the consistency, accuracy, and reliability of hESC-based systems across the breadth of NIH-supported research. Moreover, decades of NIH investment have built a strong foundation of widely used hESC lines, specialized cell lines with built-in markers to track gene activity, well-established differentiation methods, and shared research resources. Restricting access to these systems would not simply shift research to alternative platforms, but would require recreating these validated tools at significant cost and time, while introducing additional variability and making it harder to compare results across studies. In addition, the current pause on new submissions to the NIH Human Embryonic Stem Cell Registry already limits progress by restricting access to new and more diverse hESC lines. Continued access to new lines is essential to support emerging applications, including improved disease models, advanced research tools, and translational approaches aligned with current scientific and clinical needs.

This impact is illustrated by my own research. I am a faculty member at Washington University in St. Louis, where my laboratory studies early human development and how stem cells give rise to different cell types in the embryo and placenta. This work relies on hESCs that are uniquely capable of generating all cell types in the human body, as well as key placental cell types, making them the most accurate model for studying early human development. NIH-supported studies in my lab use hESCs to recreate key features of the earliest phases of human development in the laboratory and to understand how cells make decisions about their future identity. These processes cannot be faithfully modeled using iPSCs or animal systems. A central part of this work involves engineered hESC lines that contain built-in fluorescent markers, allowing us to track gene activity and cell fate decisions in real time and at scale. These tools enable rapid testing of how genes and environmental factors influence early development. Recreating these systems in alternative cell platforms would require substantial time and resources and would introduce additional variability, as they ultimately depend on comparison to hESCs to confirm that they accurately reflect human development. These hESC-based systems also serve as the starting point for generating three-dimensional tissue models used to study implantation and pregnancy-related disorders. More broadly, similar approaches are used by many laboratories to investigate early developmental processes and disease mechanisms, further underscoring the importance of these platforms across the research community.

In addition to early developmental biology, hESC-based systems are widely used to model human disease and to develop new therapeutic strategies. For example, such systems are used to study neurodevelopmental disorders, including autism, epilepsy, and intellectual disability, by enabling detailed molecular and functional analysis and supporting drug discovery efforts. Restricting access to hESCs would therefore disrupt not only basic discovery but also ongoing efforts to translate these findings into

therapeutic advances. More broadly, hESC-based approaches support a wide range of biomedical research areas, including organoid models for vision and neurodegeneration, stem-cell-derived therapies for diabetes, genome engineering platforms, and tissue engineering approaches for musculoskeletal disease. These examples reflect years of federal and institutional investment in validated hESC-based systems that support both fundamental discovery and translational research.

Importantly, restricting access to hESCs would not prevent embryo destruction, which is already prohibited under current NIH policy, but would instead impede research on existing, ethically derived cell lines. Such restrictions would reduce experimental rigor, slow progress toward understanding human development and disease, and disrupt established pipelines for therapeutic discovery.

Beyond these direct scientific impacts, such restrictions would also have broader consequences for the U.S. biomedical research enterprise. hESC-based research remains an active and competitive area internationally, and limiting its use in the United States risks ceding scientific leadership to countries with more permissive and stable policy environments. This could lead to loss of momentum in key research areas, reduced ability to attract and retain top trainees and faculty, and diminished return on decades of federal investment in stem cell biology and regenerative medicine.

For these reasons, I urge NIH to maintain access to existing hESC lines, preserve a pathway for the introduction of new lines that meet established ethical and scientific standards, and continue supporting scientifically meritorious hESC research.



Thorold W. Theunissen, PhD
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94. James Wells

I am responding: On behalf of myself

Name: James Wells

Name of Organization: N/A

Type of Organization: Non-profit Research Organization

Role: Institutional Review Oversight Committee Member

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Most basic research projects can continue with existing cell lines. Since most methods to generate therapeutic cell types used HESCs, HESCs often yield more functional cell
types that are more functional and are better therapeutics in animal models. Therefore, development of new HESCs for developing cell-based therapeutics might be
important. Also, HESCs will have fewer somatic mutations since they have undergone fewer rounds of cell division, as compared to iPSC lines from adults.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Most new protocols to generate cells and tissues were developed using HESCs, and given that they are the gold standard for functional plurioptency, new protocols will
continue to benefit from the use of HESCs. Also, there are many genetically modified HESC lines that do not exist in iPSCs, and it would be cost prohibitive to re-derive all of
these lines in an iPSC background.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
iPSCs are critical for patient-specific disease modeling, where genetic background of the patient is critical for driving disease pathology in vitro.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
In general, investments in developing differentiation protocols that work equally well across HESC and iPSC lines need to be made.

95. WiCell

I am responding: On behalf of an organization

Name: Tenneille Ludwig

Name of Organization: WiCell

Type of Organization: Non-profit Research Organization

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
The trajectory of biomedical research and its translation to clinical application is impossible to reliably predict, and therefore it cannot be determined that the currently approved lines will meet future needs in any research area. While there has been a decline in the submission for new lines to be added to the registry, that should not be equated as a lack of need for new lines to address novel research questions. Improved derivation methods may lead to the possibility of the generation of improved research models. New areas of research could be opened for particular disease indications that are not currently successfully modeled. More contemporary lines could better align with current clinical manufacturing pipelines, easing the path to FDA approval and accelerating the pace toward cures. New lines are needed to expand the genetic background of available lines to ensure robust modeling. The ability to perform life saving research depends on researcher access to the most appropriate materials, and any effort to restrict access to ethically derived, well characterized materials will inhibit progress, prolonging suffering and the human toll of diseases that might otherwise be more readily treated.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human embryonic stem cells are the "gold standard" for human pluripotency in all areas of research, including basic, applied, and clinical translation research. They are the closest in-vitro representation of normally occurring early human developmental biology because they are extracted and not derived, maintaining a "true and pure" nature. They are an essential, irreplaceable tool in research that models early human development, including research on human prenatal development meant to better understand and combat early pregnancy loss and infertility.
Substantial NIH investment has established them as a vital control and calibration standard for other technologies such as induced pluripotent stem cells (iPSC). Because of the significant NIH investment in hESC characterization and distribution, additional investment has been made in generating libraries of lines carrying disease-associated mutations with precisely engineered modifications. These lines are used to increase precision and efficiency in basic and disease related research, and demand will only continue to increase. Having to duplicate these lines in iPSCs would set research back years if not decades, incur tremendous duplicative costs, and introduce variability, reducing reliability of the data obtained.
hESCs are the foundation of many translational pipelines generating cell therapies currently showing

tremendous promise in clinical trials. Treatments for diabetes, Parkinson's, epilepsy, and macular degeneration have advanced into clinical trials, and alterations in federal approval or funding structures could disrupt trials and delay progress toward cures.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

hESCs have no biological equivalent and cannot be replaced by current available technologies. In fact, they are the appropriate reference standard in the development of alternate technologies.

While the advent of induced pluripotent stem cells (iPSCs) expanded the field, they are not the biological equivalent of hESCs and as such cannot replace them. While they have mostly similar developmental capacity, iPSCs are derived from adult cells, and do not have the same epigenetic or developmental features of hESCs. Reprogramming often includes exposure to oncogenes, can induce deleterious mutations, and requires prolonged passaging in comparison to hESCs which can accumulate mutations. Adult stem cells are more limited in developmental capacity, are not pluripotent, and have a limited lifespan when compared to hESCs. They cannot be used to research early human development are not a viable replacement for hESCs.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

There is no scientific model that is equivalent to hESCs and therefore it is not possible to replace hESCs with alternate models. hESCs are the only natural, unmodified human pluripotent stem cell. Efforts should be made around enhancing and complementing hESC research and not replacing it.

Efforts to elucidate the differences between hESCs and iPSCs including comprehensive epigenomics, metabolomics and multiomics including functional comparisons between isogenic hPSCs and hiPSCs would provide valuable information that may aid in the selection of format for a given research question or therapeutic campaign.

Notably, substantial public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed recapitulate these tools in an alternate format that may not be equivalent. The feasibility and timeline to meet all these requirements is completely unknown and would require substantial investment of funding. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

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April 24, 2026

To: National Institutes of Health Office of Science Policy

Re: NOT-OD-26-031, NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

To whom it may concern:

This submission by WiCell Research Institute is made in response to NOT-OD-26-031: Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Embryonic Stem Cell in NIH-Supported Research. WiCell Research Institute is non-profit organization dedicated to supporting research and the advancement of novel therapies through innovative technologies and services. It was established as a supporting organization of the University of Wisconsin-Madison in 1998 to advance stem cell technologies following the initial derivation of human embryonic stem cells (hESCs) by Dr. James Thomson. In 2005 WiCell was awarded the first and only NIH National Stem Cell Bank grant (16 million USD) to curate, expand, characterize, and distribute hESCs approved under President Bush. Since that time WiCell has provided these foundational materials to thousands of researchers across the United States and worldwide to use as the basis of their research toward cures for intractable diseases. WiCell now stands as the leading biorepository for the banking and distribution of human pluripotent stem cells (hPSCs), including hESCs and iPSCs, globally. We remain committed to supporting pluripotent stem cell technology from basic research through translation to improve the human condition.

--RFI Questions--

1. *Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.*

The trajectory of biomedical research and its translation to clinical application is impossible to reliably predict, and therefore it cannot be determined that the currently approved lines will meet future needs in any research area. While there has been a decline in the submission for new lines to be added to the registry, that should not be equated as a lack of need for new lines to address novel research questions. Improved derivation methods may lead to the possibility of the generation of improved research models. New areas of research could be opened for particular disease indications that are not currently successfully modeled. More



contemporary lines could better align with current clinical manufacturing pipelines, easing the path to FDA approval and accelerating the pace toward cures. New lines are needed to expand the genetic background of available lines to ensure robust modeling. The ability to perform life saving research depends on researcher access to the most appropriate materials, and any effort to restrict access to ethically derived, well characterized materials will inhibit progress, prolonging suffering and the human toll of diseases that might otherwise be more readily treated.

2. *Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.*

Human embryonic stem cells are the "gold standard" for human pluripotency in all areas of research, including basic, applied, and clinical translation research. They are the closest *in-vitro* representation of normally occurring early human developmental biology because they are extracted and not derived, maintaining a "true and pure" nature. They are an essential, irreplaceable tool in research that models early human development, including research on human prenatal development meant to better understand and combat early pregnancy loss and infertility.

Substantial NIH investment has established them as a vital control and calibration standard for other technologies such as induced pluripotent stem cells (iPSC). Because of the significant NIH investment in hESC characterization and distribution, additional investment has been made in generating libraries of lines carrying disease-associated mutations with precisely engineered modifications. These lines are used to increase precision and efficiency in basic and disease related research, and demand will only continue to increase. Having to duplicate these lines in iPSCs would set research back years if not decades, incur tremendous duplicative costs, and introduce variability, reducing reliability of the data obtained.

hESCs are the foundation of many translational pipelines generating cell therapies currently showing tremendous promise in clinical trials. Treatments for diabetes, Parkinson's, epilepsy, and macular degeneration have advanced into clinical trials, and alterations in federal approval or funding structures could disrupt trials and delay progress toward cures.

3. *Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.*

hESCs have no biological equivalent and cannot be replaced by current available technologies. In fact, they are the appropriate reference standard in the development of alternate technologies.

While the advent of induced pluripotent stem cells (iPSCs) expanded the field, they are not the biological equivalent of hESCs and as such cannot replace them. While they have mostly similar developmental capacity, iPSCs are derived from adult cells, and do not have the same epigenetic or developmental features of hESCs. Reprogramming often includes exposure to oncogenes, can induce deleterious mutations, and requires prolonged passaging in comparison to hESCs which can accumulate mutations.
Adult stem cells are more limited in developmental capacity, are not pluripotent, and have a limited lifespan when compared to hESCs. They cannot be used to research early human development are not a viable replacement for hESCs.

4. *Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.*

There is no scientific model that is equivalent to hESCs and therefore it is not possible to replace hESCs with alternate models. hESCs are the only natural, unmodified human pluripotent stem cell. Efforts should be made around enhancing and complementing hESC research and not replacing it.

Efforts to elucidate the differences between hESCs and iPSCs including comprehensive epigenomics, metabolomics and multiomics including functional comparisons between isogenic hPSCs and hiPSCs would provide valuable information that may aid in the selection of format for a given research question or therapeutic campaign.

Notably, substantial public resources have been invested in the past thirty years to establish hESCs as a well-characterized biomedical research tool that expands our ability to understand human development and disease and to devise cell therapies to mitigate disease. Furthermore, rebuilding of infrastructure (e.g. banking and characterization) and tools (e.g. gene edited cells) would be needed recapitulate these tools in an alternate format that may not be equivalent. The feasibility and timeline to meet all these requirements is completely unknown and would require substantial investment of funding. Limiting access to hESCs would represent a waste of the public resources invested over the past several decades.

Thank you for your consideration,

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96. International Society for Stem Cell Research (ISSCR)

I am responding: On behalf of an organization

Name: Andrew Bremer

Name of Organization: International Society for Stem Cell Research (ISSCR)

Type of Organization: Professional Organization/Association

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Future hESC lines may offer capabilities that extend beyond what is achievable with currently approved lines in several respects. Advances in methodology may allow for lines with improved biological properties, more stable maintenance of naive and primed states, greater genetic and epigenetic integrity, and expanded developmental potential. New lines with genomic profiles not currently represented on the NIH hESC Registry may be required as additional disease mechanisms are identified and modeled. Additional engineered lines that allow real-time monitoring and observation of pluripotency, differentiation, and disease properties could expand both basic and translational capabilities.
New hESC lines may also better align with contemporary clinical manufacturing standards. Some of the hESC lines currently being used in clinical trials were originally derived in 1998 and, in some cases, have undergone extensive passaging over the intervening years. Advances in derivation technology and culture condition technology could enable enhanced safety and efficacy of future cell-based therapies. hESC lines derived under more controlled conditions and selected for improved stability and scalability could also enhance manufacturing efficiency and product consistency for cell therapies and may offer advantages relative to existing hESC- and iPSC-based platforms. Further, new lines that enhance the histocompatibility of hESC-based cell therapies may be needed to optimize therapeutic outcomes. As more is learned from clinical research on cell therapies derived from pluripotent stem cells (discussed more in Question 2), reverse translational studies (i.e., bedside-to-bench) could refine and improve these next generation therapeutics.
High-quality, rigorous research depends on researchers being able to select the most appropriate model for the research question posed. Limiting access to the best available tools risks constraining biomedical innovation in unpredictable ways. The trajectory of biomedical discovery and its translation to clinical applications is inherently uncertain, and the examples above highlight areas for which currently approved hESC lines may be insufficient to meet emerging research needs. Therefore, maintaining access to not only existing lines, but also the derivation of and access to new lines, is necessary to preserve the flexibility and forward-looking capacity of the biomedical research enterprise as scientifically meritorious lines of inquiry are identified.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.

hESCs are the “gold standard” for human pluripotency in basic, applied, and clinical translation research. Since their derivation, they have provided the closest in vitro representation of naturally occurring, unmodified human pluripotency.4 Decades of investment have established them as a vital benchmark for defining pluripotency, developmental potential, and lineage competence. They function routinely as well-characterized control and calibration standards in differentiation protocols and translational product development, including iPSC-based cell therapies. If hESCs were unavailable, numerous lines of inquiry in basic and clinical research would be significantly hindered or not possible.

