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Health - Stem Cell Research

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. email	Holly L. Gwin to Jeffrey Smith. Pager Number (Partial) (1 page)	11/18/1998	P6/b(6)
002. email	Jeffrey M. Smith to Christopher c. Jennings. Pager Number (Partial). (1 page)	11/17/1998	P6/b(6)

COLLECTION:
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Domestic Policy Council
Elena Kagan
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FOLDER TITLE:
Health - Stem Cell Research

2009-1006-F
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RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

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PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

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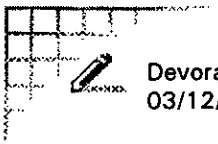
b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Health - stem cell research



Devorah R. Adler
03/12/99 09:40:31 AM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc: Laura Emmett/WHO/EOP
Subject:

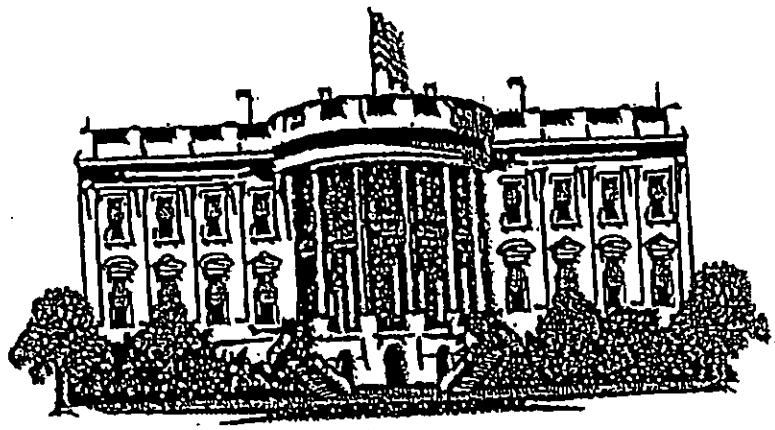
We just found out that Todd Tahrt's (KS) attempt to add a stem cell rider to the appropriations bill was blocked by Porter yesterday -- so Chris thinks that we can put the call to the groups on hold. If you feel differently, let me know.

Thanks -- please call with questions.

Devorah

Health - stem cell research

THE WHITE HOUSE



Domestic Policy Council
224 Old Executive Office Building
Washington, DC 20502
tel. 202-456-5560
fax. 202-456-5557

Facsimle Transmission Cover Sheet

To: ELENA

From: DEVORAH

Fax Number:

Telephone Number:

Pages (including cover):

Comments: Can you please look this over quickly? HHS needs comments - if we have any - this morning so they can release it before the Secretary testifies!

thx. sorry so late.

Devorah.

Deborah:
Not particularly well written. Repeats the charge but not wrong or overly problematic. Please show to quickly review if you have not already.
Thanks.

DRAFT * DRAFT * DRAFT

Response to House Letter

Thank you for your letter dated February 11, 1999, concerning the recent announcement by the Director of the National Institutes of Health (NIH) regarding federal funding for research utilizing human pluripotent stem cells. The recent isolation of human pluripotent stem cells is a powerfully important scientific advance for human biology and medical research. As you know, this research has the potential to lead to great progress in our treatment of debilitating and deadly diseases, our understanding of human development and our ability to develop and test new drugs. Stem cell research is richly promising, yet the prospect of this research raises important ethical and legal issues. Therefore, Dr. Varmus and his colleagues at the National Institutes of Health (NIH) will proceed with great caution to ensure that the highest standards are set before moving forward in this area.

In keeping with the important ethical concerns that must be considered before any federal funds could be committed to research utilizing pluripotent stem cells, the NIH plans to proceed in a careful and deliberate fashion to develop rigorous guidelines. A working group of the Advisory Committee to the Director of NIH will develop guidelines for the conduct of research using pluripotent stem cells and will recommend an oversight mechanism for protocol review. The National Bioethics Advisory Commission is studying these issues and will provide us with advice that -- together with counsel from outside experts, Congress and other interested parties -- will help ensure appropriate oversight.

First and foremost, these guidelines will ensure that any research funded in this area is consistent with the prohibition on federal funding for human embryo research contained in section 511 of the HHS appropriations law. Since this prohibition was first enacted in 1996, the Department of Health and Human Services (HHS) has conscientiously adhered to its strictures. For example, we have included the restriction on the use of funds in the NIH Grants Policy Statement and have issued notices reminding NIH intramural staff and the extramural research community that they must observe the prohibition. When necessary, we have not and will not hesitate to take appropriate enforcement action. I am firmly committed to our continued adherence to the law.

Your letter makes specific inquiries regarding a legal memorandum on this subject from the HHS General Counsel. You suggest that the legal analysis is problematic because it relies on a new definition of human embryo that would undermine the Congressional prohibition. In fact, the memorandum relies on the definition provided in the statute itself. The statute defines human embryo as "any organism ... that is derived ... from one or more human gametes or diploid cells." The legal memorandum, relying on the scientific definition of the word "organism", concludes that the stem cells at issue are not organisms and therefore cannot be considered human embryos under section 511 of the HHS appropriations law.

The prohibition on federal funding for human embryo research bars the expenditure of federal funds for the creation of a human embryo for research purposes or for research in which a human embryo is destroyed, discarded or knowingly subject to greater than minimal risk. You suggest

that this provision should be read to also bar federal funding for research which follows or depends upon the destruction of or injury to a human embryo. The plain language of the statute supports the opinion issued by the General Counsel. The law applies by its terms to research in which "a human embryo or embryos are destroyed, discarded" or subjected to more than minimal risk, and not to research preceding or following such research projects. Moreover, I have been advised that there is nothing in the legislative history to suggest that the provision was intended to prohibit funding for research in which embryos -- organisms -- are not involved.

