

FACSIMILE

DATE: 11/30
TO: General
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Department of Health and Human Services

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COMMENTS:

Here's the draft of the testimony.
Per our conversation, you should be getting the
final from OMB @ noon.

____ Pages [including this cover]

DRAFT

STATEMENT OF

HAROLD VARMUS, M. D.

DIRECTOR

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 scientific accolades, evaluation of the promise of the research, and careful ethical and legal consideration. 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?

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 cells, skin cells, nerve cells, liver cells. 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. They 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.

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.

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 pluripotent 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 birth 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

Which, if any, of these methods of producing stem cells could be funded by NIH? What are the the statutory restrictions that govern the work to *develop* human pluripotent stem cell lines?

First, let me first address Dr. Thomson's work in which cells were derived from spare embryos. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's recent work developing this cell line.

The same restrictions do not apply to Dr. Gearhart's work, although it is governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The DHHS may conduct or support human fetal tissue research and research on the transplantation of human fetal tissue for therapeutic purposes,

but such tissue may be used in research only if a number of statutory requirements are met. Thus, as long as Dr. Gearhart followed these Federal statutes and regulations, NIH could support his recent work deriving pluripotent stem cells from fetal tissue. For the record, NIH did not, however, support any of this research.

Do these statutory and regulatory restrictions affect NIH's ability to support future research that *utilizes* the stem cell lines developed by these various methods?

After consultation with the HHS Office of General Counsel, we conclude that Federal funding of future research that *utilizes* the cells and cell lines that resulted from Dr. Thomson's and Dr. Gearhart's research is not prohibited. Let me expand on this answer. Human pluripotent stem cells are not embryos -- the cells necessary for implantation and embryo development have been lost in the derivation process. Introduction into the uterus of the cells described in the two reports would not lead to the development of a fetus and, thus, a whole human being. Because human pluripotent stem cells are not embryos, research on them is not research in which an embryo is created for research purposes, and it is not research in which embryos are harmed, destroyed, or discarded. This research would not violate the statutory prohibition.

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.

Questions and Answers

- **What are human embryonic stem cells and are they related to human embryo research?**

Because the term "embryonic stem cell" can be so easily confused with the embryo itself, it is preferable to refer to these cells as "pluripotent stem cells." The term "embryonic stem cell" was borrowed from mouse research, which derived stem cells from mouse embryos. Human pluripotent stem cells are cells of an organism which have an unlimited capacity to divide, and the ability to turn into most of the cells or tissues in the body. They are related to human embryo research in that one of the ways pluripotent stem cells can be derived is from the human embryo. These stem cells are not themselves embryos and would not develop into a fetus or result in a live birth if implanted into a woman's uterus. Embryonic stem cells can also be derived from human fetal tissue. It is believed that pluripotent stem cells can also be derived from cells created by somatic cell nuclear transfer.

- **What is human embryo research?**

Human embryo research involves studies of human fertilization (entry of sperm into a mature egg) and the subsequent several cell divisions that occur in a laboratory dish. This research is also called human in vitro fertilization research. The research is only conducted at these very early stages of development. At these stages, the embryo is also referred to as a preimplantation embryo because it is not yet to the point at which it would have finished implanting into the wall of the uterus. Human embryo research does not involve human embryos (or fetuses) developing in the uterus. It does not involve abortion or aborted human fetal tissue.

Unfortunately, the widely used term "embryo research" has caused a misperception about the nature of this work. In fact, the research is conducted with the one-cell product of fertilization and the subsequent few cell divisions that follow fertilization.

- **What are pluripotent stem cells?**

Pluripotent stem cells are cells from an organism that have an unlimited capacity to divide and the ability to turn into many different types of cells or tissues in the body. These stem cells are not themselves embryos and would not develop into a fetus or result in a live birth if implanted into a woman's uterus. They can be derived from embryos, from fetal tissue germ cell tissue, and by using somatic cell nuclear transfer technology.

- **Are pluripotent stem cells embryos? Do they have the potential to become embryos?**

Pluripotent stem cells are not embryos because they do not have the capacity to develop into a fetus if implanted into a woman's uterus. On their own, pluripotent stem cells do not have the potential to become embryos.

- **Do the regulations that govern human subjects research cover embryo research? Do they cover fetal tissue research? Would they cover embryonic stem cell research?**

Human embryo research is covered by DHHS regulations, 45 CFR 46 Subpart B entitled, "Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization." The regulations require that, before being initiated, research involving human in vitro fertilization must be reviewed and approved by an institutional review board. In addition, research involving human embryos or fetuses developing in the uterus is regulated by 45 CFR 46.201-46.211. Human embryos, however, are not considered human subjects under the HHS human subjects regulations. Although NIH is currently prohibited from supporting IVF and preimplantation embryo research due to a Presidential directive and Congressional ban, this research would be permitted under the human subject regulations. The 1994 Presidential directive prohibits the use of Federal resources to support the creation of human embryos for research purposes. In addition, in FY 1996 appropriations law (P.L. 104-99), DHHS was prohibited, for the first time, from conducting or supporting human embryo research. This annual prohibition in appropriations law has been repeated in every subsequent year since. The current appropriations law is P.L. 105-277. The language prohibits DHHS from supporting research in which a human embryo or embryos—organisms derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells—are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

These regulations would not cover research on the pluripotent stem cells derived from either embryos or fetal tissue, since the stem cells themselves are neither embryos.

Human fetal tissue research—the study of tissues and cells from *nonliving* fetuses—is also addressed in Subpart B of the HHS human subject regulations (45 CFR 46.210), requiring that such research be conducted only in accordance with any applicable State or local laws regarding such activities. Furthermore, the regulations require that individuals engaged in research involving fetuses, pregnant women, and human IVF will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy

(45 CFR 46.206(a)(3)(I)). Nonliving fetuses are not considered human subjects under the regulations. In addition to these regulations governing human fetal tissue research, section 498A of the Public Health Service Act (42 U.S.C. 289g-1) permits HHS to conduct or support research on the transplantation of human fetal tissue for therapeutic purposes, but such tissue may be used for research only if a number of statutory requirements are met.

Has NIH ever funded human embryo research? Has NIH ever considered funding human embryo research?

The NIH has never funded human embryo research. From 1980 to 1993, Federal funding of human embryo research was subject to a de facto administrative moratorium. In 1993, Congress passed legislation (P.L. 103-43) that effectively nullified this moratorium, making it possible for NIH to consider funding human embryo research. The NIH did not proceed, however, without first broadly considering the moral and ethical questions raised by such research and developing guidelines for its review and conduct.

During 1994, therefore, the NIH organized a multi-disciplinary panel of experts--composed of 19 people from outside government with diverse background in science, ethics, law, sociology, theology, public health, and public policy--to study the ethical, scientific, medical, and public policy implications of Federal funding of this research. The work of this panel was carried out in open forums, involved substantial public input, and led to the formulation of recommendations for stringent guidelines that would govern the review and conduct of any future research that might be considered for funding by the NIH. The panel also recommended areas of research that were acceptable for Federal funding, were not acceptable for Federal funding, and areas that required further consideration.

Has NIH ever funded research on human pluripotent stem cells?

The NIH has not funded research involving human pluripotent stem cells from either sources of these cells, human embryos or fetal tissue. However, NIH does fund research on human stem cells that are derived from sources such as adult blood cells. These stem cells can go on to differentiate into several different kinds of blood cells. Although they are also considered pluripotent, they have limited capacity to turn into other cells of the body.

- **If Federal funding of human embryo research were allowable, would NIH institute any limits to that funding and what standards would be applied to decide which research to fund?**

When this matter was initially under consideration in 1994, the NIH carefully considered the ethical, legal, scientific, and medical issues before moving forward and, with the help of a group of diverse outside experts, defined areas that should and should not be supported with Federal funding. The panel recommended that special guidelines be applied that would go beyond what is required of other areas of research and that an ad hoc review body be established at the Federal level to provide further oversight of the research. Had subsequent funding bans not been instituted, the NIH would likely have proceeded with the development of guidelines and the establishment of the review body.

- **If Federal funding of pluripotent stem cell research were allowed, would NIH institute any limits to that funding and what standards would be applied to decide which research to fund?**

Given the ethical and legal considerations as well as the need for clarification about Federal funding restrictions in closely related areas, the NIH would develop guidelines for the conduct of this research. As always, research proposals would be peer reviewed and funded on the basis of merit.

- **What are the arguments for the Federal investment in this research?**

Federal funding of this work would engage the attention of many more people and would bring more oversight to this area. For example, more investigators would likely enter the field and the pace of this critical work would be enhanced. In addition, Federal government involvement in this research area would also provide important scientific and ethical oversight. Federally supported research goes through rigorous ethical and scientific review, including detailed discussions at local institutional review boards (IRB) meetings, peer review groups and National Advisory Council meetings. This would encourage openness, ensure that researchers could use these important research tools, and assure public access to research information and to the practical medical benefits of this research. This would also increase the opportunities for collaboration in this research arena and sharing of data.

• **Is Federal funding of human fetal tissue research allowed?**

Federal funding of human fetal tissue research is allowed, and the NIH is funding studies that involve both basic and clinical investigations. Between 1988 and 1993, an administrative moratorium was in place that prohibited research involving clinical or therapeutic transplantation of human fetal tissue. Congress overturned the moratorium and added provisions to the Public Health Service Act that spelled out stringent rules that would have to be followed by Federally funded investigators. These rules include detailed informed consent procedures and a prohibition on commercialization of fetal tissue that would need to be followed if the research were to be Federally funded.

• **How does current law apply to research on the derivation of pluripotent stem cells?**

The stem cells isolated in Dr. Thomson's research were derived from spare embryos donated by couples who had undergone infertility treatment. Public Law 105-277 prohibits Federal funding of research involving spare embryos, therefore this work clearly falls within the Congressional ban on human embryo research.