Basic research

hESCs are essential tools in basic research for modeling human development and disease, including novel approaches to study early human embryogenesis. Recently developed hESC-based models offer unique potential to shed light on the fundamental biological mechanisms underlying development, the establishment and maintenance of a healthy pregnancy, and the origins of disease. Insights from this basic research provides the foundation for the discovery and development of future therapies.

hESCs have emerged as a gold standard for the study of pregnancy disorders originating from the maldevelopment of the placenta, implantation failure, endometrial disorders, and proper development of gametes and support cells. hESC-based models also enable the investigation of genetic and environmental causes of infertility. Animal models, while appropriate in some contexts, are insufficient to fully understand these disorders due to significant differences in human development, tissue structure and function, and pregnancy. hESC-derived models to study human-specific disease etiology hold significant potential to improve human reproduction and to address root causes of maternal mortality, including pregnancy complications related to hypertension and preeclampsia, placenta accreta resulting in hemorrhage, and infections.

Utilizing hESCs in recapitulating early features of human development is entering a new era of cutting-edge, human-specific in vitro modeling. Stem cell-derived models of reproductive tissues include trophoblast organoids5, endometrial stromal fibroblasts6, female granulosa cells7, male sertoli cells8, and embryonic genital ridge progenitors9 important for the study of differences in sex organ development. Because hESCs are derived directly from embryos, they provide the most suitable building blocks for these models of development. hESCs are preferable to iPSCs because even small amounts of incomplete reprogramming in iPSCs could lead to epigenetic differences from hESCs that could alter early human development.

hESCs are also highly valued in the research community due to the significant, cumulative investments that have been made to generate and rigorously characterize extensive libraries of lines carrying disease-associated mutations and precisely engineered genetic modifications. These resources are essential for the study of gene functions, human development, and disease mechanisms. Built over many years from well-defined specific parental cell lines, these libraries represent substantial investment in genome editing, clonal selection, and functional validation to ensure reproducibility and reliability. Duplicating comparable engineered mutations in iPSCs would require substantial time, funding, and personnel. It would also introduce variability, including differences in genetic background, epigenetic state, and reprogramming history, thereby reducing reproducibility and cross-study comparability, the core principles of NIH priorities for rigor and reproducibility.

Lastly, other areas of basic research would not be possible without access to certain existing hESC lines with unique properties or derivation origins, including parthenogenic haploid cell lines and those derived through somatic cell nuclear transfer. These represent unique models for research that cannot be substituted by any other cell type.

At present, hESCs are the most established and best characterized source of pluripotent stem cells for the development of cell therapies. Their well-characterized biology, stability, and track record in translational research have enabled multiple hESC-derived products to advance into clinical trials, including several now in late-stage development. As a testament to the impact of NIH funding for hESC research, three of the four Phase III trials using cell therapies derived from hESCs taking place globally are being conducted in the U.S. Two of these trials are testing cell therapies derived from hESCs for the treatment of diabetes and Parkinson's disease. The third trial will be initiated soon, testing an hESC-derived cell therapy for epilepsy.

Notable recent clinical trials of cell therapies derived from hESCs include the following:

• In a Phase I/II trial for diabetes, all 12 patients treated with full-dose hESC-derived pancreatic islet cells displayed reduced dependence upon exogenous insulin; 10 of 12 patients were insulin free after 1 year.10 This therapy is now being tested in Phase III clinical trials.

• In a Phase I trial testing hESC-derived dopaminergic neuron progenitors for the treatment of Parkinson's, 12 patients treated displayed meaningful positive trends 3 years after treatment.11,12 This trial is advancing to a later phase.

• In a Phase I/II trial testing hESC-derived GABA interneurons for the treatment of drug-resistant mesial temporal lobe epilepsy, a 9-patient low-dose cohort displayed an 89% reduction in disabling seizures 7-12 months after administration. A 9-patient high dose cohort demonstrated a 78% median reduction in seizures at 4-6 months after administration.13 This trial is also advancing to a later phase.

In multiple clinicals trials using hESC-derived retinal pigment epithelium cells for the treatment of age-related macular degeneration, initial results display promise for disease stabilization and even improvement14,15

Restrictions on the availability of hESCs would not only affect hESC-derived therapies but could also undermine the development of related therapeutic platforms. In addition to acting as a source of cells for therapies, hESCs routinely serve as an important control and calibration standard for other pluripotent cell therapies (e.g., patient-specific iPSC-derived therapies). The establishment, validation, and ongoing quality assessment of iPSCs relies on comparison to well-characterized hESC lines.

New Approach Methodologies (NAMs)

Recent and ongoing efforts across the U.S. federal government have sought to promote the development and application of NAMs to establish human-relevant models in preclinical safety and drug discovery studies and in environmental toxicity testing. This includes efforts by the NIH16, the FDA17,18, and numerous other regulatory and research agencies.19 Similar efforts by regulatory agencies and international coordinating bodies are underway across the world. By developing and increasing the adoption of human-relevant NAMs, these efforts aim to improve the safety of drugs, accelerate and decrease costs associated with the development and approval of new therapeutics, prevent exposure to harmful substances, and reduce reliance on traditional animal studies.

As NAMS evolve from experimental systems into decision-enabling tools for scientific and regulatory use, key barriers to their adoption are the establishment of human relevance, standardization, and context-of-use validation. hESCs have emerged as a foundational tool for addressing these challenges by serving as stable, well-characterized reference materials that facilitate reproducible benchmarking across platforms. Many well-characterized and widely adopted NAMs platforms (e.g., organoids and microphysiological systems) were originally established and validated using hESCs.

hESCs also contribute to the development of specific NAMs applications. For example, hESCs have been used to develop an in vitro assay to detect human developmental toxicants, a platform that could be

used to identify harmful substances if exposure occurred during pregnancy.20 hESCs remain a gold standard for the study of reproductive disorders and are used to investigate environmental causes of infertility. More broadly, numerous hESC-derived models have been developed for drug discovery and safety evaluations across multiple organ systems, including for diseases of the brain, lung, and kidney, as well as longer-term safety endpoints.21

While the field is advancing towards alternative cell sources such as iPSCs, this transition relies on direct comparability and benchmarking studies against hESCs. Without hESCs investigators will be unable to anchor new models to established biological reference points, ensure continuity of datasets, and support regulatory confidence through reproducible benchmarks. This function is of particular importance given sources of variability in iPSC-based systems, including reprogramming-associated effects. In parallel, modern NAMs are increasingly integrated with computational and AI-driven approaches that rely on robust, standardized biological reference points for model training and evaluation.

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3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.

At present, no alternative technology can replace hESCs as none has been demonstrated to be fully biologically equivalent. Legacy hESC lines (e.g., WA01, WA09) are among the most widely characterized and most widely distributed human research materials. They provide an irreplaceable reference material for future work and for the development of alternative methods. A scientifically responsible strategy would be to strengthen complementary technologies such as iPSCs, adult stem cell-derived organoid systems, and genomic stability monitoring while maintaining access to hESCs.

Provided below are descriptions of complementary technologies to hESCs.

a. Induced Pluripotent Stem Cells (iPSCs)

iPSCs are reprogrammed adult somatic cells that exhibit similar properties as hESCs and are highly comparable across a wide range of applications but are not biologically identical.22 Since their derivation, iPSCs have provided an important additional tool for studying patient-specific cells. While iPSCs have substantially expanded the field of stem cell research and provide a cell source for certain applications, they often do not fully replicate the features of hESCs. Genome-wide epigenetic analyses have demonstrated that iPSCs frequently retain epigenetic signatures associated with their cell-of-origin, reflecting incomplete epigenetic reprogramming.23 Consistent with this, the capacity of mouse iPSCs to participate in embryonic development is highly variable. This variability, introduced during reprogramming and subsequent culture, is a central limitation of iPSCs. These residual epigenetic differences can influence the gene expression and differentiation potential of iPSCs, highlighting why hESCs remain the gold standard for human pluripotency.

iPSCs often retain residual DNA methylation patterns associated with their cell-of-origin and recurrent methylation hotspots that are not observed in hESCs.24,25,26 Imprinting control regions and X chromosome regulatory loci are among the genomic features that can exhibit epigenetic variability across iPSC lines. In addition, female iPSCs frequently exhibit abnormal or unstable X chromosome

inactivation, including incomplete reactivation, erosion of dosage compensation, and heterogeneous allele-specific expression patterns.27,28,29 These persistent questions regarding epigenetic memory, imprinting fidelity, X-inactivation, and genomic stability underscore the continued need for hESCs as the gold standard reference for pluripotency.

Reprogramming technologies are still evolving, with recent advances aimed at addressing epigenetic differences between iPSCs and hESCs. But these studies further highlight the need for continued access to hESCs as the benchmark against which the performance of reprogrammed cells is evaluated. For example, transient naïve reprogramming can partially correct epigenetic abnormalities in human iPSCs, but assessment of successful epigenetic resetting required direct comparison to hESCs.30 Similarly, efforts to generate naïve human pluripotent stem cells and related intermediate pluripotent states rely extensively on benchmarking against hESCs to confirm authentic transcriptional identity and developmental competence.31,32 Even the most advanced reprogramming and pluripotent stem cell technologies remain dependent on hESC lines as a reference material to define authentic human pluripotent ground states.

As iPSCs have come into wide use, careful comparative studies of hESCs, iPSCs, and other pluripotent stem cells (e.g., somatic cell nuclear transfer-derived ESCs) have become less frequent. As such, the persistent differences described above remain unresolved. Existing comparisons are further complicated by genetic variability across donor-derived cell lines, and very few studies have used isogenic panels for direct comparisons between hESCs and iPSCs. Further studies are required to define the extent, sources, and consequences of the differences between these stem cell types.

Finally, while iPSCs do represent a powerful platform for the development of cell therapies, clinical assessment comparing hESC-based and iPSC-based therapies is still at a very early phase of research. At present, cell therapies using hESCs have advanced the furthest in the clinic, though iPSCs are more commonly selected as a starting material for new programs.33 It is not yet possible to ascertain whether the two platforms will prove to be equivalent, whether one method may turn out superior, or whether the superior choice of cell source is context-dependent (e.g., patient- or disease-specific). This uncertainty merits continued access to hESCs to enable rigorous comparative research and ensure that the safest and most effective therapeutic approaches can be identified and translated to patients.

b. Adult Stem Cells

Adult (or somatic) stem cells are tissue-specific cells characterized by their ability to self-renew and to differentiate into more specialized cell types within their tissue of origin. Adult stem cells reside in human tissues such as skin, muscle, intestines, and the hematopoietic system (i.e., blood and immune cells). Stem cells are present throughout life in these tissues.34,35 They are useful tools for understanding the basic biological mechanisms involved in tissue regeneration but do not represent a replacement for hESCs.

Fundamental biological differences between adult stem cells and hESCs preclude adult stem cells from replacing hESCs. Adult stem cells are lineage restricted and their differentiation potential is confined to their tissue of origin. Adult stem cells also generally lack key properties that support broad research and translational use. They are not immortal (in contrast to hESCs), are more difficult to expand and scale, and display wide biological variability among individuals. In most human tissues, adult stem cells are rare and difficult to isolate. Stem cells from muscle, bone, intestine, and the nervous system cannot easily be recovered, if at all, from live or cadaveric donors, further constraining their utility.

Some common adult stem cell types used in clinical research:

• Hematopoietic stem cells (HSCs) represent the most established stem cell type that is used clinically,

but only for diseases of the hematopoietic and immune systems. Hematopoietic stem cells cannot be differentiated to cells from non-hematopoietic tissues. Despite their value in the treatment of conditions of the blood, they are not a replacement for hESCs and could not be used for the treatment of conditions that are being treated with hESC-derived cell therapies, such as diabetes, Parkinson's disease, epilepsy, or macular degeneration.

• Mesenchymal stem cells (MSCs) can differentiate into bone, cartilage, and fat and are found in bone marrow and other tissues such as adipose tissue. They have shown clinical benefit in limited indications, including steroid refractory graft-versus-host disease in children after allogeneic bone marrow transplants and treating anal fistulas that arise in Crohn's disease, but have not shown efficacy in controlled trials for other conditions. The therapeutic potential of MSCs is constrained by immune rejection of allogeneic MSCs after transplantation, preventing them from repairing or integrating into resident tissues; their senescence in culture limiting biomanufacturing capacity; and donor-to-donor variability which complicates clinical trials.36 Despite being studied clinically for over 35 years, there is only one approved cell therapy using MSCs in the U.S. (Ryoncil, from Mesoblast, for pediatric GVHD).37

For certain tissues, adult stem cell-derived organoids can be grown in culture. These structures can provide useful models for certain cell types in certain tissues but have limited structural complexity and lack the ability to model most of the cell-cell interactions within tissues. Since they are generated from adult cells, they do not have the capacity to form cells outside of their tissue of origin, unlike hESCs. While holding promise for certain research directions, adult stem cell-derived organoids do not represent a replacement for hESCs in any sense.

c. Computational models

Recent efforts have sought to establish computational models for the study of stem cell behavior and development. Sophisticated models are in their infancy, with computational models of animal development only just emerging.38 At present, these models, particularly for human development, have limited predictive value because they are not sophisticated enough to model most aspects of cell biology. Computational modeling and AI-assisted methods offer potential for future research directions, but do not represent a replacement for research using hESCs.

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4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

No alternative model or technology is directly equivalent to hESCs. hESCs represent the only naturally occurring, unmodified human pluripotent stem cell. All other methods and technologies will inherently require validation against hESCs, and should be viewed as a complement to hESC research rather than a replacement.

Efforts to complement hESC research would be aided by the following:

a. Further investigation of the impacts of iPSC reprogramming on their biological comparability to hESCs, including study of unresolved questions highlighted under Question 3 (e.g., epigenetic memory, imprinting fidelity, X-inactivation, and genomic stability). This could include isogenic studies comparing hESCs and iPSCs. b. Follow up research on clinical trials that used different kinds of pluripotent cell-derived therapies to determine whether one kind of pluripotent stem cell is more effective than another (i.e., hESC- vs. iPSC-derived).

