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To: Michelle M. Aronowitz/WHO/EOP@EOP

cc:

Subject: LRM RJP346 - - HEALTH & HUMAN SERVICES Testimony on the potential of stem cell research

Please look at this. thanks.

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From: Robert J. Pellicci on 09/01/2000 02:47:04 PM

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cc: James J. Jukes/OMB/EOP@EOP, Ingrid M. Schroeder/OMB/EOP@EOP

Subject: LRM RJP346 - - HEALTH & HUMAN SERVICES Testimony on the potential of stem cell research

COMMENTS ARE DUE BY 3:00 P.M. TUESDAY, SEPTEMBER 5TH. THE HHS TESTIMONY AND Q&As FOLLOW--

stemcelltest.wpd stemcellq&a.wp

HEARING IS BEFORE A SENATE APPROPRIATIONS SUBCOMMITTEE ON THURSDAY, SEPTEMBER 7TH.

---------- Forwarded by Robert J. Pellicci/OMB/EOP on 09/01/2000 02:39 PM ----------

LRM ID: RJP346

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

Friday, September 1, 2000

LEGISLATIVE REFERRAL MEMORANDUM

TO:	Legislative Liaison Officer - See Distribution below
FROM:	Ingrid M. Schroeder (for) Assistant Director for Legislative Reference
OMB CONTACT:	Robert J. Pellicci PHONE: (202)395-4871 FAX: (202)395-6148
SUBJECT:	**HEALTH & HUMAN SERVICES Testimony on the potential of stem cell research**

DEADLINE: **3:00 P.M. Tuesday, September 5, 2000**
In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President. **Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.**

COMMENTS: Hearing is before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies on Thursday, September 7th. NOTE: In addition to the testimony a number of Q&As are attached for your review.

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LRM ID: RJP346 **SUBJECT:** HEALTH & HUMAN SERVICES Testimony on the potential of stem cell research

RESPONSE TO
LEGISLATIVE REFERRAL
MEMORANDUM

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

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

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

FROM: _____ (Date)

_____ (Name)

_____ (Agency)

_____ (Telephone)

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

_____ **Concur**

_____ **No Objection**

_____ **No Comment**

_____ **See proposed edits on pages** _____

_____ **Other:** _____

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

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DRAFT DRAFT DRAFT DRAFT DRAFT DRAFT DRAFT DRAFT

STATEMENT OF

GERALD D. FISCHBACH, M.D.

DIRECTOR

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

AND

ALLEN M. SPIEGEL, M. D.

DIRECTOR

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

BEFORE THE

SENATE APPROPRIATIONS SUBCOMMITTEE

ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION AND RELATED AGENCIES

SEPTEMBER 7, 2000

Mr. Chairman, Ranking Member Senator Harkin, and Members of the Subcommittee, I am Dr. Gerald Fischbach, Director of the National Institute of Neurological Disorders and Stroke. I am accompanied by Dr. Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases, and Dr. Lana Skirboll, NIH Associate Director for Science Policy. We are before you again to discuss one of the most exciting areas of biomedical research: the enormous potential of human pluripotent stem cells to treat and cure debilitating and deadly diseases. Only two years ago, researchers discovered and isolated these primordial cells -- whose existence in humans had been theorized but never proven -- the precursors of most of the other cells in the body. Their unique properties of self-renewal and the ability to differentiate into the full spectrum of other cell types make them ideal candidates for repairing and replacing tissues and organs ravaged by disease. New and maybe more effective treatments, and maybe even cures, might be developed for juvenile-onset diabetes, Parkinson's Disease, spinal cord injury, Lou Gehrig's disease, Alzheimer's Disease and many other brain disorders. There is similar potential for the treatment of cancer and heart disease. Virtually every realm of medicine and human health might benefit from this innovation. Stem cell research could alleviate a great deal of human suffering.

Chairman Specter, you and Senator Harkin, in particular, have encouraged NIH to invest our resources in stem cell research in order to pursue its enormous opportunities. Patients who are suffering from the most deadly and disabling diseases, many of whom are dying because cures or adequate treatment are not available, have also asked that NIH fund this promising arena of research. We believe that federal funding would encourage openness, stimulate more discoveries and translate the promise of this research into practical use more quickly, ~~efficiently~~ safely, ~~and~~ effectively, and with procedural safeguards.

Recognizing that the ethical issues related to this research required careful consideration, NIH and the Department of Health and Human Services were committed to developing Guidelines to

help ensure that pluripotent stem cell research funded by NIH would be conducted in a legal and ethical manner. In drafting the Guidelines, the NIH sought the advice of scientists, patients and patient advocates, ethicists, clinicians, lawyers, the National Bioethics Advisory Commission, and members of Congress. Draft Guidelines were published in the Federal Register last December. The NIH reviewed and considered all comments in preparing the final Guidelines.

We are pleased to inform you that on August 25 NIH published Final Guidelines for research using human pluripotent stem cells. The NIH is now poised to fund such research. We expect broad interest from researchers seeking funding for pluripotent stem cell research, and we are hoping to begin funding this research as soon as possible.

What are stem cells?

Human pluripotent stem cells are a unique scientific and medical resource. They can develop into most of the specialized cells and tissues of the body, such as muscle cells, nerve cells, liver cells, and blood cells, and they are self-renewing, making them readily available for research, and potentially, treatment purposes. Scientists derived these unique cells from human embryos and from fetal tissue.

Why are human pluripotent stem cells important?

There are three reasons why the isolation of human pluripotent stem cells is so important to science and the future of public health. First, pluripotent stem cells could help us to understand the complex events that occur during human development. Second, 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, and ensure that only the safest drugs are tested in humans.