Dr. Gearhart derived his pluripotent stem cells from fetal tissue. The Public Health Services Act includes a restriction on fetal tissue research. The Secretary, HHS, may conduct or support fetal tissue research and research on the transplantation of human fetal tissue for therapeutic purposes, but such tissue may be used in research only if a number of statutory requirements are met. Thus, as long as Dr. Gearhart followed these Federal statutes and regulations, NIH could support his recent work. This research was, however, supported from other non-Federal sources.

The work allegedly carried out by Dr. West's company involved fusion of a skin cell from an adult with an enucleated egg from a cow. It is not clear that the product of this fusion is an embryo, and if so, whether it is a human embryo. Therefore, how current law applies to this research is not clear.

• **Would current law prohibit NIH from funding research on pluripotent stem cells derived from human embryos or fetal tissue?**

The DHHS Office of General Counsel has advised that Federal funding of research that utilizes the cells and cell lines that resulted from Dr. Thomson's research is not prohibited. Pluripotent stem cells are not embryos since the cells that are necessary for implantation and embryo development have been lost in the derivation process. Because human pluripotent stem cells are not embryos, research on them is not research in which an embryo is created for research purposes, and it is not research in which embryos are harmed, destroyed or discarded. This research, thus, would not violate the statutory

prohibition. Using human fetal tissue, Dr. Gearhart derived human pluripotent stem cells that appear to be similar to Dr. Thomson's. The cell lines developed by Dr. Gearhart are from fetal tissue, not embryos. Further research on these cell lines would not violate the human embryo research ban for the same reasons stated above with regard to Dr. Thomson's cell line.

- **Were NIH funds used to support Dr. Thomson's research? Dr. Gearhart's? Dr. West's?**

NIH did not support the research of these investigators to derive pluripotent stem cells.

- **Has NIH ever supported the work of these investigators and, if so, what was the substance of that work?**

NIH supports the work of Dr. Gearhart on Down's syndrome using a mouse model and Dr. Thomson's work on non-human primate pluripotent stem cells.

- **Since Dr. Thomson's work is prohibited and Dr. Gearhart's is not, why not just encourage scientists to work with Dr. Gearhart's cell line?**

It is not known at this time whether or not the cells derived by these two investigators have identical capacities. Therefore, both lines of inquiry should be pursued.

- **Are there examples of research that have not been legally restricted but for which NIH has established special review and oversight procedures? How has NIH provided the oversight to ensure the research moves forward, while the ethical, legal, and social implications of the research are given full and public consideration?**

In the 1970s, when it first became possible to use molecular cloning in bacteria, there was a great deal of public apprehension about possible risks of the research. Fortunately, however, legislation was not enacted to ban the research. Instead, the scientific community established a voluntary moratorium until guidelines could be developed to govern the research. Guidelines were written by the NIH in a public process to provide oversight of the research. The Recombinant DNA Advisory Committee was also established to ensure public review of the research and ongoing policy development to keep pace with scientific progress. With the advent of human gene therapy, the NIH Guidelines were extended to address specific concerns associated with human trials. For example, the NIH Guidelines state that protocols involving germline gene therapy will not be considered.

Xenotransplantation—which involves the transfer of living animal cells, tissues, and whole organs into humans—is another example. Xenotransplantation holds the promise of providing a means to treat a wide range of disorders, including diabetes, Parkinson's disease, and end-stage renal failure. However, it also presents a number of public health and ethical challenges, including the potential risk of transmission of infectious agents from animal donors to patients, their close contacts, and the general public; informed consent at individual and community levels; animal welfare issues; and social equity in access to novel biotechnologies. To this end, DHHS has issued draft Guidelines for the conduct of this research and is planning to establish a Secretarial Advisory Committee on Xenotransplantation. The Secretary's Advisory Committee on Xenotransplantation will provide an ongoing group to consider the full range of complex scientific, social, and ethical issues and the public concerns raised by xenotransplantation, including ongoing and proposed protocols, and makes recommendations to the Secretary on policy and procedures.

• **Are there any restrictions on this research in the private sector?**

With the exception of prohibitions on the commercialization of human fetal tissue, we are aware of no other restrictions in Federal statute affecting the conduct of this kind of research in the private sector.

• **If the government supports research on these cell lines, wouldn't it create an incentive to create embryos for research purposes or encourage abortions?**

Couples undergo infertility treatment and in vitro fertilization procedures for personal reasons that have little if anything to do with a desire to advance research. Likewise, the decision to terminate a pregnancy is also made for personal reasons, and there is no evidence that fetal tissue research has encouraged abortions.

Furthermore, steps can be taken to ensure that Federally funded research does not inadvertently create such incentives. For example, in part to address concerns that human fetal tissue research could encourage abortion, Federal law and regulations require a separation between fetal tissue research and decision-making regarding the termination of a pregnancy. Federal law prohibits the commercialization of fetal tissue.

• **What aspects of pluripotent stem cell research are regulated by FDA? Do you know if FDA can regulate this research? Are they exploring such an option?**

Dr. Varmus may get asked this question. How would the Department suggest we answer it?



FACSIMILE

From the Immediate Office of the Secretary
Executive Secretariat

To:

CHRIS JENNINGS / DAN MENDELSON

Fax#:

456-5557

395-5631

Re:

Date:

8/12/99

Pages: including this cover sheet

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From the desk of:

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Comments:

PAWANA ROCK 690-7463

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

CLEARANCE FORM

CLOSE HOLD

8/19/99

SUBJECT: Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (August 1999).

LETTER/MEMO DATE: 8/10/99	DATE TO CLEARANCE: 8/10/99	CONTROL NO.: LF#300
ORIGINATOR: Lorraine Fishback	ADDRESSEE: IOS/Exec. Sec.	

REFERRED TO OFFICE OF:

	Immediate Office of the Secretary		Assistant Secretary, Health (ASH)
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A-COMMENT OR RECOMMENDATION	D-COORDINATE WITH ACTION ADDRESSEES AS NECESSARY
B-CLEARANCE (INITIAL) AND RETURN.	
C-INFORMATION	

REMARKS:

PLEASE TELEPHONE YOUR CONCURRENCE OR HAND DELIVER YOUR COMMENTS TO Lorraine Fishback

OR - Annie Lamb

690-7753

aren't we waiting
for release of NBAC
report before we
do the guidelines?

Lorraine Fishback
Executive Secretariat

Extension

Room



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

CLOSE HOLD

August 10, 1999

NOTE TO REVIEWERS:

Attached is a revised *Federal Register* notice requesting comment on NIH Guidelines for Stem Cell Research. We are asking for clearance/comments by August 19. Please send you comments to Annie Lamb.

Lorraine M. Fishback
Policy Coordinator, ES

CLOSE HOLD**(Billing Code 4140-01-P)****DEPARTMENT OF HEALTH AND HUMAN SERVICES****Public Health Service****National Institutes of Health****Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (August 1999)**

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on a document entitled "Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (August 1999)." The purpose of these draft guidelines is to recommend procedures to ensure that federally-funded research in this area is conducted in an ethical and legal manner. The NIH will not fund research using human pluripotent stem cells until final guidelines are published in the Federal Register and an oversight process is in place.

DATES: Written comments should be received by NIH on or before [insert date 60 days after date of publication in FR].

ADDRESSES: The NIH welcomes public comment on the Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (August 1999), set forth below.

Comments should be addressed to: Stem Cell Guidelines, NIH Office of Science Policy, 1 Center Drive, Building 1, Room 218, Bethesda, MD 20892. Comments may also be sent by facsimile transmission to Stem Cell Guidelines at (301) 402-0280, or by e-mail to:
stemcell@mail.nih.gov.

SUPPLEMENTARY INFORMATION: In November 1998, two different groups of scientists

reported the successful isolation and culturing of human pluripotent stem cells. These human pluripotent stem cells have the ability to develop into most of the specialized cells or tissues in the human body, and can divide for indefinite periods in culture. Because of the regenerative capacity of pluripotent stem cells, a single culture of human pluripotent stem cells could supply numerous researchers.

This accomplishment represents a major step forward in human biology and has generated much enthusiasm and interest among scientists and the public, particularly among patients and their advocates. Because these cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others, they are enormously important to science and hold great promise for advances in health care. For example, further research using human pluripotent stem cells may help scientists:

- Generate cells and tissue that could be used for transplantation. Human pluripotent stem cells may be stimulated to develop into many different specialized cells of the body, which may someday be used as replacement cells and tissue to treat many diseases and conditions including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis.
- Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause diseases and conditions such as birth defects and cancer.
- Change the way we develop drugs and test them for safety and potential efficacy. New

medications could be tested using human pluripotent stem cells, such as liver cells or skin cells; only the drugs that are both safe and appear to have a beneficial effect would graduate to human testing.

Human pluripotent stem cells have been isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage human embryos in excess of clinical need donated by people who were undergoing fertility treatment in an *in vitro* fertilization (IVF) clinic. Another group of scientists derived the pluripotent stem cells from human fetal tissue obtained from pregnancies that had been terminated. In both cases, the individuals gave informed consent for the embryos or fetal tissue to be used in research. Neither research project utilized Department of Health and Human Services (DHHS) funds, but rather was funded by private industry.

Federal law currently prohibits DHHS from funding research in which human embryos are created for research purposes or are destroyed, discarded or subjected to greater than minimal risk. In light of this legislative restriction, the Director of the National Institutes of Health (NIH) sought a legal opinion from the DHHS Office of the General Counsel on whether NIH funds may be used for research utilizing human pluripotent stem cells.