Scientific and ethical governance of research with hESCs

hESC research currently proceeds under a well-established ethical and legal framework embedded in NIH's own Guidelines for Human Stem Cell Research and supported by the National Academies and leading scientific, medical, and patient advocacy organizations. These policies permit the use of hESC lines derived from embryos originally created for clinical use by in vitro fertilization (IVF) but

subsequently deemed unsuitable for transfer or no longer needed for reproductive purposes, with informed consent from donors.

Because these embryos are routinely discarded during IVF care, any new restrictions on the use of hESC lines would not save a single embryo from destruction. Rather, such limitations would constrain the ability of researchers and patients to derive scientific and medical value from materials already designated for disposal. Moreover, the donors who voluntarily supplied embryos in the hope of advancing scientific progress may be frustrated to see stem cell lines derived from their donated embryos discharged despite the clear scientific and clinical need.

Conclusion

hESCs are an essential, irreplaceable component of the biomedical research ecosystem. Decades of NIH investment in hESC research have resulted in a highly productive infrastructure that has generated foundational insights into human development and enabled novel clinical advancements. As emphasized above, though iPSCs and other emerging technologies can sometimes provide overlapping research use cases to hESCs, these alternative platforms still rely on hESCs as benchmarks and should not be thought of as substitutes.

Based on the available scientific and translational evidence, there is no scientific or ethical justification for NIH to reduce its reliance on hESC research. Any departure from NIH's long-standing support for this work would not be evidence-based and could have negative downstream effects across related research areas. We urge NIH to lift its pause on submissions to its hESC Registry and continue its commitment to supporting scientifically meritorious hESC research.

For questions or clarifications, please contact Tyler Lamb, JD, Director of Policy (tlamb@isscr.org) or Andrew Bremer, PhD, Manager of Policy (abremer@isscr.org).

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/ISSCR_NIH_NOT-OD-26-031_hESC_RFI_signaturecopy.pdf

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Executive Summary

This response addresses the National Institutes of Health's Request for Information NOT-OD-26-031 on the current and future uses of human embryonic stem cells (hESCs) in biomedical research. Research using hESCs has led to foundational discoveries important for understanding basic human biology and in advancing the development of novel therapeutic approaches. Although advances in stem cell science, such as induced pluripotent stem cells (iPSCs), have expanded the range of experimental approaches available to model human biology and disease, these systems are often developed and validated against hESCs, which remain uniquely informative in many research areas.

1. **hESCs are an essential "gold standard" for human pluripotency and are an indispensable tool for studying human development and reproductive biology.** hESCs represent the natural, unmodified reference for human pluripotency and permit the study of early developmental processes. hESC-derived models are essential for investigating reproductive and congenital disorders in ways that cannot be replicated by animal models due to species differences.

2. **Future hESC lines may offer important scientific and translational advantages while filling critical gaps not captured by existing lines.** New lines with enhanced biological properties, improved genetic and epigenetic stability, and closer alignment with modern manufacturing standards would advance the precision and reproducibility of stem cell-based research. Increasing the genomic representation of Registry lines will improve the modeling of human development and disease.

3. **NIH investment has helped to build a world-leading research infrastructure for hESC science, with benefits that have compounded over time.** Considerable federal resources have been committed to the development and characterization of widely shared cell line repositories, including engineered reporter and gene mutation libraries and standardized protocols. Changes that render these resources unusable would not only squander billions of dollars in public investment and countless hours of scientific labor but also erode reproducibility and cross-study comparability.

4. **Research in hESCs has advanced to a translational inflection point, where continued policy stability may determine whether decades of scientific progress result in approved regenerative medicine therapies.** Multiple ongoing U.S.-based clinical trials now use hESCs as starting material, including Phase III clinical trials for Type 1 diabetes, Parkinson's disease, and epilepsy. Numerous other hESC-based therapies are in early phase clinical trials and preclinical studies. Abrupt shifts in policy risk disrupting this expanding therapeutic pipeline and

jeopardizing the health and lives of the millions of patients who stand to benefit from these clinical developments.

5. **hESCs contribute to the increasing use of new approach methodologies (NAMs) in scientific and regulatory decision making.** Many well-characterized and widely adopted NAMs platforms (e.g., organoids and microphysiological systems) were originally established and validated using hESCs, and alternative cell sources for NAMs still rely on direct comparability and benchmarking studies against hESCs. Limiting access to hESCs could slow down or even undermine efforts by the NIH, FDA, and broader scientific community to reduce reliance on animal models.

6. **Alternative platforms, including iPSCs and adult stem cells, cannot fully replace hESCs as they exhibit important biological differences.** iPSCs often show residual epigenetic differences and variability from reprogramming that can affect differentiation and reproducibility, while adult stem cells are inherently limited in their developmental potential and scalability. For iPSCs, hESCs serve as a well-characterized reference material for benchmarking, validation, and optimization.

Research with hESCs is conducted under a well-established framework of rigorous ethical oversight that includes NIH's own Guidelines for Human Stem Cell Research and complementary guidance from the National Academies[1] and the ISSCR[2]. This governance framework, paired with the limitations imposed by the Dickey-Wicker Amendment, ensures that no federal funds are used for research that destroys a human embryo, including the derivation of new hESC lines. Thus, any new restrictions on hESC research would not prevent a single human embryo from being destroyed, it would only impede scientific progress.

Based on the available scientific and translational evidence, there is no scientific or ethical justification for NIH to reduce its reliance on hESC research. Any departure from NIH's long-standing support for this work would not be evidence-based and could have negative downstream effects across many related research areas. We urge NIH to lift its pause on submissions to its hESC Registry and continue its commitment to supporting scientifically meritorious hESC research.

[1] National Academies of Sciences, Engineering, and Medicine. (2010). Final report of the National Academies' human embryonic stem cell research advisory committee and 2010 amendments to the National Academies' guidelines for human embryonic stem cell research.
[2] https://www.isscr.org/guidelines

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

24 April 2026

National Institutes of Health
NIH Office of Science Policy
6705 Rockledge Drive, Suite 630
Bethesda, MD 20892

Re: Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research (NOT-OD-26-031)

Submitted online via https://osp.od.nih.gov/comment-form-reducing-reliance-on-human-embryonic-stem-cells-in-nih-supported-research/

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) provides these comments to the National Institutes of Health (NIH) in response to its request for information on the use of human embryonic stem cells (hESCs) in NIH-funded research. The ISSCR is the leading international organization for stem cell science, representing more than 5,000 stem cell researchers. Our membership includes scientists, clinicians, ethicists, and developers of cell therapies. Our members are pioneers of stem cell research, have developed medical breakthroughs that have improved patient care, and are driving innovation at the forefront of biomedicine. This RFI response is informed by their collective expertise on the current state of stem cell research and regenerative medicine and the translation of this research into the clinic.

Access to human embryonic stem cells has supported substantial scientific and translational advances. Their capacity for sustained self-renewal and their ability to generate differentiated cells for every tissue in the body enables critical research into human development, disease mechanisms, and the development of regenerative medicines. For nearly two decades, NIH has directed billions of dollars in federal funds to support research into understanding and applying this foundational platform, including the characterization and study of hESC lines under a robust ethical and oversight framework. These discoveries are now the basis for many clinical programs using hESC-derived products. As of December 2024, 20 of the 51 worldwide clinical trials testing hESC-derived products are being conducted in the U.S.[3]

Sustaining and building on these substantial investments will require continued access to the full range of scientifically validated research tools, including hESC lines. Many uses of

[3] Kirkeby, A., Main, H., and Carpenter, M. (2025). Pluripotent stem-cell-derived therapies in clinical trial: a 2025 update. Cell Stem Cell 32, 10–37. https://doi.org/10.1016/j.stem.2024.12.005

hESCs were not foreseeable when the first hESC lines were derived, and future applications for which hESCs may be the most appropriate tool cannot be fully anticipated today. Novel model systems have expanded the suite of research tools available to scientists with the development of induced pluripotent stem cells (iPSCs), adult stem cell-derived organoids, and computational models, yet hESCs continue to provide distinct biological insights and remain an important reference point for assessing alternative platforms. Accordingly, NIH should maintain access to currently approved hESC lines while preserving a pathway for the review and approval of additional lines that meet the requirements of the NIH Guidelines for Human Stem Cell Research.

--RFI Questions--

1. *Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.*

Future hESC lines may offer capabilities that extend beyond what is achievable with currently approved lines in several respects. Advances in methodology may allow for lines with improved biological properties, more stable maintenance of naive and primed states, greater genetic and epigenetic integrity, and expanded developmental potential. New lines with genomic profiles not currently represented on the NIH hESC Registry may be required as additional disease mechanisms are identified and modeled. Additional engineered lines that allow real-time monitoring and observation of pluripotency, differentiation, and disease properties could expand both basic and translational capabilities.

New hESC lines may also better align with contemporary clinical manufacturing standards. Some of the hESC lines currently being used in clinical trials were originally derived in 1998 and, in some cases, have undergone extensive passaging over the intervening years. Advances in derivation technology and culture condition technology could enable enhanced safety and efficacy of future cell-based therapies.

hESC lines derived under more controlled conditions and selected for improved stability and scalability could also enhance manufacturing efficiency and product consistency for cell therapies and may offer advantages relative to existing hESC- and iPSC-based platforms. Further, new lines that enhance the histocompatibility of hESC-based cell therapies may be needed to optimize therapeutic outcomes. As more is learned from clinical research on cell therapies derived from pluripotent stem cells (discussed more in Question 2), reverse translational studies (i.e., bedside-to-bench) could refine and improve these next generation therapeutics.

High-quality, rigorous research depends on researchers being able to select the most appropriate model for the research question posed. Limiting access to the best available tools risks constraining biomedical innovation in unpredictable ways. The trajectory of biomedical discovery and its translation to clinical applications is inherently uncertain, and the examples above highlight areas for which currently approved hESC lines may be insufficient to meet emerging research needs. Therefore, maintaining access to not only existing lines, but also the derivation of and access to new lines, is necessary to preserve the flexibility and forward-looking capacity of the biomedical research enterprise as scientifically meritorious lines of inquiry are identified.

2. *Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable*.

hESCs are the "gold standard" for human pluripotency in basic, applied, and clinical translation research. Since their derivation, they have provided the closest in vitro representation of naturally occurring, unmodified human pluripotency.[4] Decades of investment have established them as a vital benchmark for defining pluripotency, developmental potential, and lineage competence. They function routinely as well-characterized control and calibration standards in differentiation protocols and translational product development, including iPSC-based cell therapies. If hESCs were unavailable, numerous lines of inquiry in basic and clinical research would be significantly hindered or not possible.

Basic research

hESCs are essential tools in basic research for modeling human development and disease, including novel approaches to study early human embryogenesis. Recently developed hESC-based models offer unique potential to shed light on the fundamental biological mechanisms underlying development, the establishment and maintenance of a healthy pregnancy, and the origins of disease. Insights from this basic research provides the foundation for the discovery and development of future therapies.

hESCs have emerged as a gold standard for the study of pregnancy disorders originating from the maldevelopment of the placenta, implantation failure, endometrial disorders, and proper development of gametes and support cells. hESC-based models also enable the investigation of genetic and environmental causes of infertility. Animal models, while appropriate in some contexts, are insufficient to fully understand these disorders due to significant differences in human development, tissue structure and function, and pregnancy. hESC-derived models to study human-specific disease etiology hold significant

[4] Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., and Jones, J.M. (1998). Embryonic stem cell lines derived from human blastocysts. Science 282, 1145–1147. https://doi.org/10.1126/science.282.5391.1145

potential to improve human reproduction and to address root causes of maternal mortality, including pregnancy complications related to hypertension and preeclampsia, placenta accreta resulting in hemorrhage, and infections.

Utilizing hESCs in recapitulating early features of human development is entering a new era of cutting-edge, human-specific in vitro modeling. Stem cell-derived models of reproductive tissues include trophoblast organoids[5], endometrial stromal fibroblasts[6], female granulosa cells[7], male sertoli cells[8], and embryonic genital ridge progenitors[9] important for the study of differences in sex organ development. Because hESCs are derived directly from embryos, they provide the most suitable building blocks for these models of development. hESCs are preferable to iPSCs because even small amounts of incomplete reprogramming in iPSCs could lead to epigenetic differences from hESCs that could alter early human development.

hESCs are also highly valued in the research community due to the significant, cumulative investments that have been made to generate and rigorously characterize extensive libraries of lines carrying disease-associated mutations and precisely engineered genetic modifications. These resources are essential for the study of gene functions, human development, and disease mechanisms. Built over many years from well-defined specific parental cell lines, these libraries represent substantial investment in genome editing, clonal selection, and functional validation to ensure reproducibility and reliability. Duplicating comparable engineered mutations in iPSCs would require substantial time, funding, and personnel. It would also introduce variability, including differences in genetic background, epigenetic state, and reprogramming history, thereby reducing reproducibility and cross-study comparability, the core principles of NIH priorities for rigor and reproducibility.

Lastly, other areas of basic research would not be possible without access to certain existing hESC lines with unique properties or derivation origins, including parthenogenic

[5] Karvas, R., Khan, S., Verma, S., et al. (2022). Stem-cell-derived trophoblast organoids model human placental development and susceptibility to emerging pathogens. Cell Stem Cell 29, 810–825.e8. https://doi.org/10.1016/j.stem.2022.04.004

[6] Cheung, V.C., Peng, C., Marinić, M., et al. (2021). Pluripotent stem cell-derived endometrial stromal fibroblasts in a cyclic, hormone-responsive, coculture model of human decidua. Cell Reports 35, 109138. https://doi.org/10.1016/j.celrep.2021.109138

[7] Woods, D.C., White, Y.A.R., Niikura, Y., et al. (2013). Embryonic stem cell–derived granulosa cells participate in ovarian follicle formation in vitro and in vivo. Reprod. Sci. 20, 524–535. https://doi.org/10.1177/1933719113483017

[8] Liang, J., Wang, N., He, J., Du, J., Guo, Y., Li, L., Wu, W., Yao, C., Li, Z., Kee, K. (2019). Induction of Sertoli-like cells from human fibroblasts by NR5A1 and GATA4. eLife 8:e48767. https://doi.org/10.7554/eLife.48767

[9] Danti, L., Lundin, K., Sepponen, K., et al. (2023). CRISPR/Cas9-mediated activation of NR5A1 steers female human embryonic stem cell-derived bipotential gonadal-like cells towards a steroidogenic cell fate. J. Ovarian Res. 16, 194. https://doi.org/10.1186/s13048-023-01264-5

haploid cell lines and those derived through somatic cell nuclear transfer. These represent unique models for research that cannot be substituted by any other cell type.

