Stem Cell Programs

Elias Zerhouni

The U.S. National Institutes of Health place a high priority on support for research using human embryonic stem cells, as well as other types of stem cells, that will also be useful for basic, translational, and clinical studies. Research using human embryonic stem cells offers the potential to inform us about the earliest molecular and cellular processes that regulate normal development and provides a tool to discover how a cell is able to be both pluripotent and indefinitely self-renewing. In addition, research using human embryonic stem cells will help the scientific community to understand the molecular signals that specify differentiation into specific cell types, some of which may ultimately be useful for cell-based treatment of disorders that involve loss of a specific cell type (such as type 1 diabetes or Parkinson's disease, to cite two of many examples).

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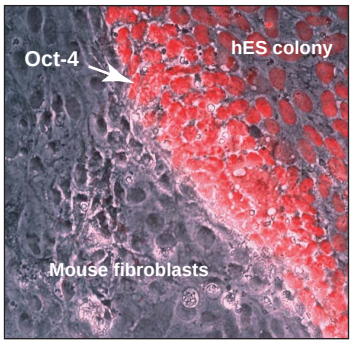
We are in the very early stages of understanding what can be accomplished with human embryonic stem cells. There are many basic research studies that need to be performed before we can begin clinical trials involving specialized cells differentiated from human embryonic stem cells. We need to understand how to drive differentiation along specific pathways, to establish techniques for isolating specific cell types, to control cell proliferation, and to control interactions between the host immune system and transplanted cells that might mediate graft rejection. The long-term stability of transplanted cells will need to be assessed.

Over the last 21 months, NIH has undertaken a number of new initiatives to encourage research scientists to seize this new opportunity, which is designed to address the rate-limiting steps to move the research agenda forward, including (i) training new investigators to culture and work with human embryonic stem cell lines, (ii) providing support to scale-up and characterize human embryonic stem cells eligible for federal funding and increasing accessibility to these lines, (iii) encouraging established investigators to initiate research projects involving human embryonic stem cells, and (iv) providing support for multidisciplinary teams of investigators to define the properties and potential of human embryonic stem cells.

By early winter of 2001, 71 independent human embryonic stem cell derivations were identified on the NIH Human Embryonic Stem Cell Registry (*1*) as eligible for research supported by federal funds. However, many of these derivations were in the early phases of development and had not been expanded or characterized to the point where they could be readily distributed to the research community. Expanding and characterizing cells derived from human embryos is a process that consumes both time and resources. To help make these cells available to the research community, NIH issued a program announcement, "Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards" (*2*) to provide support to allowable sources of human embryonic stem cells to scale-up and distribute cell lines. In April 2002, the first award was made. To date, eight such awards have been issued, with additional applications and awards anticipated in 2003. As a consequence of this support, the number of cell lines available for widespread distribution has grown from a single cell line in Spring of 2002 to 11 cell lines at present, with more anticipated in the near future.



Colonies of human embryonic stem cells (hES). hES growing with mouse embryonic fibroblasts express the transcription factor Oct-4. Oct-4 expression signifies undifferentiated and pluripotent cells.

The second way NIH is assisting the research community in accessing the human embryonic stem cell lines is in navigating the intellectual property rights and licensing agreements or material transfer agreements that needed to be obtained with the owners of the cell lines. As is true for some other valuable research resources, human embryonic stem cells available for federal funding are owned by private sources, not by the federal government. A United States patent exists for human embryonic stem cell lines and the techniques used to develop such lines. NIH negotiated a memorandum of understanding with the patent holder (WiCell Research Institute) in September 2001, as well as with several other sources, for the use of their cells (*3*). Although NIH can only develop such agreements for the NIH intramural research program, the terms of these agreements require the provider to offer the cells under no more stringent terms to other investigators using federal funds to conduct noncommercial research. NIH is continuing its efforts to work with the providers to facilitate access to human embryonic stem cell lines on equitable and reasonable terms and conditions. For example, recipients of infrastructure grants were required to submit an acceptable plan for distribution of cells that are grown and distributed with grant funding.