I have reviewed our Department's position and am reassured that proceeding cautiously with research on existing pluripotent stem cell lines is both legal and appropriate. Further, it will allow the NIH to foster world-class research on stem cells, assure appropriate oversight, and bring together the finest minds and facilities to further medical and scientific advances. Allow me to assure you that the NIH understands and respects the deep convictions of people in the research, academic and religious communities, and in Congress, and intends to seek the advice and comment of those communities as we move ahead. I look forward to working with you to ensure that the legal and ethical issues involved in this extremely promising area of research are addressed.

Health - stem cell research

HUMAN EMBRYONIC STEM CELL RESEARCH
January 19, 1999

Context: *Harold Varmus, Director of NIH, will announce today at a meeting of the President's National Bioethics Advisory Commission that the HHS General Counsel has determined that NIH and other federally funded scientists will be permitted to use human embryonic stem cells for research. The potential biomedical applications for these cells is enormous—any disease or injury that is caused by or results in damaged or dead cells, such as Parkinson's disease, heart disease, diabetes, and burn and spinal cord injuries, theoretically could be cured. The controversy that has surrounded the breakthrough announcement in November about the successful isolation of human embryonic stem cells originates from the fact that, in one of the two privately funded laboratories involved, these stem cells were isolated from human embryos. The embryos had been created during fertility treatments but were not used, and the couples involved willingly donated them for research purposes. Federally funded scientists have been barred from this area of research since FY1996, because of the Congressional ban on the use of federal funds for human embryo research. There have been two Senate hearings on this issue since the announcement, and one of the central questions has been whether or not the ban would also prohibit federally funded research on embryonic stem cells. Today's announcement will resolve that question, and is consistent with the President's December 2, 1994 Executive Order that prohibits the creation of human embryos specifically for research purposes, but does not ban research on embryos created for reproductive reasons and then subsequently donated to science.*

General

§ HHS General Counsel has determined that use of federal funds to support research on human embryonic stem cells does not violate the Congressionally mandated ban on federally funded human embryo research.
§ This decision is consistent with Administration policy on human embryo research.
§ This decision will now allow NIH and other federally funded biomedical researchers to use human embryonic stem cells for research on treating and potentially curing many debilitating diseases and injuries, including Parkinson's, diabetes, heart disease, burns, and spinal cord injury.

Q: What is the significance of this announcement?
A: Human embryonic stem cells hold enormous potential for treating and possibly curing many debilitating diseases and injuries, including Parkinson's, diabetes, heart disease, burns, and spinal cord injury. Today's announcement opens the way for the nation's federally funded biomedical scientists, who lead the world in medical research, to study these cells for ways to turn their potential into reality.

Q: Does this mean that NIH scientists can do human embryo research?

A: No. The ban on using federal funds for human embryo research is still in place, and is not affected by the HHS decision.

Health - stem cell research

Overseeing stem-cell research

Phil. Inq.

By Daniel Perry 1/9/99, A9

It's the kind of medical research news that makes politicians wince and just about guarantees full employment for bioethicists: Three different scientific groups recently have claimed the ability to make living cells that stay young forever and that can be transplanted to any part of the body where they might replace tissues damaged by disease or worn out by aging.

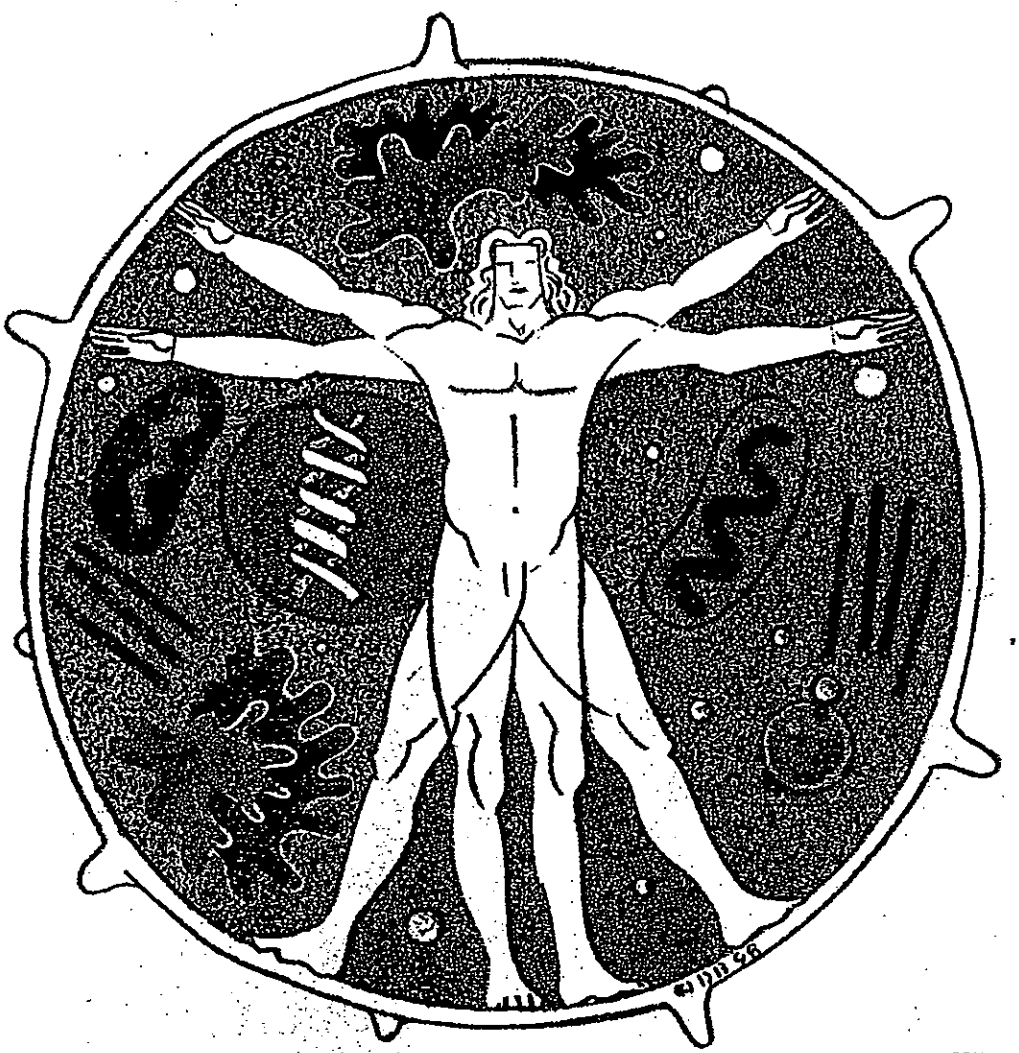
But because these magical cells are initially derived from fertilized human reproductive cells — and, in one case, reportedly from human DNA put into a cow's ovum — this research threatens to inflame a political debate. What the prospect of human cloning did in the last session of Congress, "embryonic stem cells" could do in 1999 and beyond.