Clinical research

At present, hESCs are the most established and best characterized source of pluripotent stem cells for the development of cell therapies. Their well-characterized biology, stability, and track record in translational research have enabled multiple hESC-derived products to advance into clinical trials, including several now in late-stage development. As a testament to the impact of NIH funding for hESC research, three of the four Phase III trials using cell therapies derived from hESCs taking place globally are being conducted in the U.S. Two of these trials are testing cell therapies derived from hESCs for the treatment of diabetes and Parkinson's disease. The third trial will be initiated soon, testing an hESC-derived cell therapy for epilepsy.

Notable recent clinical trials of cell therapies derived from hESCs include the following:

- In a Phase I/II trial for diabetes, all 12 patients treated with full-dose hESC-derived pancreatic islet cells displayed reduced dependence upon exogenous insulin; 10 of 12 patients were insulin free after 1 year.[10] This therapy is now being tested in Phase III clinical trials.
- In a Phase I trial testing hESC-derived dopaminergic neuron progenitors for the treatment of Parkinson's, 12 patients treated displayed meaningful positive trends 3 years after treatment.[11,12] This trial is advancing to a later phase.
- In a Phase I/II trial testing hESC-derived GABA interneurons for the treatment of drug-resistant mesial temporal lobe epilepsy, a 9-patient low-dose cohort displayed an 89% reduction in disabling seizures 7-12 months after administration. A 9-patient high dose cohort demonstrated a 78% median reduction in seizures at 4-6 months after administration.[13] This trial is also advancing to a later phase.

[10] Reichman, T.W., Markmann, J.F., Odorico, J., et al. (2025). Stem cell-derived, fully differentiated islets for type 1 diabetes. N. Engl. J. Med. 393, 858–868. https://doi.org/10.1056/NEJMoa2506549

[11] Tabar, V., Sarva, H., Lozano, A.M., et al. (2025). Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease. Nature 641, 978–983. https://doi.org/10.1038/s41586-025-08845-y

[12] BlueRock Therapeutics. (2025). BlueRock Therapeutics reports positive 36-month results from phase I trial of bemdaneprocel for treating Parkinson's disease. https://www.bluerocktx.com/bluerock-therapeutics-reports-positive-36-month-results-from-phase-i-trial-of-bemdaneprocel-for-treating-parkinsons-disease/

[13] Neurona Therapeutics. (2025). Neurona Therapeutics Presents New Long-Term Clinical Data from NRTX-1001 Cell Therapy Trials at 2025 Annual Meeting of the American Epilepsy Society. https://www.neuronatherapeutics.com/news/press-releases/120825/

- In multiple clinicals trials using hESC-derived retinal pigment epithelium cells for the treatment of age-related macular degeneration, initial results display promise for disease stabilization and even improvement[14,15]

Restrictions on the availability of hESCs would not only affect hESC-derived therapies but could also undermine the development of related therapeutic platforms. In addition to acting as a source of cells for therapies, hESCs routinely serve as an important control and calibration standard for other pluripotent cell therapies (e.g., patient-specific iPSC-derived therapies). The establishment, validation, and ongoing quality assessment of iPSCs relies on comparison to well-characterized hESC lines.

New Approach Methodologies (NAMs)

Recent and ongoing efforts across the U.S. federal government have sought to promote the development and application of NAMs to establish human-relevant models in preclinical safety and drug discovery studies and in environmental toxicity testing. This includes efforts by the NIH[16], the FDA[17,18], and numerous other regulatory and research agencies.[19] Similar efforts by regulatory agencies and international coordinating bodies are underway across the world. By developing and increasing the adoption of human-relevant NAMs, these efforts aim to improve the safety of drugs, accelerate and decrease costs associated with the development and approval of new therapeutics, prevent exposure to harmful substances, and reduce reliance on traditional animal studies.

As NAMS evolve from experimental systems into decision-enabling tools for scientific and regulatory use, key barriers to their adoption are the establishment of human relevance, standardization, and context-of-use validation. hESCs have emerged as a foundational tool for addressing these challenges by serving as stable, well-characterized reference materials that facilitate reproducible benchmarking across platforms. Many well-characterized and widely adopted NAMs platforms (e.g., organoids and microphysiological systems) were originally established and validated using hESCs.

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[14] Lebkowski, J. (2025). Presented at ISSCR's accelerating PSC-derived cell therapies symposium, Boston, MA, USA, December 2025.

[15] Lineage Cell Therapeutics. (2025). OpRegen (RG6501) 36-Month Visual Acuity Results Featured at Clinical Trials at the Summit 2025. https://investor.lineagecell.com/news-releases/news-release-details/opregenr-rg6501-36-month-visual-acuity-results-featured-clinical

[16] National Institutes of Health. Standardized Organoid Modeling (SOM) Center. https://www.nih.gov/som

[17] U.S. Food and Drug Administration. (2025). FDA announces plan to phase out animal testing requirement for monoclonal antibodies and other drugs. https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs

[18] U.S. Food and Drug Administration. (2025). FDA roadmap to reducing animal testing in preclinical safety studies. https://www.fda.gov/media/186092/download?attachment

[19] Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/iccvam-agencies

hESCs also contribute to the development of specific NAMs applications. For example, hESCs have been used to develop an in vitro assay to detect human developmental toxicants, a platform that could be used to identify harmful substances if exposure occurred during pregnancy.[20] hESCs remain a gold standard for the study of reproductive disorders and are used to investigate environmental causes of infertility. More broadly, numerous hESC-derived models have been developed for drug discovery and safety evaluations across multiple organ systems, including for diseases of the brain, lung, and kidney, as well as longer-term safety endpoints.[21]

While the field is advancing towards alternative cell sources such as iPSCs, this transition relies on direct comparability and benchmarking studies against hESCs. Without hESCs investigators will be unable to anchor new models to established biological reference points, ensure continuity of datasets, and support regulatory confidence through reproducible benchmarks. This function is of particular importance given sources of variability in iPSC-based systems, including reprogramming-associated effects. In parallel, modern NAMs are increasingly integrated with computational and AI-driven approaches that rely on robust, standardized biological reference points for model training and evaluation.

3. *Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.*

At present, no alternative technology can replace hESCs as none has been demonstrated to be fully biologically equivalent. Legacy hESC lines (e.g., WA01, WA09) are among the most widely characterized and most widely distributed human research materials. They provide an irreplaceable reference material for future work and for the development of alternative methods. A scientifically responsible strategy would be to strengthen complementary technologies such as iPSCs, adult stem cell-derived organoid systems, and genomic stability monitoring while maintaining access to hESCs.

Provided below are descriptions of complementary technologies to hESCs.

a. Induced Pluripotent Stem Cells (iPSCs)

[20] Palmer, J.A., Smith, A.M., Egnash, L.A., et al. (2013). Establishment and assessment of a new human embryonic stem cell-based biomarker assay for developmental toxicity screening. Birth Defects Res. B 98, 343–363. https://doi.org/10.1002/bdrb.21078

[21] Jeya Vandana, J., Manrique, C., Lack, L.A., Chen, S. (2023), Human pluripotent-stem-cell-derived organoids for drug discovery and evaluation. Cell Stem Cell, 30, 571-591. https://doi.org/10.1016/j.stem.2023.04.011

iPSCs are reprogrammed adult somatic cells that exhibit similar properties as hESCs and are highly comparable across a wide range of applications but are not biologically identical.[22] Since their derivation, iPSCs have provided an important additional tool for studying patient-specific cells. While iPSCs have substantially expanded the field of stem cell research and provide a cell source for certain applications, they often do not fully replicate the features of hESCs. Genome-wide epigenetic analyses have demonstrated that iPSCs frequently retain epigenetic signatures associated with their cell-of-origin, reflecting incomplete epigenetic reprogramming.[23] Consistent with this, the capacity of mouse iPSCs to participate in embryonic development is highly variable. This variability, introduced during reprogramming and subsequent culture, is a central limitation of iPSCs. These residual epigenetic differences can influence the gene expression and differentiation potential of iPSCs, highlighting why hESCs remain the gold standard for human pluripotency.

iPSCs often retain residual DNA methylation patterns associated with their cell-of-origin and recurrent methylation hotspots that are not observed in hESCs.[24,25,26] Imprinting control regions and X chromosome regulatory loci are among the genomic features that can exhibit epigenetic variability across iPSC lines. In addition, female iPSCs frequently exhibit abnormal or unstable X chromosome inactivation, including incomplete reactivation, erosion of dosage compensation, and heterogeneous allele-specific expression patterns.[27,28,29] These persistent questions regarding epigenetic memory, imprinting fidelity, X-inactivation, and genomic stability underscore the continued need for hESCs as the gold standard reference for pluripotency.

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[22] Takahashi, K., Tanabe, K., Ohnuki, M., et al. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872. https://doi.org/10.1016/j.cell.2007.11.019

[23] Nichols, J., and Smith, A. (2009). Naive and primed pluripotent states. Cell Stem Cell 4, 487–492. https://doi.org/10.1016/j.stem.2009.05.015

[24] Kim, K., Zhao, R., Doi, A. et al. (2011). Donor cell type can influence the epigenome and differentiation potential of human induced pluripotent stem cells. Nat. Biotechnol. 29, 1117–1119. https://doi.org/10.1038/nbt.2052

[25] Ohi, Y., Qin, H., Hong, C., et al. (2011). Incomplete DNA methylation underlies a transcriptional memory of somatic cells in human iPS cells. Nat. Cell Biol. 13, 541–549. https://doi.org/10.1038/ncb2239

[26] Bilic, J., and Izpisua Belmonte, J.C. (2012). Concise review: induced pluripotent stem cells versus embryonic stem cells: close enough or yet too far apart? Stem Cells 30, 33–41. https://doi.org/10.1002/stem.700

[27] Tchieu, J., Kuoy, E., Chin, M.H., et al. (2010). Female human iPSCs retain an inactive X chromosome. Cell Stem Cell 7, 329–342. https://doi.org/10.1016/j.stem.2010.06.024

[28] Mekhoubad, S., Bock, C., de Boer, A.S., et al. (2012). Erosion of dosage compensation impacts human iPSC disease modeling. Cell Stem Cell 10, 595–609. https://doi.org/10.1016/j.stem.2012.02.014

[29] Bar, S., Seaton, L.R., Weissbein, U., Eldar-Geva, T., and Benvenisty, N. (2019). Global characterization of X chromosome inactivation in human pluripotent stem cells. Cell Rep. 27, 20–29.e23. https://doi.org/10.1016/j.celrep.2019.03.019

Reprogramming technologies are still evolving, with recent advances aimed at addressing epigenetic differences between iPSCs and hESCs. But these studies further highlight the need for continued access to hESCs as the benchmark against which the performance of reprogrammed cells is evaluated. For example, transient naïve reprogramming can partially correct epigenetic abnormalities in human iPSCs, but assessment of successful epigenetic resetting required direct comparison to hESCs.[30] Similarly, efforts to generate naïve human pluripotent stem cells and related intermediate pluripotent states rely extensively on benchmarking against hESCs to confirm authentic transcriptional identity and developmental competence.[31,32] Even the most advanced reprogramming and pluripotent stem cell technologies remain dependent on hESC lines as a reference material to define authentic human pluripotent ground states.

As iPSCs have come into wide use, careful comparative studies of hESCs, iPSCs, and other pluripotent stem cells (e.g., somatic cell nuclear transfer-derived ESCs) have become less frequent. As such, the persistent differences described above remain unresolved. Existing comparisons are further complicated by genetic variability across donor-derived cell lines, and very few studies have used isogenic panels for direct comparisons between hESCs and iPSCs. Further studies are required to define the extent, sources, and consequences of the differences between these stem cell types.

Finally, while iPSCs do represent a powerful platform for the development of cell therapies, clinical assessment comparing hESC-based and iPSC-based therapies is still at a very early phase of research. At present, cell therapies using hESCs have advanced the furthest in the clinic, though iPSCs are more commonly selected as a starting material for new programs.[33] It is not yet possible to ascertain whether the two platforms will prove to be equivalent, whether one method may turn out superior, or whether the superior choice of cell source is context-dependent (e.g., patient- or disease-specific). This uncertainty merits continued access to hESCs to enable rigorous comparative research and ensure that the safest and most effective therapeutic approaches can be identified and translated to patients.

b. Adult Stem Cells

[30] Buckberry, S., Liu, X., Poppe, D., et al. (2023). Transient naive reprogramming corrects hiPS cells functionally and epigenetically. Nature 620, 863–872. https://doi.org/10.1038/s41586-023-06424-7

[31] Theunissen, T.W., Powell, B.E., Wang, H., et al. (2014). Systematic identification of culture conditions for induction and maintenance of naive human pluripotency. Cell Stem Cell 15, 471–487. https://doi.org/10.1016/j.stem.2014.07.002

[32] Bredenkamp, N., Yang, J., Clarke, J., et al. (2019). Wnt inhibition facilitates RNA-mediated reprogramming of human somatic cells to naive pluripotency. Stem Cell Reports 13, 1083–1098. https://doi.org/10.1016/j.stemcr.2019.10.009

[33] Kirkeby, A., Main, H., and Carpenter, M. (2025). Pluripotent stem-cell-derived therapies in clinical trial: a 2025 update. Cell Stem Cell 32, 10–37. https://doi.org/10.1016/j.stem.2024.12.005

Adult (or somatic) stem cells are tissue-specific cells characterized by their ability to self-renew and to differentiate into more specialized cell types within their tissue of origin. Adult stem cells reside in human tissues such as skin, muscle, intestines, and the hematopoietic system (i.e., blood and immune cells). Stem cells are present throughout life in these tissues.[34,35] They are useful tools for understanding the basic biological mechanisms involved in tissue regeneration but do not represent a replacement for hESCs.

Fundamental biological differences between adult stem cells and hESCs preclude adult stem cells from replacing hESCs. Adult stem cells are lineage restricted and their differentiation potential is confined to their tissue of origin. Adult stem cells also generally lack key properties that support broad research and translational use. They are not immortal (in contrast to hESCs), are more difficult to expand and scale, and display wide biological variability among individuals. In most human tissues, adult stem cells are rare and difficult to isolate. Stem cells from muscle, bone, intestine, and the nervous system cannot easily be recovered, if at all, from live or cadaveric donors, further constraining their utility.