Third, and perhaps the most far-reaching potential application of human pluripotent stem cells, is the generation of cells and tissue that could be used for "cell transplantation therapies." Such therapies are aimed at diseases and disorders resulting from the destruction or dysfunction of specific cells and tissue. Although donated organs and tissues can sometimes be used to replace diseased or destroyed tissue, the number of people suffering from such disorders far outstrips the number of organs and tissues available for transplantation. Pluripotent stem cells, stimulated to develop into specialized cells and tissue, offer real hope for the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions, and disabilities for which replacement tissue is in short supply. Examples of these include neurological disorders (including spinal cord injuries and ALS), diabetes, burns, heart disease, and arthritis.

Requirements of the Guidelines

The *Guidelines* prescribe procedures to enhance both the scientific and ethical oversight of this important arena of research and the pace at which scientists can explore its many promises. They specify the documentation and assurances that must accompany requests for NIH funding for research utilizing human pluripotent stem cells that were derived in the private sector from human embryos that were frozen, created for infertility treatment, and in excess of clinical need. They also set out specific conditions for the use of human pluripotent stem cells derived from fetal tissue. These *Guidelines* will encourage openness, help make certain that researchers can make use of these critical research tools, and help assure public access to the practical medical benefits of research using these cells.

First, the Guidelines help ensure that embryos will not be created for the purpose of deriving human pluripotent stem cells to be used in NIH-supported research. They require a clear separation between the fertility treatment and the decision to donate embryos for this research. In addition, the donation of the human embryos must be made without any restriction regarding the

individual who may be the ultimate recipient of the cells for transplantation. Similarly, researchers wishing to use human fetal tissue to derive stem cells must demonstrate that they are in compliance with all applicable laws and regulations. The Federal statute applicable to NIH-funded fetal tissue transplantation research also include provisions creating a separation between the decision to terminate a pregnancy and the decision to donate fetal tissue for research.

Second, the *Guidelines* ensure that an individual choosing to donate either embryos or fetal tissue cannot receive any inducements, monetary or otherwise. The *Guidelines* detail specific elements that must be included in the informed consent to help ensure that potential donors receive sufficient information to allow them to decide whether or not to donate human embryos for this type of research. The Guidelines require review and approval by an Institutional Review Board (IRB) to ensure that consent was informed, voluntary, and meaningful.

Third, the Guidelines require accountability on the part of the researcher. Detailed documentation must be submitted to NIH to demonstrate compliance. The researcher/grantee institution must sign an assurance that the research to be conducted is in compliance with the Guidelines, and that researchers and the institution will maintain documentation to support the assurance. The researcher/grantee institution must submit a sample informed consent document, with patient identifier information removed, a description of the informed consent process, and documentation of IRB review.

Fourth, the Guidelines specify types of research that the NIH will not fund. For example, NIH will not fund any research that seeks to derive pluripotent stem cells from human embryos, research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, or any research that seeks to derive or utilize stem cells from embryos that were created using somatic cell nuclear transfer (cloning technology).

Fifth, the NIH has designed an oversight process that will provide an extra level of protection, above and beyond standard peer review of grant applications, to ensure that researchers have complied with the Guidelines. A newly-created NIH working group called the Human Pluripotent Stem Cell Review Group (HPSCRG) will review documentation submitted by researchers demonstrating that they are in compliance with the *Guidelines*. Members of the HPSCRG will subsequently make recommendations to its parent committee, the Center for Scientific Review Advisory Committee (CSRAC). NIH will not fund research or allow existing funds to be used for research using human pluripotent stem cells derived from human embryos or human fetal tissue until the required compliance documentation receives HPSCRG review and approval of the NIH Center for Scientific Review Advisory Committee. Continued compliance with the *Guidelines* will be a term and condition of the NIH award.

Human Pluripotent Stem Cells and Diabetes Research

One of the best examples of the promise of this line of research is in the treatment of Type 1 diabetes. Research on islet cell transplantation and stem-cell biology offers compelling opportunities for the development of new, innovative approaches for treating and ultimately curing this disease.

Type 1 diabetes, often referred to as juvenile diabetes, is characterized by the inability of the body to produce insulin, a hormone necessary for glucose metabolism. This form of diabetes occurs when the body's immune system attacks and destroys its own insulin-producing islet cells in the pancreas. As a result of inadequate insulin production, glucose does not enter cells as readily as when insulin levels are normal. The standard treatment is to try to control the glucose level with insulin injections.

Transplantation of insulin-producing islet cells is an alternative approach to controlling glucose levels. In a recent study, seven patients receiving islet transplants became completely

independent of the need for insulin injections. NIH is currently funding a multi-center trial of the protocol used in this study to determine if the same success can be achieved in a larger number of patients. A successful outcome to this trial, as exciting as it would be for patients with Type 1 diabetes, will only serve to underscore the limitation in the supply of islets available for transplantation compared to demand. While many approaches to address the islet supply problem, including work on cell bioengineering and adult stem cells should be, and are, being vigorously pursued, human pluripotent stem cells offer the greatest promise of providing a limitless source of islet cells for treating and curing Type 1 diabetes.