DHHS concluded that the Congressional prohibition does not prohibit the funding of research utilizing human pluripotent stem cells because such cells are not embryos. Thus, NIH funding for research using pluripotent stem cells derived from human embryos is not legislatively prohibited. The legal opinion also clarified that human pluripotent stem cells derived from fetal tissue would fall within the legal definition of human fetal tissue and are, therefore, subject to federal restrictions on

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the use of such tissue. NIH funding for research to derive or utilize human pluripotent stem cells from fetal tissue is permissible, subject to applicable law and regulation.

In view of the scientific and medical benefits that may result from research using human pluripotent stem cells, it is essential that the federal government play a role in funding and overseeing the conduct of this research. Federal funding will make it possible for all scientists-- both privately and federally funded-- to have the opportunity to pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of private industry, and will also help ensure that the results of research will be accessible to the public.

The NIH understands and respects the ethical, legal, and social issues relevant to human pluripotent stem cell research and is sensitive to the need for stringent oversight of this research that goes beyond the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way, prior to funding any research utilizing human pluripotent stem cells.

In an effort to ensure that any research utilizing human pluripotent stem cells is conducted appropriately and carefully, the NIH Director convened a Working Group of the Advisory Committee to the Director, NIH (ACD) to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells. Specifically, the NIH Director charged the Working Group with developing appropriate guidelines governing research involving the derivation and use of human pluripotent stem cells from fetal tissue and research involving the use of human pluripotent stem cells derived from early human embryos in excess of clinical

need. In an effort to ensure that a broad spectrum of viewpoints was considered, the working group was made up of individuals with varied expertise and experience, among them basic and clinical scientists, ethicists, lawyers, clinicians, as well as patients and patient advocates. On April 8, 1999, the working group held a public meeting to discuss draft guidelines. During the meeting, time was set aside for public comment; several groups came forward to speak, including the American Society of Cell Biology, the National Conference of Catholic Bishops; the Society for Developmental Biology, the Alliance for Aging Research, and the House Pro-Life Caucus. The Executive Director of the National Bioethics Advisory Commission (NBAC) also presented comments reflecting the status of the deliberations of the NBAC at that time.

The text of the draft guidelines follows.

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (August 1999).

I. Scope of Guidelines

These guidelines apply to research applications or proposals for National Institutes of Health (NIH) funding or support involving 1) utilization of human pluripotent stem cells¹ derived (without Department of Health and Human Services [DHHS] funding) from early human

¹For the purposes of this document, human pluripotent stem cells are human cells derived from early human embryos or fetal tissue that can divide for indefinite periods in culture without specializing and have the potential to develop into all of the three major tissue types.

embryos² and 2) the derivation or utilization of human pluripotent stem cells from fetal tissue.³

The DHHS is prohibited by appropriations law (P.L. 105-277, section 511,112 STAT. 2681-386) from using any appropriated funds "for the creation of a human embryo or human embryos for research purposes or research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death...." The NIH asked the General Counsel of DHHS to clarify whether research utilizing human pluripotent stem cells is permissible under existing laws governing human embryo and fetal tissue research. After careful consideration, the DHHS concluded that because these cells are not embryos, current law does not prohibit the use of NIH funds for research utilizing human pluripotent stem cells. In addition, it was determined that to the extent such cells are considered human fetal tissue, they are subject to the federal requirements for fetal tissue research.

These guidelines prescribe conditions that should be met before NIH funds are used to support research involving the utilization of human pluripotent stem cells derived from early human embryos or the derivation or utilization of human pluripotent stem cells from fetal tissue. DHHS funds may not be used for the derivation of human pluripotent stem cells from early human embryos. The guidelines also designate certain areas of human pluripotent stem cell research as

²For the purposes of this document, the early human embryo is the product of in vitro fertilization that is not implanted into a woman's uterus, and has not reached the stage when the first major tissue type is formed. This defines the stage from fertilization to approximately 14 days.

³ Human pluripotent stem cells derived from embryos are also known as human embryonic stem cells.

ineligible for NIH funding.

II. Guidelines for Research Involving Human Pluripotent Stem Cells that Is Eligible for NIH Funding

A. The Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

1. Considerations for the Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

Studies utilizing pluripotent stem cells derived from early human embryos may be conducted using NIH funds only if the cells were derived from early human embryos that were created for the purposes of infertility treatment, and were in excess of clinical need of the individuals seeking such treatment.

- a. It is essential that the donation of early human embryos in excess of clinical need is voluntary. No inducements, monetary or otherwise, should be offered for the donation of early human embryos for research purposes. Infertility clinics and/or their affiliated laboratories should implement specific written policies and practices to ensure that no such inducements are made available.

- b. There should be a clear separation between the decision to create embryos for infertility treatment and the decision to donate early human embryos for research purposes. Decisions related to the creation of embryos for infertility treatment should be made free from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To avoid possible conflicts of interest, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not be one and the same person.
- c. To ensure that early human embryos donated for research are in excess of clinical need of the individuals seeking infertility treatment, and to allow potential donors time between the creation of the embryos for infertility treatment and the decision to donate, only frozen early human embryos should be used to derive human pluripotent stem cells. In addition, individuals undergoing infertility treatment should be approached about donation only at the time of deciding the disposition of embryos in excess of clinical need.
- d. Prior to the derivation of human pluripotent stem cells for use in NIH-supported research, all identifiers associated with the early human embryos should be removed.
- e. Donation of early human embryos should be made without any restriction regarding the individual(s) who may be the recipients of transplantation of the

cells derived from the human pluripotent stem cells.

2. Informed Consent Requirements for the Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

Informed consent should be obtained from individuals who have sought infertility treatment who elect to donate early human embryos for research purposes. The informed consent process should disclose to potential donors the following information, pertinent to making the decision whether to donate their embryos for research purposes.

a. Informed consent should include:

- (i) A statement that the early human embryos will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for human transplantation research.
- (ii) A statement that all identifiers associated with the embryos will be removed prior to the derivation of human pluripotent stem cells.
- (iii) A statement that donors will not receive any information regarding subsequent testing on the embryo or the derived human pluripotent cells.

- (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.
- (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.
- (vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.
- (vii) A statement that early human embryos donated will not be transferred to a woman's uterus, will not survive the human pluripotent stem cell derivation process, and will be handled respectfully, as is appropriate for all human tissue used in research.

- b. To ensure respect for the individuals donating early human embryo(s), protocols should be approved by an Institutional Review Board (IRB) established in accord with 45 CFR §46.107 and §46.108 (also known as the Common Rule) or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to utilize human pluripotent stem cells derived from early human embryos should provide in their grant application to NIH:

- a. documentation that the embryos were created for the purpose of infertility treatment;
- b. documentation that the early human embryos were frozen and in excess of clinical need;
- c. the protocol for the derivation of human pluripotent stem cells from early human embryos; and
- d. documentation of IRB approval of the research protocol.

B. Derivation and Utilization of Human Pluripotent Stem Cells from Fetal Tissue

1. Considerations for the Derivation and Utilization of Human Pluripotent Stem Cells Derived from Fetal Tissue.

Unlike pluripotent stem cells derived from early human embryos, DHHS funds may be used to support research to *derive* pluripotent stem cells from fetal tissue, as well as for research *utilizing* such cells. Such research is governed by federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g-2(a) and the federal regulations at 45 CFR § 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may at a later date be utilized in human fetal tissue transplantation, it is the policy of NIH to require that all DHHS funded research involving the derivation or utilization of pluripotent stem cells from fetal tissue also comply with the fetal tissue transplantation laws at 42 U.S.C. 289g-1, 289g-2(b).

2. Informed Consent Requirements for the Derivation and Utilization of Human Pluripotent

Stem Cells From Fetal Tissue

As a policy matter, compliance with the informed consent law applicable to all fetal tissue transplantation research (42 U.S.C. 289g-1, 289g-2(b)), and the following conditions should be met for NIH funded research deriving or utilizing human pluripotent stem cells from fetal tissue.

a. Informed consent should include:

- (i) A statement that the fetal tissue will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for transplantation research.
- (ii) A statement that all identifiers associated with the fetal tissue will be removed prior to the derivation of human pluripotent stem cells.
- (iii) A statement that donors will not receive any information regarding subsequent testing on the fetal tissue or the derived human pluripotent cells.
- (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.

- (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.
- (vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.
- (vii) A statement that the fetal tissue and cells will be handled respectfully, as is appropriate for all human tissue used in research.

- b. To ensure respect for the individual donating tissue that results from the reproductive process, it is recommended that protocols be approved by an Institutional Review Board (IRB) established in accord with 45 CFR §46.107 and §46.108 (also known as the Common Rule) or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to derive or utilize human pluripotent stem cells from fetal tissue should provide in their grant application to NIH:

- a. the protocol, including the informed consent, for the derivation of human pluripotent stem cells from fetal tissue; and
- b. documentation of IRB approval, if any, of the research protocol.

III. Areas of Research Involving Human Pluripotent Stem Cells that are Ineligible for

NIH Funding

Areas of research ineligible for NIH funding include:

- A. The derivation of pluripotent stem cells from early human embryos;
- B. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;
- C. Research in which human pluripotent stem cells are combined with an animal embryo;
- D. Research in which human pluripotent stem cells are used for human reproductive cloning;
- E. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg;
- F. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg; and
- G. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

IV. Oversight

- A. Requests to the NIH for the funding of research involving human pluripotent stem cells should include documentation that the human pluripotent stem cells have been or will be derived in accordance with these Guidelines.
- B. NIH will consider requests for funding for research utilizing human pluripotent stem cells from: (1) awardees who want to use existing funds; (2) awardees requesting an administrative supplement; and 3) applicants submitting new applications or proposals.
- C. NIH will consider funding requests for the derivation of human pluripotent stem cells from fetal tissue.
- D. All applications shall be reviewed for scientific merit by: 1) an initial review group, in the case of new applications; or 2) by Institute or Center staff in the case of requests to use existing funds or applications for an administrative supplement.
- E. The NIH will establish a Human Pluripotent Stem Cell Review Group (HPSCRG). This group will review documentation of compliance with the NIH Guidelines for Research Involving Human Pluripotent Stem Cells, and may, when warranted, seek further information in support of an application. The group will hold public review meetings when a newly derived line of human pluripotent stem cells that has not been reviewed previously is proposed in a funding request, or when an investigator proposes a protocol for the derivation of a new human pluripotent stem cell line from fetal tissue.