That we came perilously close earlier this year to passing the first law in U.S. history to criminalize biomedical research is reason for serious concern. No one who has watched the wreckage wrought by abortion politics of the last 30 years could possibly look favorably on the legislative chamber as the best place to define what constitutes human life or when it begins. Elected officials with little or no scientific training are neither well prepared nor generally comfortable with parsing issues of cell biology.

Most members of Congress would rather not choose sides where passions are aflame with religious and ethical convictions and where a wrong move fixed in legislation could derail biomedical research of enormous value for the future. Still, the danger continues that overzealous lawmakers could ban the very tools of research we will need to head off a rising tide of cancer, Alzheimer's disease and diabetes as the population ages.

During the next 30 years, the population of Americans older than age 65 will double to more than 70 million, and half of that number will be older than 75. Baby boomers take note: After age 50, your chances of being disabled by diseases of aging will double every five to seven years.

In purely economic terms, the cost of age-related diseases is staggering. Costs associated with osteoporosis, stroke, depression, arthritis, Alzheimer's, diabetes, cancer and heart disease approach $600 billion a year. Unless scientists discover better ways to treat, postpone and prevent such disabling conditions, the burden on Medicare and private insurance will be crushing as the baby boom moves into the high-risk years.



D.B. JOHNSON

Rather than flee the controversy, government should take an active role.

Without research breakthroughs, we will be left with the equivalent of very expensive hand-holding for sick older people. In truth, today's drugs and other remedies for aging-related diseases simply are not good enough. Even the better versions of current pharmaceuticals are designed to treat only the symptoms of heart failure, arthritis and cancer, not the root causes. But there are signs of a historic shift in new drug development.

We are likely heading toward a time in which therapies will work by postponing the onset of diseases or preventing them by shutting off their genetic switches. Medicines will be customized to everyone's unique needs and biochemical profile.

Personalized medications would be far more effective in promoting health and far less likely to carry side effects that too often make matters worse, not better, for older people. Human cells themselves will be engineered as therapies with the potential to produce insulin for diabetics or dopamine in the brain for Parkinson's sufferers where their original cells have failed.

This is the real promise of the embryonic stem-cell stories. It will likely take years of further research, and major technical hurdles must be overcome. Millions, if not billions, of dollars will be required to realize the full therapeutic potential. Meanwhile, the first of the 77 million baby boomers will be eligible for Medicare in a dozen years. The federal government should be actively supporting and advancing research using stem cells and other technologies that hold promise for healthier aging.

It is important to note that all the reported stem cell research was carried out in the private sector. Without federal funding and oversight, it is clear the private sector will continue to pursue this research. Rather than enact a ban out of fear of the unknown, Congress should be fully engaged to ensure that research progress is being made within acceptable ethical guidelines.

Daniel Perry is executive director of the Alliance for Aging Research.

Health - stem cell research

cc: Bruce, Chris

February 11, 1999

The Honorable Donna E. Shalala
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Shalala:

Last month, the General Counsel at HHS, Harriet Rabb, issued a memorandum to Dr. Harold Varmus, Director of the National Institutes of Health, supporting the legality of using taxpayer funds for research on stem cells taken from living human embryos. Shortly thereafter, and using the Rabb memo as a basis, Dr. Varmus announced that NIH will reverse current federal policy and begin funding research which relies on the mutilation and destruction of human embryos.

We wish to express to you, in the strongest possible terms, our objection to Ms. Rabb's memo and to Dr. Varmus's decision. Any NIH action to initiate funding of such research would violate both the letter and spirit of the Federal law banning federal support for research in which human embryos are harmed or destroyed.[1] Rather than providing guidance on how best to implement the law that Congress enacted and the President signed, the memorandum appears to be a carefully worded effort to justify transgressing that law.

In her memorandum Ms. Rabb makes significant errors on the way to her conclusion that it would be permissible for NIH to fund research using stem cells harvested from human embryos. We call upon you to correct the General Counsel's interpretation and to reverse Dr. Varmus's decision.