Human Pluripotent Stem Cell Research and the Nervous System

As significant as the promise of stem cells is for the treatment of diabetes, the potential of stem cells for treating diseases of the nervous system is equally impressive. The most obvious and exciting use of stem cells in neurological disorders is to replace nerve cells lost to disease or injury. Many diseases destroy particular types of nerve cells, and mature nerve cells cannot produce new cells to replace those that are lost. Animal experiments have demonstrated that the potential exists for coaxing stem cells to specialize and replace the dopamine cells that are lost in the brain in Parkinson's disease. A similar approach might apply to several other neurological disorders. Stem cells, given appropriate control signals, might specialize to replace the lost acetylcholine producing nerve cells in Alzheimer's disease, to restore lost motor neurons in ALS, or to produce inhibitory cells to help restrain electrical activity in epilepsy. Clinical studies in the U.S. and several other countries have demonstrated that transplantation of fetal tissue dopamine cells into Parkinson's patients improves patients' functional abilities. However, the limited availability of fetal tissue points out the urgent need for pluripotent stem cell research that may lead to effective treatments for this disorder.

Replacing lost nerve cells is only the beginning of the list of possible therapeutic applications for stem cells. For some disorders, such as multiple sclerosis, stem cells might replace supporting

cells, such as the glial cells, which provide the insulation necessary to allow some nerves to conduct electrical impulses rapidly. In addition to their potential in replacement therapy, stem cells can provided nutritive factors that might prevent the loss of nerve cells in the first place. Stem cell strategies might be useful for correcting inherited defects. For example, in disorders that devastate children's brains, we might rely on the ability of stem cells to migrate widely in the brain and supply the vital missing enzyme that leads to early and tragic death from Tay-Sach's disease. In addition, stem cells might regenerate the many different kinds of complex brain tissue that are damaged as a result of brain trauma or stroke. Transplanted stem cells might also supply natural growth and survival chemicals to pave the way for regeneration of remaining healthy neural tissue following spinal cord injury. Recent findings suggest that stem cells might be harnessed to seek out and destroy brain tumor cells that evade surgery or radiotherapy. The list of possible applications of stem cells continues to grow as we learn more about these cells.

Conclusion

Mr. Chairman, we appreciate the opportunity to discuss this promising and extraordinary science and are pleased to respond to any questions you may have.

Last updated 08/31/00

POSSIBLE STEM CELL QUESTIONS BY SUBJECT

General Questions

Q. Why is NIH issuing *Guidelines*?

A. Establishment of human pluripotent stem cell lines represents a major step forward in the understanding of human biology and has generated much interest among scientists and the public, particularly among patients and their advocates. The purpose of the NIH *Guidelines* is to prescribe procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH recognized the need to address the ethical and legal issues before providing funding for this research, which promises new treatments and possible cures for many debilitating diseases and injuries, including Parkinson's disease, diabetes, heart disease, multiple sclerosis, burns and spinal cord injuries.

Q. Was there enough public disclosure/discussion of this research or the *Guidelines*?

A. Prior to the development of draft *Guidelines*, there were two Congressional hearings on human pluripotent stem cells. In a further effort to ensure substantial discussion and comment, the NIH convened a Working Group of the Advisory Committee to the Director (ACD), NIH to advise the ACD on the development of these *Guidelines*. The Working Group was composed of scientists, patients and patient advocates, ethicists, clinicians, and lawyers. The Working Group met in public session on April 8, 1999, and heard from members of the public, as well as professional associations and Congress. In developing the draft *Guidelines*, the NIH also considered advice from the National Bioethics Advisory Commission (NBAC). Draft *Guidelines* were published for public comment in the *Federal Register* on December 2, 1999, for 60 days, and, in response to public interest, the comment period was extended an additional 28 days. Approximately 50,000 comments were received. NIH issued a national press release announcing the Federal Register Notice and many of the Nation's newspapers carried articles on this area of research and on the draft *Guidelines*. Patient groups, scientific societies, and religious organizations convened meetings and discussion groups and disseminated materials about this area of research and about the draft *Guidelines*.

Q. NBAC just submitted its recommendations to the President (11/99). Did NIH really take their recommendations into consideration when drafting the *Guidelines*?

The working group of the ACD and the NIH took the NBAC's deliberations and their recommendations into consideration. Eric Meslin, the NBAC Executive Director, presented to the working group the NBAC's draft Points to Consider in Evaluating Basic Research Involving Human Stem Cells. NIH staff have attended all of the NBAC meetings on this topic. In addition, the working group and NIH staff read and considered the NBAC stem cell recommendations while drafting the *Guidelines*.

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

A. This research promises new treatments and possible cures for many debilitating diseases and injuries, including Parkinson's disease, diabetes, heart disease, burns and spinal cord injuries. Federal funding of this work would engage the attention of many more scientists and would bring more oversight to this important arena of research. 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 review including NIH scientific peer review groups, NIH National Advisory Council meetings and review by the NIH Human Pluripotent Stem Cell Review Group, as proposed in the NIH *Guidelines*. This would encourage openness, ensure that all researchers could use these important research tools, and help assure public access to both the research information and the practical medical benefits of research using these stem cells.

Q. Does the Administration support the use of federal funding to derive stem cells from 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 appropriate ethical standards. Funding federal research using these cells is legally permissible.

Current law prohibits the use of Federal funds to derive stem cells from human embryos. We are not now requesting a change in current law to permit Federal support for derivation of stem cells from human embryos. In addition, the President's 1994 ban on the use of Federal funds for the creation of human embryos for research purposes will remain in effect.

Q. What is your reaction to the British government's recent recommendation regarding therapeutic cloning?

A. It would not be appropriate for us to comment on proposed legislation before the British Parliament. There is currently no restriction on therapeutic cloning in the U.S. private sector. However, U.S. Federal law currently prohibits the use of Department of Health and Human Services (DHHS) funds for research in which a human embryo is created for research purposes or in which an embryo is destroyed, discarded or otherwise harmed. Thus, DHHS funds cannot be used for the derivation of stem cells from human embryos. DHHS has determined, however, that the Congressional restriction does not prohibit funding for research utilizing human pluripotent stem cells because such cells are not themselves embryos.