- F. The HPSCRG will compile a yearly report which will include the number of applications reviewed, and the titles of those applications or supplements funded.
- G. The HPSCRG will also serve as a resource for recommending to the Director, NIH any revisions to the NIH HPSC Guidelines.

Dated:

Harold Varmus, M.D.

Director, NIH



DEPARTMENT OF HEALTH & HUMAN SERVICES

Melissa T. Skolfield

Assistant Secretary for Public Affairs

Phone: (202)690-7850

Fax: (202)690-5673

To: Chris Jennings

Fax: 456-5557 Phone: _____

Date: 7/13/99 Total number of pages sent: 4

Comments:

200 Independence Avenue, S.W., Bldg. HHH, Room 647-D, Washington, D.C. 20201

7/13

NOTE TO BRUCE REED AND CHRIS JENNINGS –

The National Bioethics Advisory Commission is meeting today in Cambridge, MA, and is expected for formally vote on its draft report. Attached are the existing Q and As, which we plan to stick to today if asked about their actions.

I have not sent these to OSTP – let me know if you'd like me too.

Melissa

For Internal Use Only Stem Cell Q&A's June 28, 1999

National Bioethics Advisory Commission and Stem Cells Questions and Answers

Q. Some research has shown that adult stem cells can produce many of the same cells and tissues of the body that could be developed using pluripotent stem cells derived from human embryos. Why wouldn't NIH just fund research using adult stem cells?

A. Recent research with a number of adult stem cells suggests that adult stem cells previously thought to be committed to the development of one line of specialized cells may have more flexibility than previously thought. These are preliminary results, but if this finding holds true for human adult stem cells, there is, indeed, enormous potential for using such adult stem cells as therapies for a number of diseases. These findings, although extremely important, do not, and should not exclude the pursuit of other avenues for developing important cell therapies, like exploring the potential of human pluripotent stem cells derived from embryos and fetuses, because they may have unique properties not present in other types of stem cells. It is also important to understand that human adult stem cells have only been isolated from a few types of tissue and, when they have been identified, they are often present in only minute quantities and are difficult to isolate and purify. In fact, in the report of using mouse nerve stem cells to make mouse blood cells, the mouse nerve stem cells were isolated directly from brain tissue that had to be removed from the mouse. The fact that brain tissue must be removed as the source of nerve stem cells, is likely to limit this line of experimentation in humans.

Q. Why not simply allow the private sector to pursue research on human pluripotent stem cells derived from embryos?

A. It is essential that the Federal Government play a role in funding and overseeing the conduct of this research so that all scientists-- both privately and federally funded--have the opportunity to pursue this important line of research. The NIH understands and respects the compelling ethical, legal, and social issues surrounding pluripotent stem cell research and is sensitive to the need for stringent oversight of this research that goes beyond the traditional rigorous NIH scientific peer review process. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of private industry and academe, by providing a set of guidelines for the conduct of this research, as well as a public oversight process to ensure investigators are adhering to the DHHS guidelines.

Q. Once several pluripotent stem cell lines have been established, why is it necessary to create more?

A. This is a very new area of research and there are a number of questions that remain unanswered. Initial investigations show that pluripotent stem cells replicate themselves for prolonged periods. But it is important to recognize that the immortality of these stem cell lines has not been proven. It remains to be seen if these cell lines lose any of their function and/or potential after years or even decades of culture. Hence, existing human pluripotent stem cell lines may require replenishing.

It will also be important to produce human pluripotent stem cell lines that have different genetic characteristics. For example, if such cells are developed for transplantation into humans, it will be important to reduce the chance of rejection. This may require the creation of new cell lines which more closely match the tissue type of the patient.

Q. What are the arguments for the Federal investment in this research?

A. Federal funding of this work would engage the attention of many more people and would bring more oversight to this area. For example, more investigators would likely enter the field and the pace of this critical work would be enhanced. In addition, Federal government involvement in this research area would also provide important scientific and ethical oversight. Research on human pluripotent stem cells would go through several levels of detailed discussions including NIH scientific peer review groups, and NIH National Advisory Council meetings. This would encourage openness, ensure that all researchers could use

these important research tools, and assure public access to the information and to the practical medical benefits of research using these stem cells. This would also increase the opportunities for collaboration in this research arena and sharing of data.

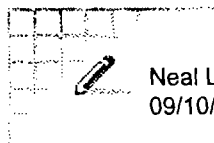
Q. Are there examples of research that have not been legally restricted but for which NIH has established special review and oversight procedures? How has NIH provided the oversight to ensure the research moves forward, while the ethical, legal, and social implications of the research are given full and public consideration?

A. In the 1970s, when it first became possible to use molecular cloning in bacteria, there was a great deal of public apprehension about possible risks of the research. Fortunately, however, legislation was not enacted to ban the research. Instead, the scientific community established a voluntary moratorium until guidelines could be developed to govern the research. Guidelines were written by the NIH in a public process to provide oversight of the research. The Recombinant DNA Advisory Committee was also established to ensure public review of the research and ongoing policy development to keep pace with scientific progress. With the advent of human gene therapy, the NIH Guidelines were extended to address specific concerns associated with human trials. For example, the NIH Guidelines state that protocols involving germline gene therapy will not be considered.

Q. NBAC has stated that it is not possible to ethically separate the derivation of human pluripotent stem cells from human embryos and the research done on these human pluripotent stem cells. How can DHHS find it acceptable to fund research using human pluripotent stem cells when it can not fund research on the embryos themselves?

A. Federal law currently prohibits DHHS from funding research in which human embryos are destroyed, discarded or subjected to greater than minimal risk. The DHHS Office of the General Counsel recently concluded that the Congressional prohibition does not prohibit the funding of research utilizing human pluripotent stem cells because such cells are not embryos. Thus, DHHS funding for research using pluripotent stem cells derived from human embryos is not prohibited. We recognize and appreciate the serious ethical and social considerations raised by this research, and maintain great respect for the full range of viewpoints surrounding these issues. Funding federal research on these stem cells is legally permissible, and such research holds great promise for treatments for Parkinson's disease, heart disease, diabetes, stroke, burns, arthritis, and other serious medical conditions. However, we intend to proceed with great care, setting up a special oversight committee, developing guidelines, and consulting with NBAC and other outside authorities as the process continues.

NPBA C
Rumt



Neal Lane
09/10/99 04:10:31 PM

Record Type: Record

To: Rachel E. Levinson/OSTP/EOP@EOP
cc: jeffrey m. smith/ostp/eop@eop, arthur bienenstock/ostp/eop@eop, clifford j. gabriel/ostp/eop@eop
bcc:
Subject: Re: Latest from DPC, reflecting Chris' talk with Harold Varmus

Thanks. Monday is fine with me and Shapiro. I have been in discussions about the statement. Neal
Rachel E. Levinson 09/10/99 02:51:37 PM



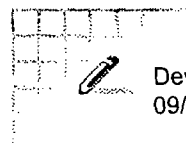
● Rachel E. Levinson 09/10/99 02:51:37 PM

Record Type: Record

To: Neal Lane/OSTP/EOP@EOP, Jeffrey M. Smith/OSTP/EOP@EOP, Arthur Bienenstock/OSTP/EOP@EOP, Clifford J. Gabriel/OSTP/EOP@EOP
cc:
Subject: Latest from DPC, reflecting Chris' talk with Harold Varmus

Is there any way we can get the grammar straightened out without having to go to third party arbitration?
At least for the statement?

----- Forwarded by Rachel E. Levinson/OSTP/EOP on 09/10/99 02:49 PM -----



Devorah R. Adler
09/10/99 02:45:51 PM

Record Type: Record

To: Rachel E. Levinson/OSTP/EOP@EOP
cc:
Subject: Re: ?



Here's the final q&a on stem cell -- Chris and Varmus talked and this is what they decided on. Also, Podesta has expressed an interest in waiting until Monday to put this out.

Devorah

QUESTIONS AND ANSWERS ON STEM CELL RESEARCH

Q: Does the Administration support the use of Federal funding to derive stem cells from human embryos, as NBAC recommends?

A: The potential medical benefits of using stem cells in research are compelling, holding great promise for treatments for Parkinson's disease, heart disease, diabetes, stroke, and arthritis, and the Administration believes that the research using these cells should go forward under strict ethical standards. Funding Federal research on these cells is legally permissible and within the confines of the ban.

However, because of the sensitive ethical issues and social considerations raised by the derivation of human stem cells, we are not now requesting a change in current law to permit Federal support for derivation of stem cells from human embryos. The President's 1994 ban will remain in effect.

Q: The Administration does believe that research on the stem cells themselves can be funded. Isn't that hypocritical – to fund research on the product of a destroyed embryo, as long as someone else actually destroys the embryo?

A: We maintain great respect for the full range of viewpoints surrounding these issues. ^{However,} ~~We believe that there is a fundamental difference between the derivation of a stem cell, which involves the destruction of an embryo, and the use of stem cells in research. Stem cells are not embryos and do not have the potential to form a child.~~

~~However,~~ because of the serious ethical and social considerations raised by this research, NIH research conducted on stem cells will proceed with great care. Currently, NIH is setting up a special oversight committee, developing guidelines, and consulting with outside authorities and experts as the process continues. We expect these guidelines to be released sometime this fall.

Q: Would you veto any legislation that would ban Federal funding for stem cell research?