In addition to these access issues, the research community consistently requested that available cell lines be more fully characterized, to allow scientists to select which lines are most suitable for their intended experiments. To address this important need, the NIH intramural program is creating a Stem Cell Characterization Unit. The mission of this unit is to provide reliable and standardized data derived from assays performed on human embryonic stem cell lines available to be shipped to the research community. A steering committee will recommend assays for the characterization unit to perform on the cell lines.

Performing these assays in a single laboratory will allow a direct, side-by-side comparison to be made among the cell lines that are available for shipment and will facilitate comparison with adult stem cells. These data will give the scientific community information about the properties of available lines, so scientists can make an informed choice when ordering one or more of the available cell lines. Data will be regularly posted on the NIH stem cell Web site as soon as they have been validated. The assays performed by this unit will be overseen by a steering committee of leading stem cell biologists in both the extramural and NIH intramural research community. Ronald D. G. McKay will provide day-to-day direction for this unit.

In a complementary effort, the Mammalian Gene Collection at NIH is constructing cDNA libraries from several human embryonic stem cell lines and will perform expressed sequence tag (EST) sample sequencing from these libraries. This sequencing ef-

The author is at the National Institutes of Health, Bethesda, MD 20892, USA.

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fort will identify ESTs in the cell lines representing both known and unknown genes. All sequences will be deposited into readily accessible public databases, and the cDNA clones will be accessible through the IMAGE (Integrated Molecular Analysis of Genomes and their Expression) Consortium.

To help established investigators begin experiments with human embryonic stem cells, NIH announced the availability of administrative supplements to existing NIH grants. These supplements are supporting collections of preliminary data that will lead to investigator-initiated research grant applications whose major focus is research with human embryonic stem cells. To date, 44 supplements have been awarded, representing a total commitment of about $4,000,000. In addition, NIH is currently supporting 14 investigator-initiated grant awards, which represent a total commitment of $14,700,000, and many additional applications will be considered for funding in 2003. The NIH institutes issued nine solicitations for research grants involving stem cell research in 2002 (see table, right). In addition to extramural efforts, six NIH intramural laboratories are currently engaged in research using human embryonic stem cell lines. These NIH intramural laboratories are exploring a variety of basic research questions. Their work includes efforts to understand the molecular mechanisms that determine differentiation of human ES cells into specific cell fates, as well as development of protocols to perform directed differentiation.

FY2002 SOLICITATIONS FOR NIH RESEARCH GRANT APPLICATIONS INVOLVING STEM CELLS

Innovative Concepts and Approaches to Developing Functional Tissues and Organs for Heart, Vascular, Lung, and Blood Applications (R21) (NHLBI)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-HL-02-017.html]

Plasticity of Human Stem Cells in the Nervous System (R01) (NINDS, NIA, NIMH, NHLBI)
[http://grants2.nih.gov/grants/guide/pa-files/PA-02-025.html]

Basic and Applied Stem Cell Research for Arthritis and Musculoskeletal Diseases (R01) (NIAMS)
[http://grants2.nih.gov/grants/rfa-files/RFA-AR-02-003.html]

Stem Cells in Development/Repair of Orofacial Structures (NIDCR)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-02-006.html]

Basic Research on Mesenchymal Stem Cell Biology (NIA, NHLBI)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-HL-02-018.html]

Comprehensive Programs in Beta Cell Biology (NIDDK)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-DK-02-014.html]

Cellular Repair Studies of the Auditory and Vestibular System (NIDCD)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-DC-02-003.html

Research on Stem Cell Biology and Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders (NHLBI)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-HL-02-019.html]

Stem Cell Research for Alcohol-Related Disorders (NIAAA)
[http://grants2.nih.gov/grants/guide/rfa-files/RFA-AA-02-010.html]

