American Society of Hematology
Helping hematologists conquer blood diseases worldwide

American Society of Hematology's Response to National Institutes of Health Request for Information on Reducing Reliance on Human Embryonic Stem Cells in NIH-Supported Research

Background

The National Institutes of Health (NIH) is seeking public input via a Request for Information (RFI) to assess the utility of human embryonic stem cells (hESCs) in biomedical research, specifically, areas of research that could not be pursued without hESCs, or areas in which newer, validated models could serve as a replacement of hESCs.

ASH Response

The following includes ASH's response to NIH's request, which was submitted electronically on April 22, 2026 through the NIH's submission platform.

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