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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

Monday, November 30, 1998

URGENT

LEGISLATIVE REFERRAL MEMORANDUM

TO: Legislative Liaison Officer - See Distribution below

FROM: Janet R. Forsgren (for) Assistant Director for Legislative Reference

OMB CONTACT: Robert J. Pellicci
PHONE: (202)395-4871 FAX: (202)395-6148

SUBJECT: **HHS Oversight Testimony on the promise of stem cell research**

DEADLINE: **10:00 a.m. Tuesday, December 1, 1998**

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President. **Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.**

COMMENTS: Hearing is before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies on Wednesday, December 2nd at 9:30 a.m. NIH Director Varmus will be the Adsministration witness.

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LRM ID: RJP345 **SUBJECT:** HHS Oversight Testimony on the promise of stem cell research

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RESPONSE TO
LEGISLATIVE REFERRAL
MEMORANDUM

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet. If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.

You may also respond by:
(1) calling the analyst/attorney's direct line (you will be connected to voice mail if the analyst does not answer); or
(2) sending us a memo or letter
Please include the LRM number shown above, and the subject shown below.

TO: **Robert J. Pellicci Phone: 395-4871 Fax: 395-6148**
Office of Management and Budget
Branch-Wide Line (to reach legislative assistant): 395-7362

FROM: _____ **(Date)**

_____ **(Name)**

_____ **(Agency)**

_____ **(Telephone)**

The following is the response of our agency to your request for views on the above-captioned subject:

_____ **Concur**

_____ **No Objection**

_____ **No Comment**

_____ **See proposed edits on pages** _____

_____ **Other:** _____

_____ **FAX RETURN of** _____ **pages, attached to this response sheet**

DRAFT

Statement of

HAROLD VARMUS, M. D.

Director

National Institutes of Health

DECEMBER 2, 1998

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves extensive scrutiny by the scientific community, further evaluation of the promise of the research, and careful consideration of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human pluripotent stem cells - cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived pluripotent stem cells from embryos donated by couples undergoing infertility treatment. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types. The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the issues raised by this research, it is absolutely essential to clarify terms and definitions. To fully understand the significance of this work and its potential application to health and disease, it is important to understand the nature of a stem cell. Stem cells are the cells of an organism that can give rise to other types of cells. Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle

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cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a child.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development. The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. These cells do not have the potential to form a child, because they do not have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation nor can they support fetal development in the womb. This is an extremely important difference between totipotent and plenipotent cells.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only a few different kinds of cells. But they do have the potential to develop into a few different cell types. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor many stem cells responsible for the body's ability to repair itself. Stem cells that permit new skin growth and renewal of blood cells are two examples.

Potential Applications of Pluripotent Stem Cells

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, big news for science and for the future of public health. At the most fundamental level,

pluripotent stem cells could help us to understand the complex events that occur during human development. How would we accomplish this? A primary goal of this work would be the most basic kind of research – the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

- Transplant of healthy heart muscle cells could provide new hope for heart attack

victims. The hope is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

- In the many individuals who suffer from Type I diabetes, the production of insulin by the pancreas by specialized cells called islet cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on modifying human pluripotent stem cells to minimize tissue incompatibility. These challenges, though significant, are not insurmountable. Then, once the science is sufficiently clarified, technological challenges remain before these discoveries can be incorporated into clinical practice.

How Are Pluripotent Stem Cells Produced?

There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear

about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluipotent stem cells was described by Dr. Thomson and his coworkers. They first used these techniques to make stem cells from non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue. Dr. Gearhart and coworkers isolated primordial germ cells, the cells that will go on to become eggs and sperm, from 5-9 week old fetal tissue obtained after pregnancy termination. When grown in culture, these stem cells appear to be pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer -- the technology that received so much attention with the announcement of the cloning of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

The Role of the Federal Government

NOTE: A passage may be added here concerning federal funding of research utilizing subsequent generations of stem cells pending discussions with the Office of General Counsel.

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Summary

The development of cell lines that may produce almost every tissue of the body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life for our children and our children's children.

Mr. Chairman, I am grateful to you for providing a forum to present information about this promising arena of science and medicine. I would be pleased to answer any questions you might have.

Sec. — —

(a) None of the funds appropriated by this Act may be used to enter into or renew a contract which includes a provision providing prescription drug coverage, except where the contract also includes a provision for contraceptive coverage.

(b) Nothing in this section shall apply to a contract with:

(1) any of the following religious plans:

(a) SelectCare
(b) Personal CareHMO
(c) Care Choices
(d) OSF Health Plans, Inc.
(e) Yellowstone Community Health Plan

(2) any existing or future plan, if the plan objects to such coverage on the basis of religious beliefs.

(c) In implementing this section, any plan that enters into or renews a contract under this section may not subject any individual to discrimination on the basis that the individual refuses to prescribe contraceptives because such activities would be contrary to the individual's religious beliefs or moral convictions.

(d) Nothing in this section shall be construed to require coverage of abortion or abortion-related services.