Some common adult stem cell types used in clinical research:

- Hematopoietic stem cells (HSCs) represent the most established stem cell type that is used clinically, but only for diseases of the hematopoietic and immune systems. Hematopoietic stem cells cannot be differentiated to cells from non-hematopoietic tissues. Despite their value in the treatment of conditions of the blood, they are not a replacement for hESCs and could not be used for the treatment of conditions that are being treated with hESC-derived cell therapies, such as diabetes, Parkinson's disease, epilepsy, or macular degeneration.
- Mesenchymal stem cells (MSCs) can differentiate into bone, cartilage, and fat and are found in bone marrow and other tissues such as adipose tissue. They have shown clinical benefit in limited indications, including steroid refractory graft-versus-host disease in children after allogeneic bone marrow transplants and treating anal fistulas that arise in Crohn's disease, but have not shown efficacy in controlled trials for other conditions. The therapeutic potential of MSCs is constrained by immune rejection of allogeneic MSCs after transplantation, preventing them from repairing or integrating into resident tissues; their senescence in culture limiting biomanufacturing capacity; and donor-to-donor variability which

[34] Cable, J., Fuchs, E., Weissman, I. (2020). Adult stem cells and regenerative medicine—a symposium report. (2020). Ann. N. Y. Acad. Sci. 1462, 27–36. https://doi.org/10.1111/nyas.14243

[35] De Morree, A., and Rando, T.A. (2023). Regulation of adult stem cell quiescence and its functions in the maintenance of tissue integrity. Nat. Rev. Mol. Cell Biol. 24, 334–354. https://doi.org/10.1038/s41580-022-00568-6

complicates clinical trials.[36] Despite being studied clinically for over 35 years, there is only one approved cell therapy using MSCs in the U.S. (Ryoncil, from Mesoblast, for pediatric GVHD).[37]

For certain tissues, adult stem cell-derived organoids can be grown in culture. These structures can provide useful models for certain cell types in certain tissues but have limited structural complexity and lack the ability to model most of the cell-cell interactions within tissues. Since they are generated from adult cells, they do not have the capacity to form cells outside of their tissue of origin, unlike hESCs. While holding promise for certain research directions, adult stem cell-derived organoids do not represent a replacement for hESCs in any sense.

c. Computational models

Recent efforts have sought to establish computational models for the study of stem cell behavior and development. Sophisticated models are in their infancy, with computational models of animal development only just emerging.[38] At present, these models, particularly for human development, have limited predictive value because they are not sophisticated enough to model most aspects of cell biology. Computational modeling and AI-assisted methods offer potential for future research directions, but do not represent a replacement for research using hESCs.

4. *Research areas in which additional investments should be made to bolster validated models to replace use of hESCs*.

No alternative model or technology is directly equivalent to hESCs. hESCs represent the only naturally occurring, unmodified human pluripotent stem cell. All other methods and technologies will inherently require validation against hESCs, and should be viewed as a complement to hESC research rather than a replacement.

Efforts to *complement* hESC research would be aided by the following:

a. Further investigation of the impacts of iPSC reprogramming on their biological comparability to hESCs, including study of unresolved questions highlighted under Question 3 (e.g., epigenetic memory, imprinting fidelity, X-inactivation,

[36] Česnick, A.B., and Švajger, U. (2024). The issue of heterogeneity of MSC-based advanced therapy medicinal products—a review. Front. Cell Dev. Biol. 12. https://doi.org/10.3389/fcell.2024.1400347
[37] U.S. Food and Drug Administration. Ryoncil. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/ryoncil
[38] Čapek, D., Safroshkin, M., Morales-Navarrete, H., et al. (2023). EmbryoNet: using deep learning to link embryonic phenotypes to signaling pathways. Nat. Methods 20, 815–823. https://doi.org/10.1038/s41592-023-01873-4

and genomic stability). This could include isogenic studies comparing hESCs and iPSCs.

b. Follow up research on clinical trials that used different kinds of pluripotent cell-derived therapies to determine whether one kind of pluripotent stem cell is more effective than another (i.e., hESC- vs. iPSC-derived).

Scientific and ethical governance of research with hESCs

hESC research currently proceeds under a well-established ethical and legal framework embedded in NIH's own Guidelines for Human Stem Cell Research and supported by the National Academies and leading scientific, medical, and patient advocacy organizations. These policies permit the use of hESC lines derived from embryos originally created for clinical use by in vitro fertilization (IVF) but subsequently deemed unsuitable for transfer or no longer needed for reproductive purposes, with informed consent from donors.

Because these embryos are routinely discarded during IVF care, any new restrictions on the use of hESC lines would not save a single embryo from destruction. Rather, such limitations would constrain the ability of researchers and patients to derive scientific and medical value from materials already designated for disposal. Moreover, the donors who voluntarily supplied embryos in the hope of advancing scientific progress may be frustrated to see stem cell lines derived from their donated embryos discharged despite the clear scientific and clinical need.

Conclusion

hESCs are an essential, irreplaceable component of the biomedical research ecosystem. Decades of NIH investment in hESC research have resulted in a highly productive infrastructure that has generated foundational insights into human development and enabled novel clinical advancements. As emphasized above, though iPSCs and other emerging technologies can sometimes provide overlapping research use cases to hESCs, these alternative platforms still rely on hESCs as benchmarks and should not be thought of as substitutes.

Based on the available scientific and translational evidence, there is no scientific or ethical justification for NIH to reduce its reliance on hESC research. Any departure from NIH's long-standing support for this work would not be evidence-based and could have negative downstream effects across related research areas. We urge NIH to lift its pause on submissions to its hESC Registry and continue its commitment to supporting scientifically meritorious hESC research.

For questions or clarifications, please contact Tyler Lamb, JD, Director of Policy (tlamb@isscr.org) or Andrew Bremer, PhD, Manager of Policy (abremer@isscr.org).

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Respectfully,

[redacted]

Hideyuki Okano, MD, PhD
ISSCR President

[redacted]

Lorenz Studer, MD
ISSCR President-elect

97. Arizona State University (ASU)

I am responding: On behalf of an organization

Name: Kristy Macdonald

Name of Organization: Arizona State University (ASU)

Type of Organization: Academic Institution

Role: Organizational Official

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
Currently approved hESC lines sufficiently support many areas of developmental biology, disease modeling, and translational research, particularly where a well-characterized pluripotent control is required. These lines are routinely used as benchmarks to validate differentiation efficiency, reproducibility, and experimental consistency. However, additional hESC lines are needed to better capture human genetic diversity and improve biological relevance across studies. Line-to-line variability, clonal differences, and the accumulation of genomic instability with extended passaging limit reliance on a small number of existing lines. Expanding the number of available hESC lines would strengthen experimental rigor and reproducibility while addressing technical challenges associated with long-term culture and heterogeneity.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
hESCs are the gold standard for studying human development and disease because they represent the only natural source of truly pluripotent human cells. They are indispensable in research requiring differentiation from a bona fide embryonic state, particularly for tissues that lack regenerative capacity or endogenous stem cell populations. This includes critical areas such as the central nervous system and cardiac tissue, where modeling development, injury, and regeneration depends on authentic pluripotency. Without hESCs, these research avenues would be significantly limited or infeasible.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
Emerging technologies, such as induced pluripotent stem cells (iPSCs), offer promising alternatives in certain contexts, particularly where patient-specific modeling and increased representation of genetic diversity are priorities. iPSCs are widely used to incorporate multiple donor backgrounds into studies, enhancing translational relevance. However, their ability to fully replace hESCs remains limited due to factors such as epigenetic memory, lineage bias, donor age effects, and differences between naïve and primed states. These limitations can affect differentiation potential and experimental outcomes, meaning that while iPSCs may substitute for hESCs in some applications, they are not yet universally equivalent.
ASU faculty are working with iPSC lines that allow them to better model human diseases such as neurological disorders and cancers. They have and continue to develop new protocols and devices to enhance the differentiation of these cell lines into relevant models of human disease. Of special note is

our capability to develop structurally layered cortical organoids that are providing glimpses into many different neurological disorders. Additionally, ASU researchers have developed CRISPR based methods to genetically modify iPSCs at single nucleotide resolution. This allows the any researcher to engineer specific variants that mimic disease into an iPSC line or remove the disease-causing allele. By combining these methods, we are developing a robust platform that will allow ASU to replace the use of hESC lines and simultaneously improve disease relevance.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.

Further investment is needed to improve alternative stem cell models so they can reliably match the rigor and consistency of hESC-based systems. Key areas include enhancing reprogramming methods for iPSCs to eliminate epigenetic memory and lineage bias, improving differentiation protocols to increase efficiency and fidelity, and developing culture systems that maintain genomic stability over time. Additionally, advancing technologies that better model true pluripotency and reduce variability across lines will be critical. Strengthening these areas will help build validated, reproducible systems that reduce reliance on hESCs in the future.

ASU thinks that there is a great need for funding to develop more disease relevant model systems like multicellular organoids developed from patient iPSC lines. With sufficient evidence and testing against gold standard hESCs and animal models we will eventually arrive at a place where neither hESCs nor animal models will be necessary. There is a need for a common biobank for iPSC lines characterized molecularly in high detail that will maintain and provide cell lines to researchers at cost, like what ATCC does currently. Additionally, funding should be provided to develop automation technology that assists in the culturing of organoids, which is a time and money intensive process. We feel that investments in these infrastructure would help researchers to adopt these model systems in their work.

98. Dosh Whye

I am responding: On behalf of myself

Name: Dosh Whye

Name of Organization: Boston Children's Hospital

Type of Organization: Non-profit Research Organization

Role: Investigator/Researcher

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
hESCs have proven to be indispensable for biomedical research on human development and disease. hESCs have not only helped biomedical researchers investigate the molecular and cellular basis for normal human development, but they have also shown utility in modeling human-specific disease. One of the most prominent medical issues of this 21st century is Infertility, and hESCs are an absolute necessity in studying & understanding the biology behind successful and unsuccessful pregnancies/live births. There is no substitute in modern medical research that will better help alleviate the suffering of human developmental disorders, like Infertility, than hESCs.

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
Human Development. Developmental Biology. Disease Modeling. Aging & Age-related disorders. Genetic disorders.

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
hESCs are the gold standard to validate any alternative methods that may resemble, but not replace, hESCs. There is no area in modern biotechnology that benefits from the disuse of hESCs.

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
hESCs are an essential basis for studying and learning about cell biology and human developmental biology. hESCs can be slightly resembled with the use of hiPSCs; however, they cannot be fully replaced. It is an absolute must that hESCs remain as a major funded resource for biomedical research.

99. Dr. Ali H. Brivanlou

I am responding: On behalf of myself

Name: Dr. Ali H. Brivanlou

Name of Organization: Rockefeller University

Type of Organization: Academic Institution

Role: Other

Role - Other: Professor/Head of Lab

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

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SCIENCE FOR THE BENEFIT OF HUMANITY

Ali H. Brivanlou, Ph.D.
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April 24, 2026

Re: NIH Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

To whom it may concern,

The policy premise that hiPSCs are simply a better or equivalent substitute to hESCs is scientifically incorrect in several critical ways. First, hiPSCs are reprogrammed adult somatic cells. The reprogramming process (Yamanaka factors: Oct4, Sox2, Klf4, c-Myc) resets the nucleus but not the cytoplasm or mitochondria, which retain somatic metabolic profiles. hESCs, derived directly from the inner cell mass (ICM) of a blastocyst, have never passed through a somatic state and carry none of that epigenetic memory. Second, hiPSCs show line-to-line and experiment-to-experiment variation in differentiation propensity that frustrates reproducibility. Well-characterized NIH-registered hESC lines (e.g., RUES2) provide a stable, validated reference standard across laboratories. Third, reprogramming introduces mutagenic risk. Even non-integrating methods expose cells to stress-induced damage. hESCs, derived without reprogramming, do not carry this class of artifact. There are also proteomic differences, which is consistent with incomplete erasure of somatic identity.

It is also important to note that hESCs are irreplaceable for embryo modeling and Developmental Biology, and this is where the policy gap is most consequential. Their self-organization behavior in embryo models faithfully recapitulates signaling dynamics of the human embryo in ways that hiPSC-derived models do not fully replicate. Similarly, adult/somatic stem cells are not totipotent and cannot recapitulate gastrulation, germ layer specification, or early embryogenesis. Proposing them as substitutes for hESCs in developmental biology research reflects a fundamental misunderstanding of cell biology.

The ISSCR and AAMC have both issued formal responses calling for parallel pursuit of all pluripotent stem cell modalities. The scientific consensus is that hESCs, hiPSCs, and adult stem cells serve complementary, not interchangeable, research functions. Restricting hESC research based on ideological grounds (the same framework that ended federal fetal tissue research funding) would disrupt ongoing federally funded programs that depend on validated, NIH-registered hESC lines with known developmental properties. It will also eliminate the gold-standard reference against which all hiPSC models are validated. Finally, it halts progress in reproductive medicine, and disease modeling that requires authentic embryonic developmental context.

Sincerely,



Ali H. Brivanlou, Ph.D.
Head of Laboratory

100. The National Catholic Bioethics Center (NCBC), the Catholic Medical Association (CMA), the National Association of Catholic Nurses, USA (NACN-USA), and the National Catholic Partnership on Disability (NCPD)

I am responding: On behalf of an organization

Name: Dr. Marie T. Hilliard

Name of Organization: The National Catholic Bioethics Center (NCBC), the Catholic Medical Association (CMA), the National Association of Catholic Nurses, USA (NACN-USA), and the National Catholic Partnership on Disability (NCPD)

Type of Organization: Other

Type of Organization - Other: N/A

Role: Other

Role - Other: N/A

Date Submitted: 04/27/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/NIH-hESC-Research-April-2026.pdf

Description: The National Catholic Bioethics Center (NCBC), the Catholic Medical Association (CMA), the National Association of Catholic Nurses, USA (NACN-USA), and the National Catholic Partnership on Disability (NCPD) write in response to the NIH request for comments regarding the use of human embryonic stem cells (hESC) in research. Our four organizations will consistently defend the dignity of every person, which is established at the moment of conception (fertilization). The superiority of iPSC/ASC in comparison to hESC is inarguably clear on multiple levels. The basic and clinical research results contrast starkly with the limited successes of hESC use. Cost/benefit ratio with iPSC/ASC is a significant factor, particularly given the fiscal responsibility of NIH in the provision of research grant

funding. While at this time hESCs often have lower production costs for large-scale, standardized therapies because they do not require the high, patient-specific reprogramming, the strong success rates are not there. However, iPSCs are generally more cost-effective for disease modeling and drug screening because they allow for patient-specific, ethically uncontroversial cell lines that can be generated without destroying embryos. When taxpayer money is utilized for funding, the most successful and least costly methods should be supported. The proven record of advances and successes with the use of iPSC/ASC are more than sufficient to expand funding of these methods.