Of note, the recently released NIH *Guidelines* set forth certain areas of research that ineligible for NIH funding, including: 1) research in which human pluripotent stem cells are derived using cloning technology, i.e., the transfer of a human somatic cell nucleus into a human or animal egg called somatic cell nuclear transfer; 2) research utilizing human pluripotent stem cells that were

derived using cloning technology; and 3) research in which human pluripotent stem cells are used in combination with somatic cell nuclear transfer for the purposes of reproductive cloning of a human.

New Q added 8/30/00: Without the current ban on Federal research using human embryos, would NIH engage in research to establish human pluripotent stem cell lines?

A. The NIH has taken no action at this time to remove the ban on funding research in which an embryo is destroyed, discarded or otherwise harmed.

New Q added 8/30/00: Does NIH believe that the current ban on Federal research using human embryos should be overturned?

A. The NIH has taken no action at this time to remove the ban on funding research in which an embryo is destroyed, discarded or otherwise harmed.

Q. How would you compare the position of the US vis-a-vis other countries on this issue?

Few countries have specifically addressed the issue of the permissibility of research involving human pluripotent stem cells. Many countries, including Australia, Canada, Denmark, Finland, Spain, Sweden, and the United Kingdom allow human embryo research under certain conditions. Many countries, including Germany and France, prohibit destructive human embryo research and therefore prohibit the derivation of stem cells from human embryos. The Science and Technology Agency of Japan plans to establish a subcommittee to deliberate on the use of human embryonic stem cells.

Q. Is there a prohibition on Federal funding for stem cell research from fetal tissue?

There is no statutory restriction on using federal funds to derive or use pluripotent stem cells from fetal tissue. The director of NIH placed a temporary moratorium on this and other human pluripotent stem cell research until *Guidelines* and an oversight process are put in place for this research.

Q. I have introduced legislation to allow Federal funds to be used for the derivation of stem cells. What is your view of my bill?

A. I understand that the Administration has not yet taken a position on your legislation. However, I should note that we believe that there will be sufficient stem cells available under current law to support research efforts.

Process Questions

Q. How soon would NIH funding of research using human pluripotent stem cells be expected to begin?

A. The NIH will notify researchers that the NIH will begin accepting proposals from investigators who wish to: 1) use existing funds; 2) submit a supplementary grant application; or 3) submit a new grant application for research utilizing human pluripotent stem cells. Funding for research using human pluripotent stem cells may begin as soon as an application for funding has met the requirements set forth in the *Guidelines* and has been reviewed and approved according to the oversight process.

The following text added by OSP on 8/31: The first meeting of the Human Pluripotent Stem Cell Review Group (HPSCRG) is scheduled for November 2000 and the CSRAC meets in January. If investigators have cells that they think are compliant with the *Guidelines* and they have prepared the supporting documentation, they will need to forward that material by November 15 for the December HPSCRG review. Recommendations from members of the HPSCRG will be forwarded to the Center for Scientific Review Advisory Committee (CSRAC) for their January meeting. Investigators/institutions proposing to use cells that are approved by CSRAC AND whose projects receive fundable priority scores, will be considered at January Council meetings. This means that the earliest NIH could fund this research is late winter, early spring of 2001.

Q. What do investigators need to submit to NIH to get approval to use human pluripotent stem cells?

A. Researchers wishing to use human pluripotent stem cells with federal funds will need to provide:

An assurance that the pluripotent stem cells were derived from human embryos in accordance with the *Guidelines* and that the institution will maintain documentation in support of the assurance;

- A sample informed consent document, with patient identifier information removed and a description of the informed consent process;
- An abstract of the scientific protocol used to derive human pluripotent stem cells; documentation of IRB approval of the derivation protocol;
- 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;

- The title of the research proposal that proposes the use of human pluripotent stem cells;

- A signed assurance that the proposed research utilizing human pluripotent stem cells is not a class of research that is ineligible for NIH funding;

- The investigator's written consent to the disclosure of all material submitted to carry out the public review and other oversight procedures.

Q. What happens to a request to use human pluripotent stem cells after submission to NIH?

A. The request will be reviewed by an NIH oversight working group called the "Human Pluripotent Stem Cell Review Group (HPSCRG)." Members of the working group will advise the NIH Center for Scientific Review Advisory Committee (CSRAC) on documentation of compliance with the *Guidelines*. The HPSCRG will hold public meetings when a request proposes the use of a line of human pluripotent stem cells that has not been previously reviewed by the HPSCRG.

Compliance materials described in the *Guidelines* should be submitted to the NIH Office of Science Policy. Recommendations of the members of HPSCRG will be reviewed, and, if appropriate, approved by the CSRAC. The Office of Science Policy will forward the CSRAC decision to the funding Institute or Center. The HPSCRG may ask the investigator to provide additional materials to clarify the proposal. This could delay a decision on the proposed use of a human pluripotent stem cell line until the additional information has been received and the HPSCRG meets again.

Q. The *Guidelines* imply that the working group will not meet in public when a request proposes the use of a line of human pluripotent stem cells that has been previously approved. Why have the HPSCRG meet in private?

A. Once a cell line has been approved, there are fewer issues for the HPSCRG to consider. The request can be considered in a closed meeting, but recommendations to approve must still be vetted at a public HPSCRG meeting and forwarded to the CSRAC for approval.

New Q added 8/30/00: Please describe further how HPSCRG will work and its relationship to the NIH ICs and the CSR. For example, who are the Committee's members and what are the differences between an IC's review of a grant and HPSCRG?