A: Clearly, we would not support such legislation. ^{gandy bk of the enormous potential for health breakthroughs} ~~However, we do not answer hypothetical veto questions, particularly over legislation that is unlikely to pass the Congress. Because of the broad-based bipartisan support for current research activities (such as Senators Specter, Harkin, and Thurmond, as well as Representative Bilbray), we do not believe that Congress would pass such ill-advised legislation.~~

Porter and

from Jack Mumbas

DRAFT STATEMENT

Today, my National Bioethics Advisory Commission (NBAC) delivered its report on "The Ethical Use of Human Stem Cells in Research." Back in November, when I asked NBAC to look at the ethical and medical issues surrounding human stem cell research, I recognized the enormous medical potential of such research. The scientific results that have come out in just the past few months already strengthen my basis for hope that one day, stem cells will be used to replace cardiac muscle cells for people with heart disease, nerve cells for hundreds of thousands of Parkinson's patients, or insulin-producing cells for children who suffer from diabetes.

recommendations
The issues addressed by NBAC's ~~report~~ are complex and difficult, and the national dialogue addressed a range of opinions that must be respected. The Commissioners are to be commended for the thoroughness with which they engaged in this discussion, seeking the views and opinions of virtually every segment of our society, including scientists, patients, scholars from most of the major religions in the United States, lawyers, philosophers, ethicists and the public.

I want to thank Dr. Harold Shapiro, Chairman of the NBAC, and other Commissioners for a thoughtful report that will contribute significantly to the efforts of my Administration as we establish the highest ethical standards for the conduct of human stem cell research.

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release

July 14, 1999

STATEMENT BY THE PRESS SECRETARY

Last November, the President asked his National Bioethics Advisory Commission to undertake a thorough review of all of the ethical and medical considerations associated with human stem cell research. In the ensuing months, a national dialogue took place highlighting the potential applications of stem cells for treating people with diabetes, heart disease, Parkinson's disease, cancer, and spinal cord injury. Ethical issues were also central to this debate, including a wide range of religious and philosophical views that are a part of the fabric of our democratic culture. NBAC has completed its deliberations and appears ready to endorse the medical promise and ethical acceptability of certain types of human stem cell research.

The Clinton Administration recognizes that human stem cell technology's potential medical benefits are compelling and worthy of pursuit, so long as the research is conducted according to the highest ethical standards. NIH is putting in place guidelines and an oversight system that will ensure that the cells are obtained in an ethically sound manner. The President's 1994 ban on the use of Federal funds for the creation of human embryos for research purposes will remain in effect. No other legal actions are necessary at this time, because it appears that human embryonic stem cells will be available from the private sector. Publicly funded research using these cells is permissible under the current Congressional ban on human embryo research.

The President acknowledges the hard work of Chairman Dr. Harold Shapiro and other members of the National Bioethics Advisory Commission in their thoughtful consideration of a complex and sensitive matter.

###

Today, my National Bioethics Advisory Commission (NBAC) delivered its report on "The Ethical Use of Human Stem Cells in Research." Back in November, when I asked NBAC to look at the ethical and medical issues surrounding human stem cell research, I recognized the enormous medical potential of such research. The scientific results that have come out in just the past few months already strengthen my basis for hope that one day, stem cells will be used to replace cardiac muscle cells for people with heart disease, nerve cells for hundreds of thousands of Parkinson's patients, or insulin-producing cells for children who suffer from diabetes.

The issues addressed by NBAC's recommendations are complex and difficult

~~I also understand that human embryonic stem cell research raises ethical concerns that need to be addressed, and the national dialogue facilitated by NBAC addressed a range of opinions that must be respected. The NBAC Commissioners are to be commended for the thoroughness with which they engaged in this discussion, seeking the views and opinions of~~ virtually every segment of our society, including scientists, patients, scholars from most of the major religions in the United States, lawyers, philosophers, ethicists and the public.

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I want to thank Dr. Harold Shapiro, Chairman of the National Bioethics Advisory Commission, and other Commissioners for a thoughtful report that will significantly contribute to the efforts of my Administration as we establish the highest ethical standards for the conduct of human stem cell research.



FACSIMILE

From the Immediate Office of the Secretary Executive Secretariat

To: Chris Jennings 456-5557
 Fax#: Dan Henderson 395-5631 % Devora
 cc - Richard Turman 395-5648
 Re: _____

Date: 9/17/1999

Pages: including this cover sheet 17

From the desk of:

☒ LaVame Burton	___ Jackie White
___ Sandy Bart	___ John Gallivan
___ Kimberly Harold	___ Carlos McCormick
___ Christy Quigley	___ Martina Varnado
___ Mirtha Beadle	___ Ann White
___ Scott Boule	___ Melvin Whitfield
___ LaJuana Caldwell	___ Other _____
___ Carlos Cano	
___ Sean Donohue	
___ Neleen Eisenger	
___ Lorraine Fishback	
___ Johnathan Frieber	

Comments: See attached note

U.S. Department of Health and Human Services
 Immediate Office of the Secretary- Executive Secretariat

200 Independence Avenue SW
 Washington, DC 20201
 Fax: 205-8870 or 205-2135

September 16, 1999

NOTE TO CHRIS JENNINGS:
DAN MENDELSON:

Subject: NIH Guidelines for Research Involving Human Pluripotent Stem Cells

Attached are guidelines for funding research involving human pluripotent stem cells that NIH plans to publish in the Federal Register for comment. I have also sent them to Rachel Levinson in OSTP for her review. This draft has been cleared by HHS and we are recommending that it be sent to the Federal Register. Please call me at 690-5627 if you have questions.

A handwritten signature in black ink, appearing to read "LaVarne Burton". The signature is fluid and cursive, with the first name "LaVarne" and the last name "Burton" clearly distinguishable.

LaVarne Burton

9/13
(Billing Code 4140-01-P)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (September 1999)

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on a document entitled "Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (September 1999)." The purpose of these draft guidelines is to recommend procedures to ensure that federally-funded research in this area is conducted in an ethical and legal manner. The NIH will not fund research using human pluripotent stem cells until final guidelines are published in the Federal Register and an oversight process is in place.

DATES: Written comments should be received by NIH on or before [insert date 60 days after date of publication in FR].

ADDRESSES: The NIH welcomes public comment on the Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (September 1999), set forth below.

Comments should be addressed to: Stem Cell Guidelines, NIH Office of Science Policy, 1 Center Drive, Building 1, Room 218, Bethesda, MD 20892. Comments may also be sent by facsimile transmission to Stem Cell Guidelines at (301) 402-0280, or by e-mail to:

stemcell@mail.nih.gov.

SUPPLEMENTARY INFORMATION: In November 1998, two different groups of scientists reported the successful isolation and culturing of human pluripotent stem cells. Such cells have the ability to develop into most of the specialized cells or tissues in the human body and can divide for indefinite periods in culture. Because of the regenerative capacity of pluripotent stem cells, a single culture of human pluripotent stem cells could supply numerous researchers.

Establishment of human pluripotent stem cell lines represents a major step forward in human biology and has generated much interest among scientists and the public, particularly among patients and their advocates, especially with regard to the ethical issues related to this research.

Because these cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others, they are enormously important to science and hold great promise for advances in health care. For example, further research using human pluripotent stem cells may help scientists:

- Generate cells and tissue that could be used for transplantation. If human pluripotent stem cells can be stimulated to develop into many different specialized cells of the body, the resulting cells may someday be used as replacement cells and tissue to treat many diseases and conditions including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis.
- Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause diseases and conditions such as birth defects and cancer.

- Change the way we develop drugs and test them for safety and potential efficacy. New medications could initially be tested using human pluripotent stem cells, such as liver cells or skin cells; only the drugs that are both safe and appear to have a beneficial effect would graduate to further testing, using laboratory animals and human subjects.

Human pluripotent stem cells have been isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage human embryos in excess of clinical need and donated by people who were undergoing infertility treatment in an *in vitro* fertilization (IVF) clinic. Another group of scientists derived the pluripotent stem cells from human fetal tissue obtained from pregnancies that had been terminated. In both cases, the individuals gave informed consent for the embryos or fetal tissue to be used in research. Neither research project utilized Department of Health and Human Services (DHHS) funds but rather was funded by private sources.

Federal law currently prohibits DHHS from funding research in which human embryos are created for research purposes or are destroyed, discarded or subjected to greater than minimal risk. In light of this legislative restriction, the Director of the National Institutes of Health (NIH) sought a legal opinion from the DHHS Office of the General Counsel on whether NIH funds may be used for research utilizing human pluripotent stem cells.

DHHS concluded that the Congressional prohibition does not prohibit the funding of research utilizing human pluripotent stem cells because such cells are not embryos. Thus, NIH funding for research using pluripotent stem cells ~~derived from human embryos~~ is not legislatively prohibited. The legal opinion also clarified that ^{deriving} human pluripotent stem cells ~~derived~~ from fetal tissue would fall within the legal definition of ^{research on} human fetal tissue and are, therefore, subject to federal restrictions on the use of such tissue. NIH funding for research to derive or utilize human pluripotent stem cells

from fetal tissue is permissible, subject to applicable law and regulation.

In view of the scientific and medical benefits that may result from research using human pluripotent stem cells, it is essential that the federal government play a role in funding and overseeing the conduct of this research. Federal funding will make it possible for all scientists— both privately and federally funded-- to have the opportunity to pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of private sources of funding and will also help ensure that the results of research will be accessible to the public.

The NIH understands and respects the ethical, legal, and social issues relevant to human pluripotent stem cell research and is sensitive to the need to subject it to oversight more stringent than that associated with the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way, prior to funding any research utilizing human pluripotent stem cells.