THE NATIONAL CATHOLIC BIOETHICS CENTER
600 REED ROAD, SUITE 102, BROOMALL, PA 19008 (215) 877-2660 (215) 877-2688 FAX NCBCENTER.ORG

April 24, 2026

Lynn Jorgensen, Ph.D.
Associate Director for Science Policy
National Institutes for Health
6705 Rockledge Drive, Suite 630
Bethesda, MD 20892

Re: National Institutes of Health (NIH) Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research – Notice Number NOT-OD-26-031

Dear Associate Director Jorgensen:

The National Catholic Bioethics Center (NCBC), the Catholic Medical Association (CMA), the National Association of Catholic Nurses, USA (NACN-USA), and the National Catholic Partnership on Disability (NCPD) write in response to the NIH request for comments regarding the use of human embryonic stem cells (hESC) in research. Our four organizations will consistently defend the dignity of every person, which is established at the moment of conception (fertilization).

Foundation for our Organizations' Concerns

Some have suggested that embryonic stem cell research is necessary for the development of treatment for persons with disabilities. Individuals who suffer from disabilities such as Parkinson's disease are often cited as reasons why the continued development of embryonic stem cell research is crucial. NACN-USA and CMA are composed of healthcare professionals who work directly with persons with disabilities. For the reasons given below, these organizations can attest that adult stem cell research has offered better hope of advancing cures within an ethical framework that respects the dignity of the person. NCPD is the premier Catholic organization that advocates for persons with disabilities within the Church and in the wider culture. A guiding ethical principle for NCPD is that any treatment that does not respect the dignity of the person erodes the dignity of all persons, including the most vulnerable and those with disabilities. NCBC has been upholding the dignity of the human person in health care and biomedical research since

1972. NCBC, with NCPD, CMA, and NACN-USA reject utilitarian calculations that would sacrifice unborn embryonic children to provide a better quality of life for others. In fact, these utilitarian claims are even more troubling given that they do not stand up to scrutiny.

Furthermore, adult stem cell research is effective, as shown below. Our four organizations ask the administration to carefully consider these comments in light of the fundamental moral principle that all persons, born or unborn, disabled or healthy, possess intrinsic dignity and may not be used as a means to an end. Our ethical opposition to the use of hESC has remained constant throughout the nearly three decades of that use. Over that time, the scientific consensus regarding human embryonic stem cells (hESCs) has shifted from treating them as a "gold standard" for research, while increasingly favoring alternatives like induced pluripotent stem cells (iPSCs) for therapeutic applications, due to ethical concerns and immunological challenges.[1] We wish to comment on both the ethical and scientific facts that definitively support the use of optimal methods, specifically with induced pluripotential stem cells and adult stem cells (iPSC/ASC).

Ethical Considerations

The moral argument against the use of hESC is definitive. There is no fundamental human right greater than the right to life. Recognizing that life begins with conception, the utilization of hESC is a discriminatory act that takes advantage of the indefensibility of the unborn person. That harm is compounded when the use of hESC is funded by taxpayer dollars. If that is allowed, the government is justifiably seen as condoning the use of unborn persons as a commodity. The intentional ending of one human life as a means of improving or healing another is immoral. The creation of human embryos, or using abandoned or “donated” embryos from fertility procedures, simply for the purpose of destroying them for research purposes is antithetical to the principles of inherent human rights.

Scientific Evidence and Clinical Progress

The scientific evidence supporting the use of ethically acceptable stem cells rather than hESC is clear. The majority of funding for stem cell usage in research currently utilizes iPSC/ASC, which does not carry the moral harm associated with hESC.[2] The goal of any biomedical research is to achieve improvements in the health and treatment of patients. In that regard, iPSC/ASC have demonstrated success. Adult stem cells, although in the past their regenerative/reparative capacity was misunderstood, are demonstrating a rapidly growing host of clinical applications; and their clinical utility is increasingly being validated, and demonstrating to be superior to hESC in the clinical setting.[3] Until recently, no human being has been

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[1] Mario Kropf, “Ethical Aspects of Human Induced Pluripotent Stem Cells and Alzheimer’s Disease: Potentials and Challenges of a Seemingly Harmless Method,” *Journal of Alzheimer’s Disease Reports* (Sept. 2, 2023) https://doi.org/10.3233/ADR-230018. Also, Mario Kropf Netherlands Center for the Clinical Advancement of Stem Cell & Gene Therapies, “The Ethical Advantages of iPSCs,” NecstGen (Copyright 2025). https://necstgen.com/ethical-advantages-ipscs/#:~:text=iPSCs%20are%20crafted%20from%20adult,the%20risk%20of%20transplant%20rejection.

[2] Cade Hildreth, Founder & President, “What Are iPSCs, Who is Funding Them, and What Trials are Underway?” Blog: *BioInformant* (December 4, 2025). https://bioinformant.com/what-are-ips-cells/#:~:text=at%20this%20link.-,Funding%20for%20iPS%20Cell%20Technology,a%20period%20of%20ten%20years..

[3] D.A. Prentice, “Adult Stem Cells: Successful Standard for Regenerative Medicine,” *Circulation Research* 124:6 (14 March 2019). https://doi.org/10.1161/CIDCRESAHA.118.313664.

cured of any disease as a result of the use of hESC,[4] and the limited successes often are in clinical trials.[5] In contrast, the use of iPSC/ASC is demonstrating the potential to improve or save many lives.[6]

Non-embryonic stem cells function as a component of the normal repair and regeneration systems in the body, functions that embryonic stem cells cannot perform without the potential for rejection.[7] Even more problematic are the dangers associated with both iPSC and hESC, given their biological and inherent property towards proliferation. They are recognized as tumorigenic, particularly in the development of teratomas. Until recently, it was assumed that human induced pluripotent stem cells (HiPSCs) would behave like/worse than their embryonic counterparts in respect to their tumorigenicity. However, a rapidly accumulating body of evidence suggests that there are important genetic and epigenetic differences between these two cell types, which seem to influence their tumorigenicity.[8] The potential ability of researchers to control this property in iPSC/ASC[9] highlights the advantage of funding iPSC/ASC, as well as the rationale to discontinue funding of the former.

The impact of iPSC/ASC on health care is wide and profound. In a relatively short period of time, the advantages of these methods have become abundantly clear, with the World Health Organization (WHO) reporting more than three thousand ongoing trials using adult stem cells,[10] yielding significant improvements and successes in treatments ranging from hematopoietic diseases[11] to severe burn injuries[12] and macular degeneration.[13] Cardiovascular benefits are increasingly evident, particularly with stem cells derived from bone marrow and umbilical cord blood.[14] The use of these cells has led to

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[4] Charlotte Lozier Institute, "Fact Sheet: Adult Stem Cell Research and Transplants" (November 21, 2017). https://lozierinstitute.org/fact-sheet-adult-stem-cell-research-transplants/.

[5] Gina Kolata, "'It's like a miracle': The man who may be the first person cured of type 1 diabetes," *The Irish Times* (Fri Dec 03 2021). 'It's like a miracle': The man who may be the first person cured of type 1 diabetes – The Irish Times.

[6] José Bragança, *et al.,* "Induced pluripotent stem cells, a giant leap for mankind therapeutic applications," *World J Stem Cells* 11:7 (2019 Jul 26). 421–430. doi: 10.4252/wjsc.v11.i7.421.

[7] Mayo Clinic Staff, "Stem cells: What they are and what they do: Stem cells offer promise for new medical treatments. Learn about stem cell types, current and possible uses, and the state of research and practice," *Mayo Clinic* (Jan. 21, 2026). https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117.

[8] Uri Ben-David, Nissim Benvenisty, "The tumorigenicity of human embryonic and induced pluripotent stem cells," *Nat Rev Cancer* 11:4 (2011 Apr) 268-77. doi: 10.1038/nrc3034. PMID: 21390058 DOI: 10.1038/nrc3034.

[9] Chaoliang Zhong, *et al.,* "Tumorigenicity risk of iPSCs in vivo: nip it in the bud," *Precis Clin Med.* 5:1 (2022 Feb 3). pbac004. doi: 10.1093/pcmedi/pbac004; also Go Itakura, "Fail-Safe System against Potential Tumorigenicity after Transplantation of iPSC Derivatives," *Stem Cell Reports: ISSCR* 8:3 (March 14, 2017) 673-684. https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(17)30047-4.

[10] R.M. Aly, "Current state of stem cell-based therapies: an overview," *Stem Cell Investig* 7:8 (15 May 2020). https://doi.org/10.21037/sci-2020-001.

[11] F. Bernaudin, *et al*., "Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease," *Blood* 110 (2007) 2749-2756, 2007, https://doi.org/10.1182/blood-2007-03-079665; HRSA, "Blood Stem Cell Program" (April 18, 2026) https://bloodstemcell.hrsa.gov/data, and https://bloodstemcell.hrsa.gov/data; and The Lancet Hematology (press release), "Experts warn of stem cell underuse as transplants reach 1 million worldwide" (Feb 27, 2015). https://www.sciencedaily.com/releases/2015/02/150227084630.html.

[12] J. Poulos, "The limited application of stem cells in medicine: a review," *Stem Cell Res Ther* 9:1 (2018). https://link.springer.com/article/10.1186/s13287-017-0735-7.

[13] M. Mandai, *et al*., "Autologous induced stem-cell-derived retinal cells for macular degeneration," *N Engl J Med* 376 (2017) 1038-46. https://www.nejm.org/doi/full/10.1056/NEJMoa1608368.

[14] M.N. Banerjee, *et al*., "Clinical studies of cell therapy in cardiovascular medicine: recent developments and future directions," *Circ Res* 123:2 (6 July 2018) 266–287. 2018, https://doi.org/10.1161/CIRCRESAHA.118.311217.

strikingly significant improvements in many neurologic conditions, including stroke,[15] multiple sclerosis,[16] and spinal cord injury.[17] The efficacy of iPSC/ASC in the field of genetic therapies is likewise demonstrated in disorders such as epidermolysis bullosa[18] and Krabbe disease.[19]

Basic research utilizing iPSC/ASC demonstrates a similarly broad range of discoveries that further support funding of these methods. Three-dimensional organoids have been developed from them to discover the mechanism of damages incurred by Zika virus[20] and to identify cell-based anomalies leading to lissencephaly.[21] Organoids of lung, kidney, brain, liver, and other organs have been developed from adult stem cells to improve the study of diseases, including the mechanisms of SARS-CoV-2 damage and its treatment.[22]

The potential improvements in multiple clinical areas can be foreseen in the expanding number of research reports utilizing these stem cells, including hearing loss,[23] thyroid disease,[24] Creutzfeld-Jakob disease,[25] congenital heart disease,[26] restoration of vision,[27] gynecologic carcinomas,[28] and intestinal disorders.[29]

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[15] G.K. Steinberg, *et al*., "Clinical outcomes of transplanted modified bone marrow–derived mesenchymal stem cells in stroke: A Phase 1/2a Study" *Stroke* 47:7 (July 2016) 1817-1824. https://doi.org/10.1161/STROKEAHA.116.012995

[16] P.A. Muraro, *et al*., "Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis," *JAMA Neurol* 74:4 (1 April 2017) 459–469. https://doi.org/10.1001/jamaneurol.2016.5867.

[17] D.A. Prentice, "Remembering pioneers in patient treatments," *J Tissue Sci Eng* 3:4. e119 (2012). DOI: 10.4172/2157-7552.1000e119

[18] T. Hirsch, *et al*., "Regeneration of the entire human epidermis using transgenic stem cells" *Nature*, 551: 7680 (* Nov. 2017) 327–332. https://doi.org/10.1038/nature24487.

[19] M.D. Wright, *et al.,* "Developmental outcomes of cord blood transplantation for Krabbe disease - A 15-year study," *Neurol* 89:13 (26 Sept 2017) 1365-1372. https://doi.org/10.1212/WNL.0000000000004418.

[20] P.P. Garcez, *et al*., "Zika virus impairs growth in human neurospheres and brain organoids," *Science* 352: 6287) (14 April 2016) 816–818. https://doi.org/10.1126/science.aaf6116.

[21] M. Bershteyn, *et al*., "Human iPSC-derived cerebral organoids model cellular features of lissencephaly and reveal prolonged mitosis of outer radial glia." *Cell Stem Cell* 20:4 (6 April 2017) 435-449.e4. https://doi.org/10.1016/j.stem.2016.12.007.

[22] S. Mallapaty, "The mini lungs and other organoids helping to beat COVID" (News Feature) *Nature* (26 May 2021). https://www.nature.com/articles/d41586-021-01395-z; and J. Jansen, *et al*., "SARS-CoV-2 infects the human kidney and drives fibrosis in kidney organoids," *Cell Stem Cell* 29:2 (3 Feb 2022) 217-231.e8. https://doi.org/10.1016/j.stem.2021.12.010.

[23] Q. Liu, *et al*., "High-throughput screening on cochlear organoids identifies VEGFR-MEK-TGFB1 signaling promoting hair cell reprogramming," *Stem Cell Reports* 16:9 (14 Sept 2021) 2257-2273. https://doi.org/10.1016/j.stemcr.2021.08.010.

[24] V. Ogundipe, *et al*., "Generation and Differentiation of Adult Tissue-Derived Human Thyroid Organoids," *Stem Cell Reports* 16:4 (13 April 2021) 913-925. https://doi.org/10.1016/j.stemcr.2021.02.011.

[25] B. R. Groveman, *et al*., "Human cerebral organoids as a therapeutic drug screening model for Creutzfeldt–Jakob disease," *Sci Rep* 11 (2021) 5165. https://doi.org/10.1038/s41598-021-84689-6.

[26] Y.R. Lewis-Israeli, *et al*., "Self-assembling human heart organoids for the modeling of cardiac development and congenital heart disease," *Nat Commun* 12 (2021) 5142. https://doi.org/10.1038/s41467-021-25329-5; and D. Srivastava, "Modeling human cardiac chambers with organoids," *N Engl J Med* 385:9 (25 Aug. 2021) 847-849. https://doi.org/10.1056/NEJMcibr2108627.

[27] B. Mahato, *et al*., "Pharmacologic fibroblast reprogramming into photoreceptors restores vision," *Nature* 581 (2020) 83-88. http://dx.doi.org/10.1038/s41586-020-2201-4.

[28] N. Yucer, *et al*., "Human iPSC-derived fallopian tube organoids with BRCA1 mutation recapitulate early-stage carcinogenesis," *Cell Reports* 37:13 (28 Dec. 2021). https://doi.org/10.1016/j.celrep.2021.110146.