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[1] Since January 1996, Congress has included in the annual Labor, Health and Human Services, Education Appropriations Act a section prohibiting funding for this type of research. Section 511 of the most recently enacted research funding bill, Public Law 105-277, provides (in part) that--

> (a) None of the funds made available in this Act may be used for--
> (1) the creation of a human embryo or embryos for research purposes; or
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

The Honorable Donna E. Shalala

At the start of her analysis, the General Counsel unilaterally narrows the meaning of "research in which a human embryo or embryos are destroyed" and states that it prohibits only direct federal funding of the specific act of destroying the embryo. In this way she limits the scope of the law passed by Congress and signed by the President. While the *act* of destroying or injuring an embryo would certainly be ineligible for Federal funding, the law has a broader application. It also bars the use of tax dollars to fund research which follows or depends upon the destruction of or injury to a human embryo.

Congress could have structured paragraph (2) of subsection (a) of the law like paragraph (1) and simply prohibited the use of funds for the destruction or discarding of human embryos. We did not do that, and by established rules of statutory construction, HHS may not construe the law's provision on "research in which" embryos are destroyed as narrowly as its provision on the creation of embryos.[2] Instead, we prohibited the funding of research projects in which the lethal dissection or harmful manipulation of living human embryos is a necessary prerequisite, including projects where the material used in the experiments is obtained by destruction of an embryo that would not otherwise be done (or not otherwise done in the same way). In congressional testimony, Dr. Varmus has confirmed that it is impossible to obtain stem cells from embryos for these experiments without destroying the embryos.

The Rabb memo also ignores the policy reflected in current law on fetal tissue transplantation research using tissue from intentionally aborted children. While that law is itself open to criticism, it at least bans the use of fetal tissue in federally funded research if abortion was induced for the purpose of providing the tissue. Under current law, federal funds may not be used for fetal tissue transplantation experiments following an abortion if the timing and method of the abortion were altered solely for the purpose of providing usable tissue for research. Yet, in the embryonic stem cell research which NIH proposes to fund, the timing, method and procedures for destroying the embryonic child would be determined solely by the federally funded researcher's need for usable stem cells.

Finally, both Ms. Rabb's memorandum and Dr. Varmus's testimony before a Senate subcommittee present a new definition of "human embryo" that would undermine both the congressional rider on embryo research, and the President's own 1994 directive against using federal funds to create human embryos for research purposes. They now say that an entity is an "embryo"only if one can show that it is capable, if implanted in the womb, of becoming a born "human being." This narrow definition has no support whatsoever in federal law.

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[2]When a law has two parallel clauses, one of which is deliberately written in broader terms than the other, it may not be interpreted to have the same meaning as the narrower clause. See *Russello v. United States*, 464 U.S. 16, 23 (1983), and cases cited therein.

The Honorable Donna E. Shalala

Nevertheless, researchers are already offering to use damaged human embryos in their destructive research, or even to engineer lethal defects in advance into the embryos they create for such research, in order to take advantage of this Administration cover and ignore the congressional and presidential directives altogether.

For more than 20 years, Federal laws and regulations have protected the human embryo and fetus from harmful experimentation at the hands of the Federal government -- regardless of whether the embryo is "perfect" or damaged, wanted or unwanted, intended for abortion or intended for live birth. This area of law has provided a bulwark against government's misuse and exploitation of human beings in the name of medical progress. It would be a travesty for this Administration to attempt to unravel this accepted ethical standard.

We urge you to review this issue carefully, and to put a stop to a proceeding which so clearly does violence to the meaning and intent of Federal law.

Sincerely,

Health - stem cell research

To: Rachel E. Levinson/OSTP/EOP
cc: See the distribution list at the bottom of this message
bcc:
Subject: Re: Stem Cell Meeting

Thanks Rachel: I take it HHS GC has not yet reached a decision on the legal aspects? Also, what is NBAC's plan to address the specific issue Harold is concerned about, i.e., the use of the cell line? Neal

Rachel E. Levinson

Rachel E. Levinson
01/07/99 10:45:50 AM

Record Type: Record

To: Neal Lane/OSTP/EOP

cc: Arthur Bienenstock/OSTP/EOP, Clifford J. Gabriel/OSTP/EOP, jtornow @ worldnet.att.net
Subject: Re: Stem Cell Meeting

In addition to the invitees listed, Harold Varmus and Lana Skirboll will attend the Monday meeting. Lana said that it is her understanding that the purpose of the meeting will be to discuss the roll-out of the HHS opinion on use of human stem cells by federally funded scientists. Harold will address NBAC on Jan. 19 and has made it clear to HHS GC that he wants to be able to say that researchers will be able to use the cells under careful NIH oversight. I think his feeling is that by developing guidelines and a record of responsible use of the cells isolated with private funding, NIH will engender credibility and trust that will allow further steps to be taken eventually toward lifting the ban.

OMB (Dan Mendelson) MAY use the meeting to float a proposal to suggest lifting the ban in the FY 2000 budget request. OSTP's comments to OMB earlier this week supported the proposed language which identified the positive aspects of stem cell research without making a stronger statement regarding the Congressional ban than was stated in the FY 97 and 98 (but not FY99) budgets. Incidentally, Dan Perry's op/ed in today's Post makes a fairly compelling argument in favor of use of stem cells, without addressing the ban directly.