A. The *Guidelines* outline the documentation that must be submitted by intramural investigators and by institutions on behalf of extramural investigators requesting the use of NIH funds to conduct research using human pluripotent stem cells derived from human embryos or human fetal tissue. This applies to investigators who want to use existing funds and who are requesting an administrative or competing supplement, and to those who are applying for new NIH

funding. This documentation will be reviewed for compliance with the *Guidelines* by a working group of the NIH Center for Scientific Review Advisory Committee (CSRAC), called the Human Pluripotent Stem Cell Review Group (HPSCRG). Recommendations of the members of HPSCRG will be reviewed by CSRAC, and, if appropriate, approved in its public meetings.

For existing awards and administrative supplements, the applicant institution should reference the grant number under which the proposed research using human pluripotent stem cells derived from human embryos or human fetal tissue is to be conducted. If the proposed research constitutes a change in scope of the funded project, the principal investigator must obtain prior approval for the change in scope from NIH. In the case of intramural projects, investigators should send documentation materials to their Scientific Director, who should forward the materials to the Office of Science Policy (with a copy to the Deputy Director of Intramural Research). Only after these materials have been reviewed by the HPSCRG and approved by the CSRAC will the research be allowed to proceed. It is important to note that review for scientific merit will be conducted in parallel with HPSCRG and CSRAC review. These submissions will be considered on the same schedule as outlined below for extramural requests. NIH is in the process of naming the members of the HPSCRG. This will be a 7-10 member committee made up of ethicists, physicians, members of the public and scientists.

Q. Will all human pluripotent stem cell products be labeled that "human embryos and/or fetuses were used in the development of this product?"

A. These *Guidelines* pertain to research using human pluripotent stem cells, not to the development of any products that may subsequently be developed.

Q. If human pluripotent stem cell research results in the development of a product for transplantation into patients, would laws or regulations in addition to these *Guidelines* apply?

As with any product intended for transplantation into human patients, clinical trials of cell therapies developed from human pluripotent stem cells would be conducted under FDA regulations as an Investigational New Drug (IND) application. In addition, FDA regulations concerning how preclinical research is conducted, known as Good Laboratory Practice (GLP), would apply.

Oversight Questions

Q. How will adherence to these *Guidelines* be monitored?

A. The NIH Human Pluripotent Stem Cell Review Group (HPSCRG) will review documentation of compliance with the NIH *Guidelines*. Requests for NIH funds for research utilizing human pluripotent stem cells must include documentation indicating that the human pluripotent stem cells have been derived in compliance with the NIH *Guidelines* for Research Utilizing Human Pluripotent Stem Cells. The HPSCRG will be responsible for reviewing documentation of compliance on a case by case basis. The group will meet in public session when a request proposes the use of a line of human pluripotent stem cells that has not been previously reviewed by the HPSCRG. The HPSCRG will publish a yearly report which will include: 1) the number of applications and proposals reviewed and (2) the titles of all awarded applications, supplements or administrative approvals for the use of existing funds and intramural projects.

Q. What happens if an investigator does not follow the *Guidelines*?

A. If an investigator fails to comply with the terms and conditions of the *Guidelines* following the award of funds, the NIH has the authority to take a variety of actions, including (1) imposing special conditions on the research, such as increased oversight/monitoring/reporting requirements for an institution, project or investigator; (2) withholding research funds pending correction of the problem or pending more severe enforcement action; (3) disallowing all or part of the costs of the activity that was not in compliance; (4) withholding further awards for the project; (5) or suspending or terminating all or part of the funding for the project.

Q. Can NIH really be trusted to appropriately oversee this new and complicated area of research, given all the criticisms regarding oversight of gene therapy?

A. The problems regarding gene therapy have involved lapses by investigators in reporting appropriate data once the trial is in progress. In contrast, the NIH *Guidelines* on Human Pluripotent Stem Cells require that certain conditions be met *prior* to NIH funding. Provisions of the *Guidelines* that affect the expenditure of grant funds for stem cell research will be made a condition of the individual awards and will be enforced in the same manner as any other condition of award.

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 and many advocated for legislation banning this research. The scientific community responded rapidly to public concern

by establishing voluntary moratorium until *Guidelines* could be developed to govern the research. *Guidelines* were written and the Recombinant DNA Advisory Committee was established to ensure public review of the research.

Q. Given the recent allegations regarding fetal tissue, are you amending the *Guidelines* to require additional protections for fetal tissue research to ensure that researchers are in compliance with the law banning profit from the sale of fetal tissue?

A. No. Federal law currently prohibits any entity - both private and federally-funded - from knowingly transferring or acquiring fetal tissue for valuable consideration; researchers deriving stem cells from fetal tissue would be expected to adhere to all local, state and federal laws.

Q. How can the *Guidelines* prevent the creation of embryos for research purposes?

A. Investigators seeking NIH funds for research using human pluripotent stem cells are required to provide documentation, prior to the award of any NIH funds, that embryos were created for the purposes of fertility treatment.

Q. How will the *Guidelines* prevent the creation of a "black market" for human embryos, or prevent individuals from being coerced into donating embryos?

A. The *Guidelines* state that there can be no incentives for donation and that a decision to donate must be made free of coercion. In addition, the *Guidelines* set forth conditions that will help ensure all donations are voluntary. For example, with regard to human pluripotent stem cells derived from embryos, research using federal funds may only be conducted if the cells were derived from frozen embryos that were created for the purpose of fertility treatment and that were in excess of clinical need.

Q. Will Federal funding of this research and the issuing of these *Guidelines* create a " market" for the creation of human embryos for research purposes?