[29] M. Nikolaev, *et al*., "Homeostatic mini-intestines through scaffold-guided organoid morphogenesis," *Nature* 585 (2020) 574–578. https://doi.org/10.1038/s41586-020-2724-8.

Safety & Practical Advantages of iPSC and ASCs

The superiority of iPSC/ASC in comparison to hESC is inarguably clear on multiple levels. The basic and clinical research results contrast starkly with the limited successes of hESC use.[30] Cost/benefit ratio with iPSC/ASC is a significant factor, particularly given the fiscal responsibility of NIH in the provision of research grant funding. While at this time hESCs often have lower production costs for large-scale, standardized therapies because they do not require the high, patient-specific reprogramming, the strong success rates are not there. However, iPSCs are generally more cost-effective for disease modeling and drug screening because they allow for patient-specific, ethically uncontroversial cell lines that can be generated without destroying embryos.[31] When taxpayer money is utilized for funding, the most successful and least costly methods should be supported. The proven record of advances and successes with the use of iPSC/ASC are more than sufficient to expand funding of these methods.

Policy Recommendations & Conclusions

The National Institutes of Health (NIH) announced on January 23, 2026, that it would pause new submissions to the NIH Human Embryonic Stem Cell Registry, effectively ending the registry that has been in place for 17 years.[32] The registry was created pursuant to President Barack Obama's Executive Order 13505 (2009), "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells."[33] The cessation of all funding for hESC research is warranted. The funding of iPSC/ASC will not violate Executive Order 13505, which while focusing on support for hESC, does not prohibit support for iPSC/ASC. An additional and appropriate action is that EO 13505 should be either revoked or replaced as there is no further need for hESC funding. The funding of iPSC/ASC research will help meet the Trump Administration's goals of decreasing wasteful spending, the promotion of innovation, and ultimately, improving the health of Americans.

Most importantly, as discussed in the opening of this letter, the moral and ethical path forward is to fund research that maintains respect for each person, regardless of their stage in life. From the time of conception, each individual deserves protection from harm and the opportunity to flourish. Furthermore, the intent of the *Hyde Amendment* is to prohibit federal funding of procedures that terminate the life of a human embryo or fetus.[34] Clearly, the derivation of any hESC lines for subsequent scientific studies requires the killing of originating embryos in the pursuit of subsequent biomedical research, violating the very protections of human life intended by Hyde. However, Executive Order 13505 (2009) is enabled by an unjust and unethical "work around" of the *Dickey-Wicker Amendment*. This Amendment is a longstanding federal appropriations rider, consistently renewed that prohibits the U.S. Department of Health and Human Services (HHS) and NIH from using federal funds for research that creates or destroys

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[30] Jun Takahashi, "iPSC-based cell replacement therapy: from basic research to clinical application," *CytoTherapy* 27:7 (July 2025) 835-842. https://www.isct-cytotherapy.org/article/S1465-3249(25)00053-2/fulltext.

[31] Yanhong Shi, *et al.,*" Induced pluripotent stem cell technology: a decade of progress," *Nat Rev Drug Discov*. 16:2 (2016 Dec 16) 115–130. doi: 10.1038/nrd.2016.245.

[32] NIH, "NIH Pause on New Submissions to the NIH Human Embryonic Stem Cell Registry and Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research" (January 23, 2026) Notice Number: NOT-OD-26-031. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-031.html.

[33] President Barac Obama, "Executive Order 13505 -- Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," *The White House* (March 9, 2009). https://obamawhitehouse.archives.gov/the-press-office/removing-barriers-responsible-scientific-research-involving-human-stem-cells.

[34] 113th Congress (2013-2014) S.142 - *Hyde Amendment Codification Act*.

human embryos. It maintains a strict ban on taxpayer funding for research causing injury or death to human embryos.[35] However, the funding of research using hESC has been justified by the fact that the actual destruction of the embryo, required by the very garnering of the embryo's cells, kills the human embryo, not the resulting research using the destroyed embryo's cells. The funding of hESC research not only ignores the human rights for which *Hyde* and *Dickey-Wicker* were promulgated but is inconsistent with existing laws that prohibit the use of goods obtained through illicit means.[36] Additional moral injury to the human family that is the United States, is incurred when federal funding is provided to research using means that allow human lives to be lost intentionally and unnecessarily.

The advantages of iPSC/ASC are indisputable and profound, to the degree that NIH funding for hESC should be halted, and all funding should be allocated to research efforts that are reliable, economical, effective, and of paramount importance, ethical.

Our organizations are grateful for this opportunity to contribute to your review of this important topic. We stand ready to help in any way as your deliberations proceed and look forward to NIH's exclusive support for iPSC/ASC.

Sincerely yours,

[redacted]

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[35] "Public Law No. 111-8". *Thomas H.R.1105*. The Library of Congress. Archived from the original on 2009-05-06.
[36] As an example: 18 U.S. Code § 2315 - Sale or receipt of stolen goods, securities, moneys, or fraudulent State tax stamps.

101. American Center for Law and Justice (ACLJ)

I am responding: On behalf of an organization

Name: Olivia F. Summers

Name of Organization: American Center for Law and Justice (ACLJ)

Type of Organization: Other

Type of Organization - Other: N/A

Role: Other

Role - Other: N/A

Date Submitted: 05/01/2026

1. Research areas in which currently approved hESC lines sufficiently meet the needs of the research community as well as research areas for which new hESC lines are needed.
N/A

2. Research areas for which hESCs are the gold standard and could not be pursued if hESCs were unavailable.
N/A

3. Research areas in which the robustness of emerging biotechnologies such as induced pluripotent stem cells, adult stem cells, etc., can replace the use of hESCs.
N/A

4. Research areas in which additional investments should be made to bolster validated models to replace use of hESCs.
N/A

Upload a File: https://osp.od.nih.gov/wp-content/uploads/ninja-forms/66/Comment-on-Stem-Cell.pdf

AMERICAN CENTER
for LAW & JUSTICE

April 21, 2026

NIH Office of Science Policy
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Bethesda, MD 20892
(301) 496-9838
SciencePolicy@od.nih.gov

RE: Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

To Whom It May Concern,

The American Center for Law and Justice (ACLJ) submits the following comments, on behalf of itself and over 100,000 of its pro-life supporters,[1] to encourage the National Institutes of Health (NIH) to end the use of human embryonic stem cells in scientific research. We agree with Health and Human Services Deputy Secretary Jim O'Neil: "Over the past 20 years, induced pluripotent stem cells and adult stem cells have proven to be flexible and useful across biomedical research and therapy. . . . The American people deserve better alternatives to human embryonic stem cells."[2] The ACLJ is an organization dedicated to the defense of constitutional liberties secured by law, including the defense of the sanctity of human life. ACLJ attorneys have argued before the Supreme Court of the United States and filed as *amici* in a number of significant cases involving the freedoms of speech, religion, and the right to life of the preborn[3] and have submitted formal comments regarding proposed rulemaking on a wide variety of issues.

[1] *Stop Using Our Tax Dollars to Buy Aborted Babies*, ACLJ.ORG, https://aclj.org/pro-life/stop-using-our-tax-dollars-to-buy-aborted-babies (last visited Apr. 16, 2026).
[2] *NIH Proposes Embryonic Stem Cell Research Shift to Put Patients First*, NIH (Jan. 23, 2026) https://www.nih.gov/news-events/news-releases/nih-proposes-embryonic-stem-cell-research-shift-put-patients-first.
[3] *See, e.g.*, *A Woman's Concern, Inc. d/b/a Your Options Medical Centers v. Healey, et al.*, No. 1:24-cv-12131 (D. Mass. 2024) (currently on appeal to the First Circuit); *Pleasant Grove City v. Summum*, 555 U.S. 460 (2009);

The NIH is right to reconsider the use of human embryonic stem cells (hESC) for scientific research. This line of research should never have been pursued in the first place. The broad promises of the early promoters of hESCs have gone unrealized, while ethical alternatives have proven to be effective without destroying innocent human life. Ethical alternatives exist that do not sacrifice scientific effectiveness. We applaud even the temporary pause on review and approval of new hESC lines.[4] The intrinsic evil of ending innocent human life should no longer be endorsed or funded by the NIH. Instead, NIH should establish new scientific guidelines that are the "gold standard" in both ethics and medical research.

I. The Myth of Embryonic Stem Cell Research: Promises That Were Never Kept

While ethical methods of stem-cell research were available, they were unpursued. Now, advances in stem cell research have clearly established that hESCs are unnecessary for medical progress. Claims that fetal tissue and human embryos are still essential for stem cell research are simply false. Despite the intense media and scientific enthusiasm for hESC research in the late 20th and early 21st centuries, hESCs have failed to deliver the groundbreaking medical breakthroughs that were widely promised.

In the period preceding broad public support of and federal funding for hESCs, academics aggressively promoted it as a potential cure for many diseases. Lawrence Goldstein, professor of Pharmacology at UC San Diego, said in testimony before Congress:

> Already, in the short time since the generation of these cells was announced, we can conceive of many important applications in the treatment of heart disease, diabetes, Parkinson's disease, and Alzheimer's disease. . . . In fact, the list of possible therapeutic uses is almost endless. These broad applications are likely,

Livingwell Med. Clinic, Inc. v. Becerra, 138 S. Ct. 2701 (2018); *Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022); *June Medical Servs. v. Russo*, 140 S. Ct. 2103 (2020), *FDA v. All. for Hippocratic Med.*

[4] *NIH Proposes Embryonic Stem Cell Research Shift to Put Patients First*, *supra* note 2.

> because it may be possible to coax stem cells to become the many types of cells often lost to the ravages of disease.[5]

Other testimony assured Congress that "Virtually every realm of medicine and human health might benefit from this innovation. [Human Embryonic] Stem cell research could alleviate a great deal of human suffering."[6] HESCs were hailed as one of the gifts "that mankind occasionally is given . . . that can greatly advance the human condition."[7] Not only were hESCs an answer, they were the only answer, the American public was told: "for any of these diseases, Alzheimer's disease, Parkinson's disease, a variety of spinal cord injuries, certain types of diabetes, many others … The only hope on the horizon is through transplantation of these [embryonic] stem cells."[8] The promises of breakthrough have proven untrue. "[A] quarter-century after the human embryonic stem cells were first isolated, those predicted 'biological miracles' haven't happened."[9] Almost as soon as California had adopted funding for hESC research, the L.A. Times was reporting "no breakthroughs in sight."[10] "Gone are the allusions to healing such afflictions as spinal cord injuries and Parkinson's and Alzheimer's diseases that dominated the 2004 campaign for Proposition 71. In fact, scientists say, there is no guarantee of cures . . . ."[11] While hESCs have proven

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[5] Eugene C. Tarne, *Human Embryonic Stem Cell Research 25 Years On*, LOZIER INST. (Oct. 20, 2023), https://lozierinstitute.org/human-embryonic-stem-cell-research-25-years-on/#_ftn3, quoting STEM CELL RESEARCH: HEARINGS BEFORE A SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS UNITED STATES SENATE, 105TH CONGRESS, 95 (1999) (statement of Dr. Lawrence Goldstein, Professor of Pharmacology, Division of Cellular and Molecular Medicine, University of California at Sen Diego).

[6] *Id.*, quoting STEM CELL RESEARCH, PART 3: HEARINGS BEFORE A SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS UNITED STATES SENATE, 106TH CONGRESS 55 (2000) (joint statement of Dr. Gerald D. Fischbach, Director of the National Institute of Neurological Disorders and Stroke, and Dr. Allen M. Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases).

[7] *Id.*, QUOTING STEM CELLS, 2001: HEARINGS BEFORE A SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS UNITED STATES SENATE, 107TH CONGRESS 105 (2001) (statement of Dr. Michael D. West, President and CEO, Advanced Cell Technology).

[8] *Id.*, quoting STEM CELLS, 2001: HEARINGS BEFORE A SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS UNITED STATES SENATE, 107TH CONGRESS 136 (2001) (statement of Dr. Bert Vogelstein, Professor of Oncology and Pathology, John Hopkins Oncology Center; Chairman, National Research Council Institute of Medicine Committee on the Biological and Medical Applications of Stem Cell Research).

[9] *Id.*

[10] *Id.*, quoting Mary Engel, *Reality Check for Stem Cell Optimism*, L.A. TIMES (Dec. 3, 2006), https://www.latimes.com/archives/la-xpm-2006-dec-03-me-stemcell3-story.html.

[11] *Id.*

disappointing, significant progress continues through ethical adult stem-cell research, as discussed *infra* Part III.

From the beginning, many raised profound moral objections to hESC research, which necessarily requires the destructions of living human embryos.[12] Despite those objections, proponents aggressively promoted hESCs as the key to curing countless diseases, insisting that the promised breakthroughs were worth the cost of innocent human life. Yet, those promises remain unfulfilled. As a result, the moral cost – the destruction of innumerable human lives – has come into sharp focus. Even if every promised medical miracle had materialized, it would never have justified the deliberate destruction of countless innocent human lives.

II. The Destruction of Human Embryos for Stem Cells is Morally Reprehensible.

At the heart of hESC research is the "E": a living human embryo. This is a genetically unique human being, distinct from the mother and father, who, if allowed to develop naturally, would grow into a full person capable of laughter, relationships, memories, and love. Yet this tiny life is deliberately killed[13] at just a few days old, at the "blastocyst",[14] precisely when, in the natural course of things, it is about to implant in the mother's uterus[15] and continue its natural journey toward birth. What would have become a newborn baby is instead destroyed in a cold, calculated extraction to harvest its stem cells. And it is, in fact, killed. This is not abstract—it is

[12] *See, e.g.*, Anton-Lewis Usala, *The Case Against Funding Human Embryonic Stem Cell Research*, USCCB (2001), https://www.usccb.org/issues-and-action/human-life-and-dignity/stem-cell-research/the-case-against-funding-human-embryonic-stem-cell-research; Richard M. Doerflinger, Testimony before the Subcomm. on Lab., Health and Hum. Servs., and Educ. Sen. Appropriations Comm. (July 18, 2001), https://www.usccb.org/issues-and-action/human-life-and-dignity/stem-cell-research/human-embryo-research-is-illegal-immoral-and-unnecessary.

[13] *Embryonic Stem Cell Research: An Ethical Dillema*, EUROSTEMCELL, https://www.eurostemcell.org/embryonic-stem-cell-research-ethical-dilemma (last visited Mar. 24, 2026).