Another related issue is the Senate hearing (Specter/Harkin) scheduled for Jan. 12. Witnesses are Todd Dickinson (PTO) and Maria Freire (NIH) talking about IPR issues related to stem cells on the first panel and a second panel representing patient advocacy groups; a patient with Parkinsons' and a Harvard physician with a child with diabetes. Paul Berg may also be present representing the American Society for Cell Biology. If present, his testimony would argue against legislation and for an advisory committee structure to oversee cloning and other controversial research, along the lines of the Recombinant DNA Advisory Committee, which he helped to found.

Message Copied To: _____

Health - stem cell research

HHS FACT SHEET

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

January 19, 1999

Contact: HHS Press Office
(202) 690-6343

STEM CELL RESEARCH

The Department of Health and Human Services has concluded that current law permits federal funds to be used for research utilizing human pluripotent stem cells. This decision is consistent with existing congressional restrictions on human embryo research and with federal law and regulations governing human fetal tissue research. The National Institutes of Health (NIH) plans to move forward in a careful and deliberate fashion to develop rigorous guidelines that address the special ethical, legal, and moral issues surrounding this research. The NIH will not be funding any research using pluripotent stem cells until guidelines are developed and widely disseminated to the research community and an oversight process is in place.

The Promise of Stem Cell Research

Scientists at the University of Wisconsin and another group of scientists at Johns Hopkins University recently have isolated and successfully cultured human pluripotent stem cells and have grown these cells for prolonged periods in culture dishes. Human pluripotent stem cells have an unlimited capacity to divide, and the ability to turn into most of the cells or tissues in the body.

This exciting advance represents a huge step forward in human biology and has generated tremendous enthusiasm among scientists and the public, particularly patients and their families. 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 pluripotent stem cells can help us:

- Generate cells and tissue that could be used for transplantation. Pluripotent stem cells can be stimulated to develop into specialized cells, which can 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, osteoarthritis and rheumatoid arthritis.

- Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause birth defects and cancer.

- Change the way we develop drugs and test them for safety. Rather than evaluating the safety of candidate drugs in an animal model, the drugs could be initially tested against a human cell line; only the safest candidate drugs would be likely to graduate to animal and then human testing.

Legal Issues

The stem cells produced by the scientists in Wisconsin and Maryland were developed by different methods. The Wisconsin scientists derived the pluripotent stem cells from early-stage embryos donated by people who were undergoing fertility treatment in an in vitro fertilization (IVF) clinic; all of the

individuals gave informed consent for the embryos to be used in research. The scientists at Johns Hopkins University isolated the pluripotent stem cells from non-living fetuses obtained from pregnancies that had been terminated. Neither research project utilized federal funds. Because of the regenerative capacity of pluripotent stem cells, these cells alone could supply numerous other researchers without the need to generate a new line of cells.

Federal law currently prohibits the NIH from funding human embryo research. In light of this legislative ban, the Director of the NIH sought a legal opinion from the DHHS Office of the General Counsel on whether federal funds may be used for research utilizing human pluripotent stem cells.

After a thorough analysis of the law, DHHS concluded that the congressional prohibition on the use of DHHS funds for certain types of embryo research does not apply to research utilizing human pluripotent stem cells because such cells are not an embryo as defined by statute. Moreover, because pluripotent stem cells do not have the capacity to develop into a human being, they cannot be considered human embryos consistent with the commonly accepted or scientific understanding of that term. The legal opinion also clarified that pluripotent stem cells derived from non-living fetuses would fall within the legal definition of human fetal tissue and are, therefore, subject to certain Federal restrictions on the use of such tissue.

Thus, research using pluripotent stem cells derived from human embryos can be funded by DHHS. Research that generates and uses pluripotent stem cells from non-living fetuses can also be supported by DHHS, subject to existing law and regulation.

NIH Support

In view of the tremendous scientific and medical benefits that may result from research using pluripotent stem cells, the NIH plans to fund research using these cells. 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. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of industry and academe.

The NIH understands and respects the compelling ethical, legal, and moral 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. In light of these issues, the NIH plans to move forward in a careful way prior to funding any research utilizing pluripotent stem cells. The NIH will develop and issue guidelines regarding special considerations that must be met in conducting such research, including an assurance that the research is consistent with current federal law governing embryo research. Also, the NIH will convene a special oversight group to review all research grant applications in this area, in addition to the rigorous scientific and programmatic reviews that all NIH-funded research currently undergoes. The NIH has asked the National Bioethics Advisory Board (NBAC) for additional guidance, and those views will be factored into the process of approving research proposals. The NIH will not be funding any research using pluripotent stem cells until guidelines are developed and widely disseminated to the research community and an oversight process is in place.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

The General Counsel
Washington, D.C. 20201

January 15, 1999

TO: Harold Varmus, M.D.
Director, NIH

FROM: Harriet S. Rabb

SUBJECT: Federal Funding for Research Involving Human Pluripotent Stem Cells

The Office of the General Counsel of the U.S. Department of Health and Human Services (HHS) has prepared the following in response to your request for a legal opinion on whether federal funds may be used for research conducted with human pluripotent stem cells derived from embryos created by *in vitro* fertilization or from primordial germ cells isolated from the tissue of non-living fetuses. This inquiry arises from the recently reported research of: (1) Dr. James A. Thomson of the University of Wisconsin-Madison, who isolated pluripotent stem cells from embryos donated for research by persons undergoing fertility treatment[1]; and (2) Dr. Michael Shamblott of the Johns Hopkins University School of Medicine, who derived pluripotent stem cells from primordial germ cells from non-living fetuses.[2] The research described in these two published reports was not funded by HHS.

