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,

Hideyuki Okano, MD, PhD
ISSCR President

Lorenz Studer, MD
ISSCR President-elect