A. The *Guidelines* require investigators to document that the embryos were not created for research purposes. In addition, the *Guidelines* require the informed consent of the donating individuals and that the treating physician and the person deriving the stem cells from human embryos not be one and the same.

Q. Will there be a sunset period on the oversight?

A. No. The *Guidelines* do not have a finite period of authority. The NIH Director can make changes to the *Guidelines*. Any proposed change will, however, first be published in the Federal Register for public comment. The NIH Director's final decision, along with a response to public comments, will also be published in the Federal Register.

Q. Shouldn't the HPSCRG, or its equivalent, be placed in an agency or commission independent of the NIH, to avoid a perception of conflict of interest?

A. The HPSCRG will come under the jurisdiction of the NIH since this oversight group will review whether individual proposals requesting funds to conduct research using human pluripotent stem cells are in compliance with the NIH *Guidelines* and, therefore, eligible for NIH funding. — doesn't answer why no conflict

Q. Do the *Guidelines* require IRB approval for the donation of embryos for the derivation of stem cells?

The NIH *Guidelines* will make IRB approval of a protocol a prerequisite for NIH funding of research using human pluripotent stem cells derived from human embryos.

Q. Do the *Guidelines* require IRB approval for the donation of fetal tissue for the derivation of stem cells?

Although some IRBs currently review protocols involving the donation of human fetal tissue for research, such IRB review and approval is not required by Federal regulations. The *Guidelines* recommend that protocols for the derivation of pluripotent stem cells from human fetal tissue be approved by an IRB.

Ethical Questions

New Q added 8/30/00: Is it ethical to conduct research using human pluripotent stem cells? If so, what sources did NIH consult before reaching this conclusion?

A. The purpose of the NIH *Guidelines* is to prescribe procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH heard from NBAC, invited the participation of ethicists in the development of the *Guidelines* and from the public, Congress, investigators, and constituency groups during the public comment period on the *Guidelines*.

New Q added 8/30/00: Is an embryo a human life? Isn't NIH saying, through its funding of human pluripotent stem cell research, that it is ethical to destroy human life?

A. There are many different views on this issue, even among scientists and we respect all views. NBAC and others looked at the ethics and determined it is appropriate to proceed with this type of research.

Q. The Administration is supporting Federal funding for research using human pluripotent stem cells. 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 will abide by existing law that permits the use of DHHS funds to conduct stem cell research, but prohibits the use of DHHS funds to derive stem cells from human embryos.

Q. Isn't it impossible to separate abortion/infertility treatment from the derivation of human pluripotent stem cells?

A. The *Guidelines* state that human pluripotent stem cells may be derived from embryos only if the embryos were created for reproductive purposes, were in excess of clinical need and were frozen. These conditions help ensure that there is a separation between the fertility treatment and the decision to donate excess embryos for the derivation of stem cells for research.

In the case of fetal tissue, the *Guidelines* mandate following existing federal law regarding the use of fetal tissue in transplantation research to help ensure that the research will not influence the abortion process.

New Q added 8/30/00: When there are ethical issues regarding certain types of biomedical research, who makes the decision that a particular course of action of study is "ethical?"

A. In this case the NIH heard from NBAC, invited the participation of ethicists in the development of the *Guidelines* and from the public, Congress, investigators, and constituency groups during the public comment period on the *Guidelines*.

Derivation and Use Questions

Q. Can an investigator who derived human pluripotent stem cells from an embryo without DHHS funding receive funds from NIH for research utilizing these pluripotent stem cells?

A. Yes, but only if no DHHS funds were used for the derivation of the cells and the cells were derived in compliance with the *Guidelines*. DHHS funds can only be used for research *utilizing* human pluripotent stem cells derived from human embryos and not for any part of their derivation.

Q. Dr. Varmus said in a recent (11/99?) Science Magazine article that he believes NIH should be supporting research on the derivation of stem cells from spare embryos. Doesn't this put Dr. Varmus at odds with the Administration's position?

A. Dr. Varmus fully supports the draft NIH *Guidelines* issued today. The *Guidelines* do not support using federal funds for the derivation of stem cells from human embryos.

Q. What authority does NIH have to dictate requirements for the derivation of stem cells from human embryos when NIH cannot fund derivation of the cells themselves?

A. These *Guidelines* will govern research proposals in which the investigator is requesting NIH funding for utilizing human pluripotent stem cells derived (without DHHS funding) from human embryos. An investigator will be required to submit an application containing the information referenced in the *Guidelines* in order to be eligible for an award and will have to comply with the conditions imposed upon any grant that is awarded on the basis of that application.

Q. Do the *Guidelines* require IRB approval for the donation of embryos for the derivation of stem cells?

A. The NIH *Guidelines* will make IRB approval of a protocol a prerequisite for NIH funding of research using human pluripotent stem cells derived from human embryos.

Q. Do the *Guidelines* require IRB approval for the donation of fetal tissue for the derivation of stem cells?

A. Although some IRBs currently review protocols involving the donation of human fetal tissue for research, such IRB review and approval is not required by Federal regulations. The *Guidelines* recommend that protocols for the derivation of pluripotent stem cells from human fetal tissue be approved by an IRB.

Q. Wouldn't it be better for federally-funded researchers to derive their own stem cells, rather than depending on others to do it for them?

A. There appears to be an ample supply of stem cells available for research. There is no

evidence, at this time, that additional derivation is necessary.

Q. I have introduced legislation to allow Federal funds to be used for the derivation of stem cells. What is your view of my bill?

A. I understand that the Administration has not yet taken a position on your legislation. However, I should note that we believe that there will be sufficient stem cells available under current law to support research efforts.