Summary Answer

The statutory prohibition on the use of funds appropriated to HHS for human embryo research would not apply to research utilizing human pluripotent stem cells because such cells are not a human embryo within the statutory definition. To the extent human pluripotent stem cells are considered human fetal tissue by law, they are subject to the statutory prohibition on sale for valuable consideration, the restrictions on fetal tissue transplantation research that is conducted or funded by HHS, as well as to the federal criminal prohibition on the directed donation of fetal

[1] James A. Thomson et al., Embryonic Stem Cell Lines Derived from Human Blastocysts, Science, vol. 282, November 6, 1998, pp. 1145-1147.

[2] Michael J. Shamblott et al., Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells, 95 Proc. Nat'l. Acad. Sci. USA 13726 (Nov. 1998).

tissue. Research involving human pluripotent stem cells excised from a non-living fetus may be conducted only in accordance with any applicable state or local law. Finally, the Presidential Directive banning federal funding of human cloning would apply to pluripotent stem cells, only if they were to be used for that purpose.

Analysis

I. Prohibition on Federal Funding for Human Embryo Research

In the appropriations provision for the Departments of Labor, Health and Human Services, and Education, and Related Agencies in the Omnibus Consolidated and Emergency Supplemental Appropriations Act, Fiscal Year 1999, Public Law 105-277, section 511 provides that none of the funds made available in that appropriation may be used for:

> (1) the creation of a human embryo or embryos for research purposes; or
> (2) research in which a human embryo or embryos 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)).

The term "human embryo or embryos" is defined in the statute to include "any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Pluripotent stem cells are not a human "organism" as that term is used in the definition of human embryo provided by statute. The term "organism" is not itself defined by law, and the question of what is an organism calls for a science-based answer. According to the McGraw-Hill Dictionary of Scientific and Technical Terms (hereinafter McGraw-Hill), an organism is "[a]n individual constituted to carry out all life functions."[3] Pluripotent stem cells are not organisms

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[3] McGraw-Hill Dictionary of Scientific and Technical Terms 1408 (5th edition 1994). See also N. Campbell, Biology, (4th edition 1996) pp. 8-9, which defines organism as follows:

> While cells are the units of organisms, it is organisms that are the units of life. It's an important distinction. Except for unicellular life, 'cell' does not equal 'organism.' A single-celled organism such as an amoeba is analogous not to one of your cells, but to your whole body. What the amoeba accomplishes with a single cell -- the uptake and processing of nutrients, excretion of wastes, response to environmental stimuli, reproduction, and other functions -- a human or other multicellular organism accomplishes with a division of labor among specialized tissues, organs, and organ systems. Unlike the amoeba, none of your cells could live for long on its own. The organism we recognize as an animal or plant is not a

and do not have the capacity to develop into an organism that could perform all the life functions of a human being -- in this sense they are not even precursors to human organisms.[4] They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin producing cells.

Moreover, a human embryo, as that term is virtually universally understood, has the potential to develop in the normal course of events into a living human being. The scientific definition of embryo, as described in McGraw-Hill, is "[t]he product of conception up to the third month of human pregnancy."[5] Pluripotent stem cells do not have the capacity to develop into a human being, even if transferred to a uterus.[6] Therefore, in addition to falling outside of the legal definition provided by statute, pluripotent stem cells cannot be considered human embryos consistent with the commonly accepted or scientific understanding of that term. Thus, based on

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collection of unicells, but a multicellular cooperative with the emergent properties of 'whole organism.'

[4] At a December 2, 1998, stem cell research hearing before the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Senate Appropriations Committee, Senator Tom Harkin asked five scientists, two bioethicists, and a theologian testifying before the committee if, in their view, stem cells were organisms. All of the experts who responded concluded that human pluripotent stem cells are not organisms. Use of Fetal Tissue in Brain Stem Cell Research: Hearing Before the Subcomm. on Labor, Health and Human Services, and Education of the Senate Appropriations Comm., 105th Cong. (December 2, 1998) available in LEGI-SLATE, Transcript No. 983360015 [hereinafter Stem Cell Hearing] (statement of Dr. Harold Varmus, Director, National Institutes of Health; Dr. John Gearhart, Johns Hopkins University School of Medicine; Dr. James Thomson, Wisconsin Primate Research Center, University of Wisconsin; Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System; and Mr. Richard Doerflinger, Associate Director for Policy Development, Secretariat of Pro-Life Activities, National Conference of Catholic Bishops). One expert, Dr. Eric Meslin, Executive Director of the National Bioethics Advisory Commission, stated that he could not speak on behalf of the Commission because it had not considered the question. Stem Cell Hearing, supra, (statement of Dr. Eric Meslin).

[5] McGraw-Hill Dictionary, supra note 3, at 673.

[6] See Letter from the Chair of the National Bioethics Advisory Commission, to the President of the United States, response to question no. 2, November 20, 1998; National Institutes of Health, Report of the Human Embryo Research Panel, Sept. 1994, p. 26. See also Stem Cell Hearing, supra note 4, (statements of Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; and Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System).

an analysis of the relevant law and scientific facts, federally funded research that utilizes human pluripotent stem cells would not be prohibited by the HHS appropriations law prohibiting human embryo research, because such stem cells are not human embryos.

II. Restrictions on the Use of Human Fetal Tissue

There are a number of potential sources of human pluripotent stem cells; some of these stem cells may fall within the legal definition of human fetal tissue and would, therefore, be subject to federal regulations. Section 498A of the Public Health Service Act specifies that fetal tissue "means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth." 42 U.S.C. 289g-1(g). Some stem cells, for example those derived from the primordial germ cells of non-living fetuses, would be considered human fetal tissue for purposes of Section 498A.