In an effort to ensure that any research utilizing human pluripotent stem cells is conducted appropriately, the NIH Director convened a Working Group of the Advisory Committee to the Director, NIH (ACD) to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells. Specifically, the NIH Director charged the Working Group with developing appropriate guidelines governing research involving the derivation and use of human pluripotent stem cells from fetal tissue and research involving the use of human pluripotent stem cells derived from early human embryos in excess of clinical need. In an effort to ensure that a broad spectrum of viewpoints was considered, the working group was made up of individuals

with varied expertise and experience, among them basic and clinical scientists, ethicists, lawyers, clinicians, as well as patients and patient advocates. On April 8, 1999, the working group held a public meeting to discuss draft guidelines. During the meeting, time was set aside for public comment; several groups came forward to speak, including the American Society of Cell Biology, the National Conference of Catholic Bishops; the Society for Developmental Biology, the Alliance for Aging Research, and the House Pro-Life Caucus. The Executive Director of the National Bioethics Advisory Commission (NBAC) also presented comments reflecting the status of the deliberations of the NBAC at that time.

The text of the draft guidelines follows.

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (September 1999).

I. Scope of Guidelines

These guidelines apply to research applications or proposals for National Institutes of Health (NIH) funding or support involving 1) utilization of human pluripotent stem cells¹ derived (without Department of Health and Human Services [DHHS] funding) from early human embryos^{2,3} and 2) the derivation or utilization of human pluripotent stem cells from fetal tissue.

¹For the purposes of this document, human pluripotent stem cells are human cells derived from early human embryos or fetal tissue that can divide for indefinite periods in culture without specializing and have the potential to develop into all of the three major tissue types.

²For the purposes of this document, the early human embryo is the product of in vitro fertilization that is not implanted into a woman's uterus, and has not reached the stage when the

The DHHS is prohibited by appropriations law (P.L. 105-277, section 511,112 STAT. 2681-386) from using any appropriated funds "for the creation of a human embryo or human embryos for research purposes or research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death...." The ~~NIH~~^{stat} asked the General Counsel of DHHS ~~to clarify~~^{stat} whether research utilizing human pluripotent stem cells is permissible under existing laws governing human embryo and fetal tissue research. After careful consideration, the DHHS concluded that, because these cells are not embryos, current law does not prohibit the use of NIH funds for research utilizing human pluripotent stem cells. ~~In addition, it was determined that, to the extent such cells are considered human fetal tissue, they are subject to the federal~~^{stat} ~~requirements for fetal tissue research.~~

These guidelines prescribe conditions that should be met before NIH funds are used to support research involving the utilization of human pluripotent stem cells derived from early human embryos or the derivation or utilization of human pluripotent stem cells from fetal tissue. DHHS funds may not be used for the derivation of human pluripotent stem cells from early human embryos. The guidelines also designate certain areas of human pluripotent stem cell research as ineligible for NIH funding.

II. Guidelines for Research Involving Human Pluripotent Stem Cells that Is Eligible

first major tissue type is formed. This defines the stage from fertilization to approximately 14 days.

³Human pluripotent stem cells derived from embryos are also known as human embryonic stem cells.

for NIH Funding

A. The Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

1. Considerations for the Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

Studies utilizing pluripotent stem cells derived from early human embryos may be conducted using NIH funds only if the cells were derived from early human embryos that were created for the purposes of infertility treatment and were in excess of clinical need of the individuals seeking such treatment.

- a. It is essential that the donation of early human embryos in excess of clinical need is voluntary. No inducements, monetary or otherwise, should be offered for the donation of early human embryos for research purposes. Infertility clinics and/or their affiliated laboratories should implement specific written policies and practices to ensure that no such inducements are made available.
- b. There should be a clear separation between the decision to create embryos for infertility treatment and the decision to donate early human embryos in excess of clinical need for research purposes. Decisions related to the creation of embryos for infertility treatment should be made free from the influence of researchers or

investigators proposing to derive or utilize human pluripotent stem cells in research. To avoid possible conflicts of interest, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not be one and the same person.

- c. To ensure that early human embryos donated for research are in excess of clinical need of the individuals seeking infertility treatment and to allow potential donors time between the creation of the embryos for infertility treatment and the decision to donate for research purposes, only frozen early human embryos should be used to derive human pluripotent stem cells. In addition, individuals undergoing infertility treatment should be approached about donation only at the time of deciding the disposition of embryos in excess of clinical need.
- d. Prior to the derivation of human pluripotent stem cells for use in NIH-supported research, all identifiers associated with the early human embryos should be removed.
- e. Donation of early human embryos should be made without any restriction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

2. Informed Consent Requirements for the Utilization of Human Pluripotent Stem Cells Derived

from Early Human Embryos

Informed consent should be obtained from individuals who have sought infertility treatment who elect to donate early human embryos in excess of clinical need for research purposes. The informed consent process should disclose to potential donors the following information, pertinent to making the decision whether to donate their embryos for research purposes.

- a. Informed consent should include:
 - (i) A statement that the early human embryos will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for human transplantation research.
 - (ii) A statement that all identifiers associated with the embryos will be removed prior to the derivation of human pluripotent stem cells.
 - (iii) A statement that donors will not receive any information regarding subsequent testing on the embryo or the derived human pluripotent cells.
 - (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.

- (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.
- (vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.
- (vii) A statement that early human embryos donated will not be transferred to a woman's uterus, will not survive the human pluripotent stem cell derivation process, and will be handled respectfully, as is appropriate for all human tissue used in research.

- b. To ensure respect for the individuals donating early human embryo(s), protocols should be approved by an Institutional Review Board (IRB) established in accord with 45 CFR §46.107 and §46.108 or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to utilize human pluripotent stem cells derived from early human embryos should provide in their application or proposal to NIH:

- a. documentation that the embryos were created for the purpose of infertility treatment;

- b. documentation that the early human embryos were frozen and in excess of clinical need;
- c. the protocol, including the informed consent document, used for the derivation of human pluripotent stem cells from early human embryos; and
- d. documentation of IRB approval of the research protocol.

B. Derivation and Utilization of Human Pluripotent Stem Cells from Fetal Tissue

1. Considerations for the Derivation and Utilization of Human Pluripotent Stem Cells Derived from Fetal Tissue.

Unlike pluripotent stem cells derived from early human embryos, DHHS funds may be used to support research to *derive* pluripotent stem cells from fetal tissue, as well as for research *utilizing* such cells. Such research is governed by federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g-2(a) and the federal regulations at 45 CFR § 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may at a later date be utilized in human fetal tissue transplantation, it is the policy of NIH to require that all DHHS funded research involving the derivation or utilization of pluripotent stem cells from fetal tissue also comply with the fetal tissue transplantation laws at 42 U.S.C. 289g-1, 289g-2(b).

2. Informed Consent Requirements for the Derivation and Utilization of Human Pluripotent Stem Cells From Fetal Tissue

As a policy matter, NIH funded research deriving or utilizing human pluripotent stem cells from fetal tissue should comply with the informed consent law applicable to all fetal tissue transplantation research (42 U.S.C. 289g-1, 289g-2(b)) and the following conditions.

a. Informed consent should include:

- (i) A statement that the fetal tissue will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for transplantation research.
- (ii) A statement that all identifiers associated with the fetal tissue will be removed prior to the derivation of human pluripotent stem cells.
- (iii) A statement that donors will not receive any information regarding subsequent testing on the fetal tissue or the derived human pluripotent cells.
- (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.
- (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial

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development.

(vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.

(vii) A statement that the fetal tissue and cells will be handled respectfully, as is appropriate for all human tissue used in research.

- b. To ensure respect for the individual donating tissue that results from the reproductive process, it is recommended that protocols be approved by an Institutional Review Board (IRB) established in accord with 45 CFR §46.107 and §46.108 or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to derive or utilize human pluripotent stem cells from fetal tissue should provide in their application or proposal to NIH:

- a. the protocol, including the informed consent document, for the derivation of human pluripotent stem cells from fetal tissue; and
- b. documentation of IRB approval, if any, of the research protocol.

III. Areas of Research Involving Human Pluripotent Stem Cells that are Ineligible for NIH Funding

Areas of research ineligible for NIH funding include:

- A. The derivation of pluripotent stem cells from early human embryos;

- B. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;
- C. Research in which human pluripotent stem cells are combined with an animal embryo;
- D. Research in which human pluripotent stem cells are used for reproductive cloning of a human;
- E. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg;
- F. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg; and
- G. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

IV. Oversight

- A. Requests to the NIH for the funding of research involving human pluripotent stem cells should include documentation that the human pluripotent stem cells have been or will be

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- F. The HPSCRG will compile a yearly report that will include the number of applications reviewed and the titles of all awarded applications, supplements or administrative approvals for the use of existing funds.
- G. The HPSCRG will also serve as a resource for recommending to the Director, NIH any revisions to the NIH Guidelines for Research Involving Human Pluripotent Stem Cells.

Dated:

Harold Varmus, M.D.

Director, NIH

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derived in accordance with these Guidelines.

- B. NIH will consider requests for funding for research utilizing human pluripotent stem cells from: (1) awardees who want to use existing funds; (2) awardees requesting an administrative supplement; and 3) applicants or intramural researchers submitting applications or proposals.
- C. NIH will consider funding requests for the derivation of human pluripotent stem cells from fetal tissue.
- D. All applications shall be reviewed for scientific merit by: 1) an initial review group, in the case of new or competing continuation (renewal) applications; or 2) by Institute or Center staff in the case of requests to use existing funds or applications for an administrative supplement prior to submission to the HPSCRG.
- E. The NIH will establish a Human Pluripotent Stem Cell Review Group (HPSCRG). This group will review documentation of compliance with the NIH Guidelines for Research Involving Human Pluripotent Stem Cells, and may, when warranted, seek further information in support of an application. The group will hold public review meetings when a funding request proposes the use of a newly derived line of human pluripotent stem cells that has not been reviewed previously by the HPSCRG in a public process or when an investigator proposes a protocol for the derivation of a new human pluripotent stem cell line from fetal tissue.