At the present time, there is a limited pool of scientists with the hands-on experience needed to reliably perform experiments with approved human embryonic stem cells. Therefore, NIH issued a program announcement soliciting applications for short-term courses in human embryonic stem cell culture techniques (*4*). Five applications were received in October 2002, underwent peer review, and awards are currently pending. In addition, to assist midcareer investigators in their efforts to initiate research studies, NIH issued the program announcement "Career Enhancement Award for Stem Cell Research" (*5*). These grants will provide salary support, as well as some support for other research costs, to allow scientists to join an established research group working with approved human embryonic stem cells for 6 to 24 months.

The research community also articulated the need for recruitment of basic biologists with little or no prior human embryonic stem cell experience to join multidisciplinary, multi-investigator teams of researchers. They will explore the growth and maintenance, biochemical and molecular properties, and other unique properties of human embryonic stem cells and will support pilot projects that capitalize on human embryonic stem cells as a model system for understanding fundamental research problems. In response to a June 2002 workshop sponsored by the National Institute of General Medical Sciences (*6*), a request for applications to support exploratory center grants has been issued (*7*). These awards are intended to lead to research centers that will address this need, so clearly articulated by the research community.

In August 2002, the NIH Stem Cell Task Force (*8*) was established to oversee and coordinate the activities across the NIH institutes and centers that involve human embryonic stem cells, as well as all other types of stem cells. The task force will continue to monitor the state of this rapidly evolving science by identifying barriers to research progress and addressing the needs of the research community. This group of experienced NIH scientists will receive advice from the research community at a series of working groups designed to identify and address potential roadblocks to research progress. Two such working groups focusing on training and resource access have already met, and their recommendations are being implemented. The task force recognizes that adult and cord blood stem cells also have remarkable potential, and these sources will continue to be an important and expanding aspect of the NIH research portfolio, as they have in the past.

In our ongoing effort to keep the research community fully informed about NIH-sponsored activities, several Web sites have been established. The Human Embryonic Stem Cell Registry is a Web site that identifies cell lines ready for shipment (*1*). A listing of all derivations eligible for federal support can be found at the Web site for eligibility criteria (*9*). Activities of the NIH Stem Cell Task Force, as well as research opportunities offered by the NIH, are also cataloged on a Web site (*8*). Additional information about NIH stem cell–related activities is also listed on the NIH news Web site (*3*). The NIH plans to showcase its scientific progress in human embryonic stem cell research by sponsoring a scientific conference at NIH on 12 June 2003. Principal investigators with NIH-supported research programs have been invited to give plenary talks, to participate in discussions, and to present posters on their work. In addition, there will be afternoon workshops on stem cell research training, stem cell culturing techniques, federal policies, and intellectual property issues. Information on registration for the 12 June conference can be found on the stem cell task force Web site (*9*).

The research community is at the beginning of a very exciting new research opportunity made possible by the historic decision made by President Bush on 9 August 2001. NIH will continue its efforts to help the community capitalize on this opportunity, with the ultimate goal of developing a robust, rigorous portfolio of investigator-initiated research studies that will define and exploit the full potential of stem cells to improve the health of the nation and the world.

References and Notes

1. See http://escr.nih.gov
2. See http://grants2.nih.gov/grants/guide/pa-files/PAR-02-023.html
3. See www.nih.gov/news/stemcell/index.htm
4. See http://grants.nih.gov/grants/guide/pa-files/PA-02-054.html
5. See http://grants1.nih.gov/grants/guide/pa-files/PAR-02-069.html
6. See www.nigms.nih.gov/news/reports/stemcellworkshop.html
7. See http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-03-003.html
8. See http://stemcelltaskforce.nih.gov
9. See http://escr.nih.gov/eligibilitycriteria.html

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Elias Zerhouni (May 9, 2003)
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Editor's Summary

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