The Public Health Service Act (hereinafter "The Act") contains three relevant provisions governing the use and transfer of human fetal tissue: (1) a criminal prohibition against the sale of human fetal tissue for valuable consideration; (2) restrictions on fetal tissue transplantation research supported by federal funds; and (3) a prohibition on the directed donation of fetal tissue for transplantation. We explore each of these restrictions in turn.

Section 498B(a) of the Act states that it is unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration,[7] if the transfer affects interstate commerce.[8] 42 U.S.C. 289g-2(a). It is common practice for scientists throughout the United States to share research materials through transactions that result in such materials crossing state boundaries. Such exchanges, as well as transactions within the District of Columbia, or exchanges within a state that "affect interstate commerce" would meet the statutory criterion of affecting interstate commerce, but would not fall within the scope of the criminal

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[7] The term "valuable consideration" encompasses both monetary and non-monetary payments. Section 498B (d)(3) provides that the term does not include "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue."

[8] The statute adopts the definition of interstate commerce in section 201(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(b): ". . . commerce between any State or Territory and any place outside thereof, and . . . commerce within the District of Columbia or within any other Territory not organized with a legislative body." The statute does not define what "affects" interstate commerce, but, in interpreting similar language in another criminal statute the Supreme Court found that "affecting interstate commerce" is an expression of Congress' intent to broadly exercise its Commerce Clause power under the Constitution. Scarborough v. United States, 431 U.S. 563, 571-72 (1977).

prohibition unless the scientist providing the materials sought payment in excess of the expenses included in the statutory definition of "valuable consideration."

In addition, the law places some restrictions on federal support for research on the transplantation of fetal tissue. Section 498A of the Act provides that the Secretary may conduct or support research on the "transplantation of fetal tissue for therapeutic purposes," only if certain statutory requirements are met. 42 U.S.C. 289g-1. These requirements include obtaining: (1) the informed consent of the woman donating the tissue; (2) a statement by the attending physician regarding the woman's consent and the method of obtaining the tissue; (3) a statement by the researcher regarding his or her understanding of the source of the tissue, that such information has been conveyed to the donee, and that the researcher has not participated in any decision regarding termination of the pregnancy.

Finally, section 498B(b) of the Act provides that it shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purpose of transplantation into another person if the tissue will be or is obtained pursuant to an induced abortion, and there is a promise to the donor: (1) to transplant the tissue into a person specified by the donor; (2) the tissue will be transplanted into a relative of the donor; or (3) the donee of the tissue has provided valuable consideration for the costs associated with the abortion. 42 U.S.C. 289g-2(b). The Act provides criminal penalties for violation of the prohibition on directed donations.

III. Federal Restrictions on Fetal Research

Federal regulation provides that activities involving cells, tissues, or organs excised from a non-living fetus shall be conducted only in accordance with any applicable state or local law. 45 CFR 46.210, Subpart B. This regulation would apply to certain human pluripotent stem cells, including those derived from the primordial germ cells of non-living fetuses.

IV. Prohibition on Federal Funding for Cloning of Human Beings

In a March 4, 1997, memorandum to the heads of executive departments and agencies, the President directed that no federal funds will be used for the cloning of human beings and that federal funds shall not be allocated for that purpose.[9] There are myriad uses for human pluripotent stem cells that are completely unrelated to cloning. However, to the extent such stem cells were to be used for human cloning, the prohibition on the use of federal funds for that purpose would apply.

[9] Memorandum from the President of the United States to Heads of Executive Departments and Agencies (March 4, 1997).

STEM CELL RESEARCH - TALKING POINTS

- The recent announcements by scientists at universities in Wisconsin and Maryland that they have isolated "pluripotent" human stem cells are among the most exciting scientific advances for human biology and medical research in years. This research has the potential to lead to profound advances in our understanding of human development and disease, our ability to develop and test new drugs, and our ability to treat some of the most debilitating, painful and deadly diseases of mankind.

- Because of the regenerative capacity of pluripotent stem cells, these cells alone could supply numerous other researchers without the need to generate a new line of cells.

- Pluripotent stem cells cannot develop into a human being, but they have the potential to grow into most of the tissues and cells of the human body, such as heart cells, nerve cells, muscle cells, and blood cells. Their versatility provides an incredible range of targets for promising research. They may allow us to more safely test new drugs and therapies. They may help us prevent or repair the ravages of birth defects. And perhaps most importantly, they may help us generate cells and tissue vitally needed for transplantation -- including possible treatments for Parkinson's disease, stroke, spinal cord injury, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis, and a range of diseases from the commonplace to the rare.

- While the private sector has already invested resources in such research, the rich promise of stem cell research makes it imperative that the Federal government play a role in funding and overseeing the conduct of that research. Federal funding will help provide oversight and direction that would be lacking if this research were the sole province of industry and academe.

- The decision to fund stem cell research at NIH is the right decision. As one of the premier medical research entities in the world, the NIH can foster world-class research on stem cells, and bring together the finest minds and facilities to further that research.

- While stem cell research is richly promising, it does raise real moral and ethical concerns. While the stem cells produced by the scientists in Wisconsin and Maryland could never develop into human beings, they were derived through two separate processes. In Wisconsin, the cells were derived from embryos donated by couples undergoing in vitro fertilization procedures. In Maryland, the cells were derived from terminated pregnancies.

- The NIH appreciates the compelling moral, ethical and legal issues surrounding these issues, and will proceed with great caution to ensure that the highest standards are set before research proposals are funded, and that extraordinary measures are taken to insure strict internal and external oversight. The NIH also understands and respects the deep convictions of people in the research, academic and religious communities, and in Congress, and intends to seek the advice and comment of those communities as this research continues.