F A C S I M I L E

DATE: 11/30

TO: Rachel Weisner / Deborah Adler

FAX#: 456-6027 / 456-5557

FROM: Elizabeth Summy
Deputy Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

Stem cell guidelines; fact sheet; press release

 Pages [including this cover]

FOR IMMEDIATE RELEASE
December 1, 1999

Contact: NIH Press Office
(301) 496-5787

NIH PUBLISHES DRAFT GUIDELINES FOR STEM CELL RESEARCH

The National Institutes of Health (NIH) published its draft guidelines for research involving human pluripotent stem cells in the Federal Register today. The draft guidelines recommend procedures to help ensure that NIH-funded human pluripotent stem cell research is conducted in an ethical and legal manner.

Such research promises new treatments and possible cures for many debilitating diseases and injuries, including Parkinson's, diabetes, heart disease, multiple sclerosis, burns and spinal cord injuries. While the potential medical benefits of human stem cell technology are compelling and worthy of pursuit, all research should be supported in accordance with strict ethical standards. And, as the draft guidelines note, "NIH understands and respects the ethical, legal and social issues relevant to human pluripotent stem cell research and is sensitive to the need to subject it to oversight more stringent than that associated with the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way prior to funding any research using stem cells."

Human pluripotent stem cells hold great promise for advances in health care because they can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others. Further research using human pluripotent stem cells may help scientists generate cells and tissue that could be used for transplantation to treat many diseases; improve understanding of the complex events that occur during normal human development

and of what goes wrong to cause diseases and conditions such as birth defects and cancer; and change the way drugs are developed and tested for safety and potential efficacy.

The draft guidelines describe conditions that should be met before NIH funds are used to support human pluripotent stem cell research. The guidelines propose specific criteria for informed consent for the utilization of human pluripotent stems cells and the establishment of a Human Pluripotent Stem Cell Review Group to review documentation of compliance with the NIH guidelines and, when warranted, seek further information in support of a research application. In addition, the draft guidelines delineate areas of research involving human pluripotent stem cells that are ineligible for NIH funding including studies in which stem cells are used to create or contribute to a human embryo; are combined with an animal embryo; are used for reproductive cloning of a human; are derived using somatic cell nuclear transfer into a human or animal egg; or are derived from human embryos created for research purposes.

In an effort to ensure that any research utilizing human pluripotent stem cells is conducted appropriately, the NIH Director convened a Working Group of the Advisory Committee to the Director to help develop the draft guidelines. The working group included a broad spectrum of individuals with varied expertise and experience, including basic and clinical scientists, patients and patient advocates, ethicists, lawyers, and clinicians and met in a public session on April 8 to discuss the issues that should be addressed in the guidelines. The Working Group also considered comments from the President's National Bioethics Advisory Commission (NBAC), Congress and the general public.

The draft guidelines will be open for public comment for 60 days. The NIH will not fund research using human pluripotent stems cells until final guidelines are published in the Federal Register and an oversight process is in place.

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FACT SHEET ON HUMAN PLURIPOTENT STEM CELL RESEARCH GUIDELINES

Dec 99

- The NIH is seeking public input on draft Guidelines for NIH-supported research involving human pluripotent stem cells. These draft Guidelines recommend procedures to help ensure that NIH funded research in this area is conducted in an ethical and legal manner.

The Promise of Stem Cell Research

- Human pluripotent stem cells are a unique scientific and medical resource in that they can divide for indefinite periods in culture, and can develop into most of the specialized cells and tissues of the body, such as muscle cells, nerve cells, heart cells, blood cells.
- These human pluripotent stem cells were isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage embryos in excess of clinical need donated by people who were undergoing fertility treatment in an *in vitro* fertilization (IVF) clinic. Another group of scientists isolated the pluripotent stem cells from non-living fetuses obtained from pregnancies that had been terminated.

Legal

- Federal law currently restricts the use of DHHS funds for human embryo research. DHHS has determined, however, that the Congressional restriction does not prohibit funding for research utilizing human pluripotent stem cells because such cells are not embryos. DHHS funds cannot be used for the derivation of stem cells from human embryos.

Development of Stem Cell Guidelines

- In an effort to help ensure that any research utilizing human pluripotent stem cells is appropriately and carefully conducted, the NIH convened a Working Group of the Advisory Committee to the Director (ACD), NIH to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells. The working group was composed of scientists, patients and patient advocates, ethicists, clinicians and lawyers.
- In developing the draft guidelines, NIH considered advice from the National Bioethics Advisory Commission (NBAC), the public, and the Congress.
- Draft guidelines for this research were published for public comment in the Federal Register December 2, 1999. After reviewing and considering all comments received, the NIH will make revisions to the guidelines, as appropriate, and publish the final guidelines in the Federal Register.
- Until the final guidelines and the oversight process are in place, the DHHS will not fund research using human pluripotent stem cells derived from either human embryos or fetal tissue.

Draft NIH Guidelines

- The guidelines apply to research applications or proposals for NIH funding or support that involve the utilization of human pluripotent stem cells derived (without NIH funding) from early human embryos and the derivation or utilization of human pluripotent stem cells derived from human fetal tissue.
- HHS will fund research using human pluripotent stem cells derived from early human embryos only if investigators use cells derived from frozen embryos that were created for the purposes of infertility treatment and were in excess of clinical need. In addition, the investigator can offer no inducements, monetary or otherwise for the donation of the embryo and there must be a clear separation between the infertility treatment and the decision to donate embryos.
- With regard to deriving or using cells from fetal tissue, investigators will be expected to follow the NIH Human Pluripotent Stem Cell Guidelines and all laws and regulations governing human fetal tissue research. Because cells derived from fetal tissue may later be utilized in human fetal tissue transplantation research, NIH will fund this research only if investigators comply with the fetal tissue transplantation research statute.
- The Guidelines specify what should be contained in the informed consent document for the donation of human embryos or human fetal tissue.
- In submitting an application or proposal for funding, investigators will be required to provide documentation showing compliance with the Guidelines. This documentation will be submitted to a newly established Human Pluripotent Stem Cell Review Group (HPSCRG). The review group will hold public meetings when a funding request proposes the use of a newly derived line of human pluripotent stem cells. The HPSCRG will also compile a yearly report which will include the number of applications reviewed, and the titles of all awarded applications.
- The Guidelines state that no NIH funds may be used to derive pluripotent stem cells from human embryos.
- The Guidelines also address the other areas of research that are ineligible for funding, including studies in which human pluripotent stem cells are: utilized to create or contribute to a human embryo; combined with an animal embryo; used for reproductive cloning of a human; derived using somatic cell nuclear transfer into a human or animal egg; derived using somatic cell nuclear transfer into a human or animal egg; derived from human embryos created for research purposes.

(Billing Code 4140-01-P)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999)

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on a document entitled "Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999)." The purpose of these draft guidelines is to recommend procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH will not fund research using human pluripotent stem cells until final guidelines are published in the Federal Register and an oversight process is in place.

DATES: Written comments should be received by NIH on or before [insert date 60 days after date of publication in FR].

ADDRESSES: The NIH welcomes public comment on the Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999), set forth below.

Comments should be addressed to: Stem Cell Guidelines, NIH Office of Science Policy, 1 Center Drive, Building 1, Room 218, Bethesda, MD 20892. Comments may also be sent by facsimile transmission to Stem Cell Guidelines at (301) 402-0280, or by e-mail to: stemcell@mail.nih.gov

conditions such as birth defects and cancer.

- Change the way we develop drugs and test them for safety and potential efficacy. New medications could initially be tested using human pluripotent stem cells, such as liver cells or skin cells; only the drugs that are both safe and appear to have a beneficial effect would graduate to further testing, using laboratory animals and human subjects.

Human pluripotent stem cells have been isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage human embryos in excess of clinical need and donated by people who were undergoing infertility treatment in an *in vitro* fertilization (IVF) clinic. Another group of scientists derived the pluripotent stem cells from human fetal tissue obtained from pregnancies that had been terminated. In both cases, the individuals gave informed consent for the embryos or fetal tissue to be used in research. Neither research project utilized Department of Health and Human Services (DHHS) funds but rather was funded by private sources.

Federal law currently prohibits DHHS from funding research in which human embryos are created for research purposes or are destroyed, discarded or subjected to greater than minimal risk. In light of this legislative restriction, the Director of the National Institutes of Health (NIH) sought a legal opinion from the DHHS Office of the General Counsel on whether NIH funds may be used for research utilizing human pluripotent stem cells.

DHHS concluded that the Congressional prohibition does not prohibit the funding of research

utilizing human pluripotent stem cells because such cells are not embryos. Thus, NIH funding for research using pluripotent stem cells derived from human embryos is not legislatively prohibited. The legal opinion also clarified that human pluripotent stem cells derived from fetal tissue would fall within the legal definition of human fetal tissue and are, therefore, subject to federal restrictions on the use of such tissue. NIH funding for research to derive or utilize human pluripotent stem cells from fetal tissue is permissible, subject to applicable law and regulation.

In view of the scientific and medical benefits that may result from research using human pluripotent stem cells, it is essential that the federal government play a role in funding and overseeing the conduct of this research. Federal funding will make it possible for scientists-- both privately and federally funded-- to have the opportunity to pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of private sources of funding and will also help ensure that the results of research will be accessible to the public.

The NIH understands and respects the ethical, legal, and social issues relevant to human pluripotent stem cell research and is sensitive to the need to subject it to oversight more stringent than that associated with the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way, prior to funding any research utilizing human pluripotent stem cells.