Q. How can we be sure that there will be an adequate supply of pluripotent stem cells if Federally-funded researchers can't derive the cells?

A. Human pluripotent stem cells can divide for indefinite periods in culture; therefore there should be an adequate supply of stem cells derived from human embryos by the private sector.

Q. If federally-funded researchers are able to derive stem cells themselves, wouldn't this speed up the amount of time it will take to have a cure for Parkinson's Disease and Diabetes?

A. As long as the pluripotent stem cells derived in the private sector are made available to researchers, scientists will be able to pursue important research using these cells.

Financial Questions

Q. May NIH investigators pay for human pluripotent stem cells?

A. Investigators wishing to utilize stem cells derived from human embryos or fetal tissue will need to provide in their application to NIH 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.

Q. Won't human pluripotent stem cell research encourage the sale of fetal tissue for profit, or clinics or doctors profiting from the derivation of human pluripotent stem cells and/or their sale?

A. Section 498B of the Public Health Service Act prohibits any individual from knowingly acquiring or selling human fetal tissue for "valuable consideration." In addition, the *Guidelines* prohibit any inducement for the donation of human embryos for research purposes. The *Guidelines* also call for an assurance that the human pluripotent stem cells to be used in NIH-funded research were 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 human pluripotent stem cells. All grantees must sign an assurance that they are in compliance with all applicable Federal, State, and local laws. Each funded research institution is responsible for monitoring compliance by individual investigators with any such applicable laws.

Q. Why can't embryo donors benefit financially from their donation?

A. This clause in the *Guidelines* helps ensure that the donating individuals are offered no inducements to donate and that all donations are voluntary.

Q. What about payments for donation for research and/or for fertility treatments and their associated expenses?

A. The *Guidelines* state explicitly that "No inducements, monetary or otherwise, should have been offered for the donation of human embryos for research purposes." This clause makes clear that financial and other incentives are not allowable. The *Guidelines* require an assurance that the human pluripotent stem cells to be used in the research were 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 human pluripotent stem cells.

Q. Would it violate the Federal ban on funding of human embryo research if NIH investigators paid for human pluripotent stem cells?

Under these *Guidelines*, DHHS-funded researchers can acquire previously derived human pluripotent stem cells for research; such acquisitions would not violate the federal restrictions on human embryo research. Investigators wishing to utilize stem cells derived from human embryos or fetal tissue will need to provide in their application to NIH 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.

Q. Some have raised concerns about fetal tissue research and possible violations of the law concerning profiting from the sale of fetal tissue. Do NIH funded scientist spend more than the appropriate funds charged for fetal tissue? Or do they pay a flat fee that simply covers the cost of processing and transporting the tissue?

A. All NIH funded researchers are required to follow all local, state and Federal laws governing fetal tissue research. There is a Federal law that prohibits an individual or entity from profiting from sale of human fetal tissue. It also prohibits any individual or entity from knowingly acquiring fetal tissue from an entity for "valuable consideration." According to this law, " valuable consideration" *does not* include reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue. Violation of this statute carries criminal penalties. There is no evidence that NIH funded researchers spend more than appropriate charges. Appropriate charges for processing and transportation of fetal tissue may or may not take the form of a "flat fee".

Scientific Questions

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 can divide for indefinite periods in culture. 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 derivation of cell lines that more closely match the tissue type of the patient.

Q. Is there a scientific difference between stem cells derived from embryos and stem cells derived from fetal tissue? Do we need to do both?

A. At this point in time, research on human pluripotent stem cells is new. Although the pluripotent stem cells derived from embryos and fetal tissue appear to have many similarities, there is some data that suggests some subtle, but perhaps important, differences. It is too early to know if these differences are significant, especially with regard to their ability to develop into transplantable tissue. It is important to continue research on human pluripotent stem cells derived from both embryos and fetal tissue.

Q. Why is it important to study adult stem cells as well as human pluripotent stem cells that are derived from embryos and fetuses?

A. Given the enormous potential of stem cells, it is important to simultaneously pursue all lines of promising research. It is possible that no single source of stem cells will be best or even suitable/usable for all therapies. Different types or sources of stem cells may be optimal for treatment of specific conditions. Unless all stem cell types are studied, the differences between adult stem cells and embryo and fetal-derived human pluripotent stem cells will not be known.

Q. Are there any limitations to the potential of adult stem cells?

A. There is evidence that adult stem cells may have more limited potential than human pluripotent stem cells. The following features of adult stem cells should be considered:

First, stem cells for all cell and tissue types have not yet been found in the adult human. For example, cardiac stem cells have not been identified in adult humans.
Second, stem cells in adults are often present in only minute quantities, are difficult to isolate

and purify, and their numbers may decrease with age. For example, adult brain cells that may be neural stem cells have only been obtained by removing a portion of the brain of an adult with epilepsy, a complex and invasive procedure that carries the added risk of further neurological damage.

Third, adult stem cells may contain more DNA abnormalities caused by exposure to daily living, including sunlight, toxins, and errors made during DNA replication than will be found in fetal or embryonic human pluripotent stem cells.

Fourth, there is evidence that stem cells from adults may not have the same capacity to multiply as do younger cells. These potential weaknesses may limit the usefulness of adult stem cells

Q. Scientists have reported that they were able to grow nerve cells from adult stem cells taken from bone marrow. Doesn't this weaken your argument that research using human pluripotent stem cells is necessary because adult stem cells have a limited potential?

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.

Q. What do you think has been the negative impact on stem cell research from the year and a half delay we have had waiting for the NIH *Guidelines* to be put in place?

