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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,

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Chief Scientific Officer

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