[14] *Embryonic Stem Cells: Where Do They Come From and What Can They Do?*, EUROSTEMCELL, https://www.eurostemcell.org/embryonic-stem-cells-where-do-they-come-and-what-can-they-do (last visited Apr 16, 2026).

[15] *Fetal Development: The First Trimester*, MAYO CLINIC (Mar. 18, 2025), https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-care/art-20045302.

the intentional ending of a distinct, innocent human life before it ever has the joy, sorrows, and fulfilments we all know. The physical horror of this act is undeniable, and beyond it lies a deeper spiritual dimension. "Even if the presence of a spiritual soul cannot be ascertained by empirical data, the results themselves of scientific research on the human embryo provide 'a valuable indication for discerning by the use of reason a personal presence at the moment of the first appearance of a human life: how could a human individual not be a human person?'"[16]

Many of these embryos originate from in vitro fertilization (IVF), a commercial process in which unique human lives are deliberately "manufactured" on demand, graded for quality, purchased by paying customers, and then either implanted or discarded as surplus inventory. Some are selected for implantation, while the rest are thrown away as medical waste or frozen indefinitely. Treating nascent human beings as consumer commodities – created bought, discarded at will, and killed and used for medical research – is profoundly immoral. These humas are denied the inherent right and dignity of being the fruit of a loving union between mother and father,[17] and are instead reduced to disposable products:

> At the moment of their conception by fertilization, new human beings (nascent human beings) are called zygotes, and they are alive. They take up chemical energy from their environment and turn it into the unique cell work of life, self-duplication, which only living cells can do. They have a full-complement human genome (DNA) activated by the unique cytoplasm of the egg for spontaneous and independent human development. In the instant of their conception, their full-complement of human DNA is sufficient to achieve the constituents, properties, and activities that define single-celled nascent living human beings.[18]

[16] Joseph Meaney, *Bioethics and the Human Embryo*, NAT'L CATH. BIOETHICS CTR. (Aug. 8, 2023), https://www.ncbcenter.org/messages-from-presidents/embryo (quoting St. John Paul II, *Evangelium Vitae*).
[17] *See id.*
[18] *Public Comment: Lozier Institute on CDC's Notice of Proposed Modifications to Assisted Reproductive Technology Program Reporting*, CHARLOTTE LOZIER INST. (Feb 21, 2024), https://lozierinstitute.org/public-comment-lozier-institute-on-cdcs-notice-of-proposed-modifications-to-assisted-reproductive-technology-program-reporting/.

These are fully human beings at an early stage of development. They are killed for their hESCs. The use of hESCs is a moral wrong, and the ACLJ stands strongly against it. "All research that creates, exploits, manipulates, and destroys human beings at any stage of development is controversial and unethical, because it involves the intentional harm and destruction of nascent human life."[19] We urge the NIH to not only stop the approval of new lines of hESCs, but to stop using existing lines in research altogether, including the funding of private research using hESCs, to respect the inherent worth and dignity of these innocent human lives.

III. The Government Should Fund Alternative Stem Cell Sources as they are Effective and Ethical

Because of the ready and effective alternatives to embryonic stem cells for medical research, the NIH should end the use of unethical hESCs and focus funding on proven and effective ethical adult stem cell options. Previously, researchers feared that adult stem cells could "not be able to be manipulated to produce all cell types," making embryonic stem cells appear necessary for comprehensive research.[20] However, adult stem cells have proven versatile and useful while hESCs have not. Despite more than two decades of research and persistent optimism, hESC research has produced no valid, successful patient treatments. Moreover, growing safety concerns remain because of the well-documented tendency of hESCs to form tumors, including teratomas.[21] Because hESCs are cells that build and grow a child from an embryo, they sometimes try to grow tissue when used in other treatments, with tumors that have hair, teeth, muscle, and bone.[22] The NIH itself admits that, unlike other forms of stem cells, "[embryonic stem] cells can potentially

[19] *Id.*
[20] *Stem Cells: What They Are and What They Do*, MAYO CLINIC (Jan. 21, 2026), https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117.
[21] *See* Paul S. Knoepfler, *Deconstructing Stem Cell Tumorigenicity: A Roadmap to Safe Regenerative Medicine*, 27 STEM CELLS 1050-56 (May 2009).
[22] *See* Chris Centeno, M.D., *Blog: Stem Cell Treatment Cancer Risk? There is No Cancer Risk with Adult Stem Cells*, REGENEXX (July 1, 2014), https://regenexx.com/blog/stem-cell-treatment-cancer-risk/.

transform into cancerous tissue."[23] A 2017 research survey warned that "cancer-associated mutations in [hESCs] may go unnoticed during most applications" and that scientists should carefully check for cancer genes before using in gene therapies.[24] Thankfully, there are safe, effective, and useful options for stem cell therapy and research that don't involve ending human life.

Adult stem cells have proven to be safe and effective as the "gold standard" in regenerative medicine.[25] By 2007, there were at least 73 conditions that were being treated by adult stem cell transplants and by December 2012, over 1 million patients worldwide had been treated with adult stem cells and experienced improved health.[26] Adult stem cell treatments have been used to successfully treat a wide range of diseases and conditions, such as: auto-immune diseases, liver disease, kidney disease, bladder disease, immunodeficiencies, cancers, cardiovascular issues, neurodegenerative diseases and injuries, anemias, and more.[27] And more treatments continue to be found, such as a recent development for Sickle Cell Disease, a disease that affects over 20 million people globally and has had few treatment options in the past.[28] Today there are more than 150 diseases and conditions to which adult stem cell treatments have been successfully applied.[29]

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[23] See A. Leventhal et al., *The Benefits and Risks of Stem Cell Technology*, 18 ORAL DISEASES 217, 218 (2012).
[24] Florian T. Merkle et al., *Human Pluripotent Stem Cells Recurrently Acquire and Expand Dominant Negative p53 Mutations*, 545 NATURE 229-33 (2017), https://doi.org/10.1038/nature22312.
[25] David A. Prentice, *Adult Stem Cells: Successful Standard for Regenerative Medicine*, 124 CIRCULATION RSCH. 837, (Mar. 15, 2019), https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.118.313664.
[26] *Fact Sheet: Adult Stem Cell Research and Transplants*, CHARLOTTE LOZIER INST. (Nov. 21, 2017), https://lozierinstitute.org/fact-sheet-adult-stem-cell-research-transplants/.
[27] *List of Diseases & Conditions Treated by Stem Cells*, STEM AID INST., https://stemaidinstitute.com/treatments/list-of-diseases-treated-by-stem-cells; *Diseases Treated with Stem Cell Transplants*, MEM. SLOAN KETTERING CANCER CTR., https://www.mskcc.org/cancer-care/diagnosis-treatment/cancer-treatments/blood-bone-marrow-stem-cell-transplants/transplantation-process/diseases-treated (last visited Apr. 16, 2026); *Treatments*, STEM CELL RSCH. FACTS, https://stemcellresearchfacts.org/answers/treatments/ (last visited Apr. 16, 2026).
[28] David Prentice, Ph.D., *Stopping the Pain and Saving Lives: Successful Treatments for Sickle Cell Disease*, CHARLOTTE LOZIER INST. (Feb. 5, 2024), https://lozierinstitute.org/stopping-the-pain-and-saving-lives-successful-treatments-for-sickle-cell-disease/.
[29] *Conditions Treated by Stem Cells*, REPAIR STEM CELLS INST., https://www.repairstemcells.com/Stem-Cell-Treatment/Conditions-Treated-By-Stem-Cells.aspx.html (last visited Apr. 16, 2026).

Adult stem cells aren't the only viable alternative. Induced pluripotent stem cells **(**iPSCs), created by reprogramming adult somatic cells (cells other than eggs, sperm, or embryos), offer another option for an ethical and safe source of stem cells.[30] These cells have "tremendous therapeutic potential."[31] These stem cells have been used in research on Parkinson's disease, Huntington's disease, and other blood and cardiac disorders.[32] They are "powerful tools for modeling disease processes."[33] The NIH should fund these ethical alternatives and end the funding and use of unethical and infective hESCs.

IV. Ending hESC Funding is Consistent with the Historical Legislative Posture Towards Human Embryos.

The Congressional intent regarding human embryos could hardly be clearer. Congress has shown a repeated intention to divert federal funding away from programs that result in the destruction of human embryos. The Hyde Amendment is one example that demonstrates this intent, as it prohibits tax dollars from being used to fund abortions.[34] Because this is part of an appropriations act, this language must be re-voted on regularly along with the rest of the appropriations text. Despite this law, though, taxpayer dollars still indirectly support abortions.

Abortion groups like Planned Parenthood claim that no federal funding it receives is used for abortion services.[35] However, when the Government Accountability Office (GAO) conducted a review of Planned Parenthood's utilization of federal funds, it was unable to determine what specific services federal funding was being directed towards.[36] This is not due to a lack of effort

[30] A. Leventhal et al., *supra* note 23.
[31] *Id.*
[32] *Id.*
[33] *Id.*
[34] Consolidated Appropriations Act, 2026, Pub. L. No. 119-75 § 506(a).
[35] FACTS ON PLANNED PARENTHOOD DEFUNDING, PLANNED PARENTHOOD (May 25, 2017), https://www.plannedparenthood.org/uploads/filer_public/7a/17/7a172da3-4d51-42cc-80c5-a5a20b834d7e/common_questions_about_pp_defunding.pdf.
[36] *See* HEALTH CARE FUNDING: PLANNED PARENTHOOD FEDERATION OF AMERICA AFFILIATES' EXPENDITURES

on the part of GAO. The simple reason is that money is fungible. One dollar cannot be meaningfully distinguished from another dollar, so once Planned Parenthood receives that money it is truly impossible to determine exactly what it does with it. This casts serious doubt on whether the reality on the ground reflects the legislative intent not to fund the destruction of human embryos. The evidence for this legislative intent is not limited to the Hyde Amendment, though.

The Dickey-Wicker Amendment, another appropriations amendment, prohibits federal funding for "research in which a human embryo or embryos are destroyed. . . ."[37] However, the legislative intent of this amendment has also been circumnavigated by a sly interpretive maneuver. This maneuver was first articulated in 1999 by Harriet Rabb. Rabb, an attorney for the HHS, issued a memo advising the then-NIH director that the Dickey-Wicker ban on federal funding for embryo-destructive research would not apply to embryotic stem cell lines "because such cells are not a human embryo within the statutory definition."[38] These stem cell lines are not themselves embryos, but are obtainable *only* after an embryo has been destroyed.[39] As a result, scientists have used "non-Federal funds to establish cell lines from embryos [destroying them in the process] before using their NIH funds to study these cells."[40] So technically federal funding is not being used to directly destroy embryos, but the indirect influence can hardly be denied. Because there is so much funding available for post-destruction research, it incentivizes scientists to use private resources to create more embryotic stem cell lines and thus destroy more embryos. Further, the legal

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OF FEDERAL FUNDS, 2016 THROUGH 2018, GOV. ACCOUNTABILITY OFF. (June 22, 2021), https://www.gao.gov/assets/gao-21-608r.pdf.

[37] Consolidated Appropriations Act, 2026, Pub. L. No. 119-75 §§ 508(a)(1).

[38] Letter from HHS General Counsel Harriet Rabb to Harold Varmus, Director, NIH (Jan. 15, 1999), available at https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101584926X407-doc.

[39] *Stem Cell Basics*, NIH, https://stemcells.nih.gov/info/basics/stc-basics (last visited Apr. 15, 2026).

[40] Nefi D. Acosta & Sidney H. Golub, *The New Federalism: State Policies Regarding Embryonic Stem Cell Research*, 44 J.L. Med. & Ethics 419-36, PDF p. 2 (2016), https://pmc.ncbi.nlm.nih.gov/articles/PMC5812675/pdf/nihms940529.pdf.

foundations on which this interpretation rests are shaky at best considering recent changes in the law.

The interpretation proposed by Rabb was adopted by the NIH as its official stance and was challenged in the D.C. Circuit case *Sherley v. Sebelius.*[41] One of the key questions in that case was whether the word "research" in the Dickey-Wicker amendment described a discrete project—meaning a single act like destroying embryos—or an extended process like the research that followed the embryotic destruction.[42] If the court had held that "research" only described a discrete project, then funding could still be distributed to hESC research as long as it wasn't used to obtain or destroy embryos.[43] If the court had held that "research" meant an extended process, then funding could not be distributed since the whole process was initiated by destroying embryos.[44] However the court did neither. Instead, it held that the meaning of the word "research" in the Dickey-Wicker amendment was "flexible enough to describe either a discrete project or an extended process."[45] In order to resolve the ambiguity, the court relied on *Chevron, U.S.A., Inc. v. NRDC, Inc*.[46]

Chevron established the principle that when legislative language was sufficiently ambiguous, courts were to defer to the interpretation of the agency tasked with administrating that legislation.[47] This became known as "*Chevron* deference," and was the approach applied by the court in *Sherley*, which resulted in favoring the administrative interpretation of "research" to mean a discrete project, therefore legitimizing embryotic stem cell research.[48] It is under this framework

[41] 644 F.3d 388 (D.C. Cir. 2011).
[42] *See generally id.*
[43] *See id.* at 390-96.
[44] *See id.*
[45] *Id.* at 394.
[46] 467 U.S. 837 (1984).
[47] *See id.* at 844, 65.
[48] *See generally Sherley*, 644 F.3d at 393-99.

that even the current funding of hESC finds any legal support, and that framework has significantly changed since the days of *Sherley*.

The recent Supreme Court decision in *Loper Bright Enterprises v. Raimondo* overruled *Chevron* and the deference it once required.[49] The Court held that "[c]ourts must exercise their independent judgment in deciding whether an agency has acted within its statutory authority, as the APA [Administrative Procedure Act] requires."[50] That means the entire justification for the *Sherley* court to allow even the current funding of hESC research is defunct. Were a similar challenge to be brought to the NIH guidelines, it is highly likely that the court would swing in a different direction in the absence of *Chevron* deference. Considering these developments, the moment could not be riper for the NIH to clarify its guidelines and bring them into line with the clear and consistent anti-embryotic destruction priority that Congress has maintained for decades.

CONCLUSION

The use of taxpayer dollars to fund research based on the ending of unique human life should stop here. Setting aside the millions of consciences violated by such spending, the alternative sources of stem cells for research are safe, effective, and ethical. The ACLJ urges the NIH to make the pause on funding permanent, and base our medical research on preserving and saving life, not on ending it.

Thank you for the opportunity to provide comment on this critical matter.

Sincerely,

[redacted]

OLIVIA F. SUMMERS
Senior Litigation Counsel

[49] 603 U.S. 369, 412 (2024).
[50] *Id.*