A. As soon as it is possible to use federal funds for this research, more researchers will be able to participate and contribute to this new arena of biomedical investigation. As more people are involved, it is conceivable that progress may proceed more quickly.

Q. How would stem cell research be impacted if fetal tissue research were restricted?

A. If Federally funded researchers were no longer permitted to conduct research using fetal tissue, then researchers may not be able to conduct research using human pluripotent stem cells derived from fetuses. At this point in time, it is not certain that pluripotent stem cells derived from embryos and fetal tissue have the same potential for the development of new treatments.

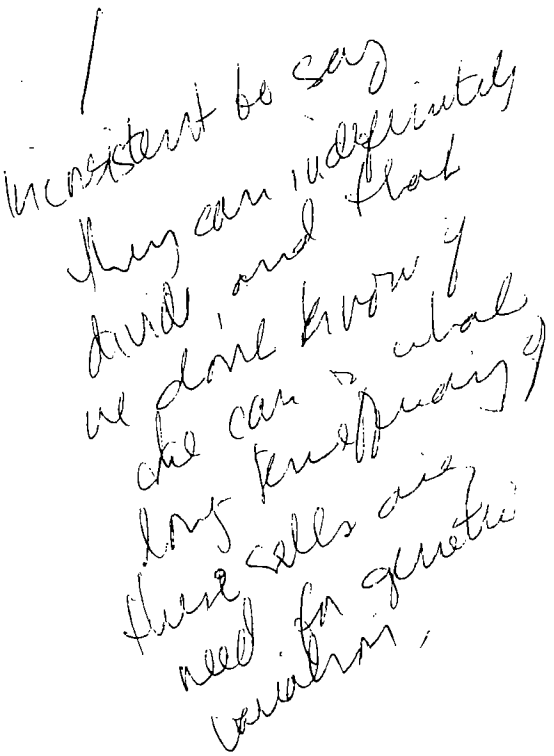
Q. What about the recent reports that scientists were successful in directing neural stem cells in mice to shrink tumors? Does this study show that adult stem cells have greater promise than has previously been realized?

A. In order to determine the very best source of many of the specialized cells and tissues of the body for new treatments and even cures, it will be vitally important to study the developmental potential of adult stem cells and compare it to that of pluripotent stem cells.

Given the enormous promise of stem cells to the development of new therapies for the most devastating diseases, it is important to simultaneously pursue all lines of research. Science and scientists need to search for the very best sources of these cells. When they are identified, regardless of their sources, researchers will use them to pursue the development of new cell therapies.

Q. How can we be sure that there will be an adequate supply of pluripotent stem cells if Federally-funded researchers can't derive the cells?

A. Human pluripotent stem cells can divide for indefinite periods in culture; therefore there should be an adequate supply of stem cells derived from human embryos by the private sector.



Research Ineligible/Eligible for Funding Questions

Q. Why are certain areas of research deemed ineligible, particularly research that is not restricted by statute or regulation, such as 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 egg?

A. The NIH determined that, at this time, the ethical, legal, and social issues raised by research using human pluripotent stem cells derived from such sources have not received adequate discussion and consideration. Therefore, that research is not eligible for NIH funding.

Q. Will the NIH support research involving the use of cells that have the potential to develop and mature as would a normal human zygote or embryo?

A. The NIH would be prohibited by law from conducting or supporting research using any cells that fall under the definition of an embryo.

New Q added 8/30/00: Will the researchers who already have developed human pluripotent stem cells using private funds, as is allowable under law, be eligible to receive NIH funding? Would NIH consider "grand fathering in" the cells if they do not meet the criteria of the *Guidelines*?

A. If NIH received request to "grandfather in" cells that do not meet the requirement of the Guidelines, it would give due consideration to such a request, however, at present all pluripotent stem cells used in NIH funded research must be compliant with the Guidelines.

New Q added 8/31: If existing stem cell cultures do not meet the criteria of the *Guidelines*, how long will it take scientists to develop new ones?

Informed Consent Questions

Q. From whom must consent for donation of embryos for research be obtained?

A. The *Guidelines* call for informed consent from individual(s) who have sought fertility treatment. Only the individual(s) who were part of the decision to create the embryo for reproductive purposes should have been part of the decision to donate for the derivation of human pluripotent stem cells.

Q. Will Federal funding of this research and the issuing of these *Guidelines* create a " market" for the creation of human embryos for research purposes?

A. The *Guidelines* require investigators to document that the embryos were not created for research purposes. In addition, the *Guidelines* require the informed consent of the donating individuals and that the treating physician and the person deriving the stem cells from human embryos not be one and the same.

Legal Questions

Revised Q29 8/30/00: Is it legal for NIH to conduct research using human pluripotent stem cells? What is the basis for this legal opinion? What sources did NIH consult before reaching this decision?

A Federal law currently restricts the use of Department of Health and Human Services (DHHS) funds for human embryo research. DHHS funds cannot be used for the derivation of stem cells from human embryos. The Congressional restriction, however, does not prohibit funding for research utilizing human pluripotent stem cells because such cells are not embryos. The use of NIH funds for both the derivation and use of stem cells derived from fetal tissue is legal, as long as investigators comply with all local, state and federal law.

Q. What authority does NIH have to dictate requirements for the derivation of stem cells from human embryos when NIH cannot fund derivation of the cells themselves?

These *Guidelines* will govern research proposals in which the investigator is requesting NIH funding for utilizing human pluripotent stem cells derived (without DHHS funding) from human embryos. An investigator will be required to submit an application containing the information referenced in the *Guidelines* in order to be eligible for an award and will have to comply with the conditions imposed upon any grant that is awarded on the basis of that application.

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