In an effort to ensure that any research utilizing human pluripotent stem cells is conducted appropriately, the NIH Director convened a Working Group of the Advisory Committee to the

Director, NIH (ACD) to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells. Specifically, the NIH Director charged the Working Group with developing appropriate guidelines governing research involving the derivation and use of human pluripotent stem cells from fetal tissue and research involving the use of human pluripotent stem cells derived from early human embryos in excess of clinical need. In an effort to ensure that a broad spectrum of viewpoints was considered, the working group was made up of individuals with varied expertise and experience, among them basic and clinical scientists, ethicists, lawyers, clinicians, as well as patients and patient advocates. On April 8, 1999, the working group held a public meeting to discuss draft guidelines. During the meeting, time was set aside for public comment; several groups came forward to speak, including the American Society of Cell Biology, the National Conference of Catholic Bishops; the Society for Developmental Biology, the Alliance for Aging Research, and the House Pro-Life Caucus. The Executive Director of the National Bioethics Advisory Commission (NBAC) also presented comments reflecting the status of the deliberations of the NBAC at that time.

The text of the draft guidelines follows.

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999).

I. Scope of Guidelines

These guidelines apply to research applications or proposals for National Institutes of Health

(NIH) funding or support involving (1) utilization of human pluripotent stem cells (also known as human embryonic stem cells) derived (without Department of Health and Human Services [DHHS] funding) from early human embryos and (2) the derivation or utilization of human pluripotent stem cells from fetal tissue. For purposes of these guidelines, human pluripotent stem cells are cells derived from early human embryos or fetal tissue that can divide for indefinite periods in culture without specializing and have the potential to develop into all of the three major tissue types. NIH research funded under these guidelines will involve only human pluripotent stem cells derived either from fetal tissue or from early human embryos that are the products of in vitro fertilization in excess of clinical need, that are not implanted in a woman's uterus and that have not reached the stage when the first major tissue type is formed.

The DHHS is prohibited by appropriations law (P.L. 105-277, section 511,112 STAT. 2681-386) from using any appropriated funds "for the creation of a human embryo or embryos for research purposes; or research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death...." The NIH asked the General Counsel of DHHS to clarify whether research utilizing human pluripotent stem cells is permissible under existing laws governing human embryo and fetal tissue research. After careful consideration, the DHHS concluded that, because these cells are not embryos, current law does not prohibit the use of NIH funds for research utilizing human pluripotent stem cells. In addition, it was determined that, to the extent such cells are considered human fetal tissue, they are subject to the federal requirements for fetal tissue research.

These guidelines prescribe conditions that should be met before NIH funds are used to support

research involving the utilization of human pluripotent stem cells derived from early human embryos or the derivation or utilization of human pluripotent stem cells from fetal tissue. DHHS funds may not be used for the derivation of human pluripotent stem cells from early human embryos. The guidelines also designate certain areas of human pluripotent stem cell research as ineligible for NIH funding.

II. Guidelines for Research Involving Human Pluripotent Stem Cells that Is Eligible for NIH Funding

A. The Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

1. Considerations for the Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

Studies utilizing pluripotent stem cells derived from early human embryos may be conducted using NIH funds only if the cells were derived from early human embryos that were created for the purposes of infertility treatment and were in excess of clinical need of the individuals seeking such treatment.

1. It is essential that the donation of early human embryos in excess of clinical need is voluntary. No inducements, monetary or otherwise, should have been offered for the donation of early human embryos for research purposes. Infertility clinics

and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available.

- b. There should have been a clear separation between the decision to create embryos for infertility treatment and the decision to donate early human embryos in excess of clinical need for research purposes. Decisions related to the creation of embryos for infertility treatment should have been made free from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To avoid possible conflicts of interest, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person.
3. To ensure that early human embryos donated for research are in excess of clinical need of the individuals seeking infertility treatment and to allow potential donors time between the creation of the embryos for infertility treatment and the decision to donate for research purposes, only frozen early human embryos should have been used to derive human pluripotent stem cells. In addition, individuals undergoing infertility treatment should have been approached about donation of early human embryos for the derivation of pluripotent stem cells only at the time of deciding the disposition of embryos in excess of clinical need.
4. Prior to the derivation of human pluripotent stem cells for use in NIH-supported

research, all identifiers associated with the early human embryos should have been removed.

5. Donation of early human embryos should have been made without any restriction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

2. Informed Consent Requirements for the Utilization of Human Pluripotent Stem Cells Derived from Early Human Embryos

Informed consent should have been obtained from individuals who have sought infertility treatment who elect to donate early human embryos in excess of clinical need for research purposes. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether to donate their embryos for research purposes.

1. Informed consent should have included:
 - (1) A statement that the early human embryos will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for human transplantation research.

- (ii) A statement that all identifiers associated with the embryos will be removed prior to the derivation of human pluripotent stem cells.
- (iii) A statement that donors will not receive any information regarding subsequent testing on the embryo or the derived human pluripotent cells.
- (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.
- (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.
- (vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.
- (vii) A statement that early human embryos donated will not be transferred to a woman's uterus, will not survive the human pluripotent stem cell derivation process, and will be handled respectfully, as is appropriate for all human tissue used in research.

2. To ensure respect for the individuals donating early human embryo(s), protocols

should have been approved by an Institutional Review Board (IRB) established in accord with 45 CFR §46.107 and §46.108 or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to utilize human pluripotent stem cells derived from early human embryos should provide in their application or proposal to NIH:

1. documentation that the embryos were created for the purpose of infertility treatment;
2. documentation that the early human embryos were frozen and in excess of clinical need;
2. the protocol, including the informed consent document, used for the derivation of human pluripotent stem cells from early human embryos;
3. documentation of IRB approval of the research protocol; and
1. an assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells.

B. Derivation and Utilization of Human Pluripotent Stem Cells from Fetal Tissue

1. Considerations for the Derivation and Utilization of Human Pluripotent Stem Cells Derived from Fetal Tissue.

Unlike pluripotent stem cells derived from early human embryos, DHHS funds may be used to support research to *derive* pluripotent stem cells from fetal tissue, as well as for research *utilizing* such cells. Such research is governed by federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g-2(a) and the federal regulations at 45 CFR § 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may at a later date be utilized in human fetal tissue transplantation research, it is the policy of NIH to require that all DHHS funded research involving the derivation or utilization of pluripotent stem cells from fetal tissue also comply with the fetal tissue transplantation research statute at 42 U.S.C. 289g-1.

2. Informed Consent Requirements for the Derivation and Utilization of Human Pluripotent Stem Cells From Fetal Tissue

As a policy matter, NIH funded research deriving or utilizing human pluripotent stem cells from fetal tissue should comply with the informed consent law applicable to fetal tissue transplantation research (42 U.S.C. 289g-1) and the following conditions. The informed consent process should include discussion of the following information with potential donors, pertinent to making the decision whether to donate their embryos for research purposes.

4. Informed consent should include:

- (i) A statement that the fetal tissue will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for transplantation research.

- (ii) A statement that all identifiers associated with the fetal tissue will be removed prior to the derivation of human pluripotent stem cells.
 - (iii) A statement that donors will not receive any information regarding subsequent testing on the fetal tissue or the derived human pluripotent cells.
 - (iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.
 - (v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.
 - (vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.
 - (vii) A statement that the fetal tissue and cells will be handled respectfully, as is appropriate for all human tissue used in research.
- b. To ensure respect for the individual donating tissue that results from the reproductive process, it is recommended that protocols be approved by an Institutional Review

Board (IRB) established in accord with 45 CFR §46.107 and §46.108 or FDA regulations at 21 CFR §56.107 and §56.108.

3. Investigators planning to derive or utilize human pluripotent stem cells from fetal tissue should provide in their application or proposal to NIH:

5. the protocol, including the informed consent document, for the derivation of human pluripotent stem cells from fetal tissue;
6. documentation of IRB approval, if any, of the research protocol; and
7. an assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells, as permitted by 42 U.S.C. 289g-2.

III. Areas of Research Involving Human Pluripotent Stem Cells that are Ineligible for NIH Funding

Areas of research ineligible for NIH funding include:

1. The derivation of pluripotent stem cells from early human embryos;
2. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;
3. Research in which human pluripotent stem cells are combined with an animal embryo;

4. Research in which human pluripotent stem cells are used for reproductive cloning of a human;
5. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg;
6. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg; and
7. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

IV. Oversight

1. Requests to the NIH for the funding of research involving human pluripotent stem cells should include documentation that the human pluripotent stem cells have been or will be derived in accordance with these Guidelines.
2. NIH will consider requests for funding for research utilizing human pluripotent stem cells from: (1) awardees who want to use existing funds; (2) awardees requesting an administrative supplement; and 3) applicants or intramural researchers submitting applications or proposals.

3. NIH will consider funding requests for the derivation of human pluripotent stem cells from fetal tissue.
4. All applications shall be reviewed for scientific merit by: 1) an initial review group, in the case of new or competing continuation (renewal) applications; 2) by Institute or Center staff in the case of requests to use existing funds or applications for an administrative supplement; or 3) by the Scientific Director in the case of intramural proposals prior to submission to the HPSCRG.
5. The NIH will establish a Human Pluripotent Stem Cell Review Group (HPSCRG). This group will review documentation of compliance with the NIH Guidelines for Research Involving Human Pluripotent Stem Cells, and may, when warranted, seek further information in support of an application. The group will hold public review meetings when a funding request proposes the use of a newly derived line of human pluripotent stem cells that has not been reviewed previously by the HPSCRG in a public process or when an investigator proposes a protocol for the derivation of a new human pluripotent stem cell line from fetal tissue.
6. The HPSCRG will compile a yearly report that will include the number of applications and proposals reviewed and the titles of all awarded applications, supplements or administrative approvals for the use of existing funds, and intramural projects.
7. The HPSCRG will also serve as a resource for recommending to the Director, NIH any

Dated:

Director, NIH