- Before making the decision to fund stem cell research, the NIH asked for a legal opinion to ensure that any research undertaken was consistent with federal laws and regulations governing fetal tissue research, and consistent with the ban on human embryo research. That carefully considered opinion states that these stem cell lines cannot be considered human embryos under the law, and therefore research using them is legal and appropriate. However, research that *generates* pluripotent stem cells **from embryos** cannot be funded by DHHS. **But, research in which the pluripotent stem cells are derived from non-living human fetuses is allowable, subject to certain restrictions in law and regulation.**

- The NIH has long experience in overseeing ethical standards in medical research, and will of course apply its traditional stringent standards to stem cell research. Over and above those traditional standards, the NIH plans to set out guidelines for research proposals. The NIH will also establish a separate oversight board to review stem cell research. And of course, the NIH has sought the advice of the President's National Bioethics Advisory Commission, and will continue to consult with that commission and other outside experts as questions regarding stem cell research arise. NIH will not be funding any research using pluripotent stem cells until guidelines are **developed and** widely disseminated to the research community and **an oversight** process is in place.

Cloning
(and)
Health - stem cell research

BRITISH POLICY ON HUMAN CLONING
December 9, 1998

Context: *Today's Washington Post reports that a British scientific panel recommended that research into the cloning of human embryos be permitted in Britain. This follows in the wake of the new advances in culturing embryonic stem cells that dominated the news a few weeks ago, and led to a Senate hearing on the topic last week. The same ethical questions that we are facing on this issue, centering on the creation and destruction of embryos for research, are confronting the British. Britain has a limited ban on embryo research at the present, but does allow both privately and publicly funded research on embryos that are less than 14 days old. This is in contrast to US policy, which bans all public sector research on embryos completely. The British panel was careful to stress that reproductive cloning should never be permitted, but that therapeutic cloning (the production of a cloned embryo for the purpose of isolating stem cells to create replacement tissues) held such significant potential benefits that "it would not be right to rule out limited research" on human cloning techniques.*

General

A British advisory panel recommended that research be permitted into the cloning of human embryos for *therapeutic purposes only.* They recommended that reproductive cloning never be permitted.

The opening paragraph of the article suggests allowing this research could lead to a "genetic spare parts industry for damaged human bodies." This is an inflammatory and inaccurate phrase that infers that cloned human beings would be created as a source of organs. The panel limited its recommendation to permit research on the cloning of human embryos for the production of embryonic stem cells, and specifically stated that the cloned embryos not be used to reproduce a human being.

The article does not indicate how the British government will use the recommendation of the scientific advisory panel for developing policy.

Q. What do you think about the panel's recommendations?

A. The British scientific advisory panel addressed the same questions that the President's National Bioethics Advisory Commission is now considering. We believe that these are important issues from both a biomedical and ethical standpoint that deserve careful consideration, both here and in other nations throughout the world.

Q. Will research on cloning human embryos lead to creating a "genetic spare parts industry?"

A. That is a misleading description of the potential outcome of research on therapeutic cloning. The British panel recommended that research on cloning human embryos be permitted, as a means to generate stem cells that would then be used to generate replacement tissues. They clearly stated their opposition to the cloning of a human being as a source of organs.

Health-stem cell research

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To Elena K	From Jeff S.
Co./Dept.	Co.
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Fax # 6-2878	Fax #

Washington Fax
December 4, 1998

Senate hearing focuses on whether the current embryo research ban extends to any or all stem cell research

Delving into such matters as what constitutes an organism and whether a funding ban on one type of research applies to its derivatives, a Senate panel Wednesday waded into the legal and ethical thicket surrounding the potential of primitive cells extracted from human embryos and fetuses to grow tissue for damaged hearts, treat Parkinson's disease and provide a range of other therapies and scientific insights.

The consensus from most of the scientists appearing before the Senate Appropriations Labor, Health and Human Services, Education and Related Agencies subcommittee (L/HHS) was that the scientific opportunities and ethical concerns surrounding research with stem cells demand federal support and oversight. Harold Varmus, the director of the National Institutes of Health (NIH), stopped short of joining his colleagues and calling for public funding, as the matter is still under review at his agency. But he spoke glowingly of the potential benefits of work with stem cells, which currently is being carried out in the private sector or by scientists who have other sources of funds.

"The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough," he said. "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."

Varmus and the other scientists testifying--including the two investigators responsible for the recent breakthroughs in isolating stem cells--John Gearhart of Johns Hopkins and James Thomson of the University of Wisconsin--discussed the issue with two Senators who are particularly sympathetic to their concerns: Sen. Arlen Specter, R-PA, the chair of the panel, and Sen. Tom Harkin, D-IA, the subcommittee's highest ranking Democrat.

Specter said he is intrigued by the medical potential of stem cells, but wants to proceed cautiously on the issue of public funding, given the uncertainty about whether a federal ban on funding research with human embryos precludes supporting work with their derivatives, in this case stem cells.

"I think it's fuzzy, and I believe we have to do some work on it," he said in an interview. "This is a start on a very complex legal issue. I don't believe when the (embryo research ban) was enacted it was in the context of seeing the tremendous application. And now we need to take a much closer look at it and refine it to match the scientific research. I don't think you can rush to judgement on it. This is obviously on the cutting edge."

Harkin, however, concluded that because stem cells do not appear to have the potential to become human life, stem cell research is not covered by the embryo ban and should receive immediate federal support. "The research conducted by the distinguished scientists sitting before us today holds such hope, such potential for millions of Americans who are sick and in pain, that I believe it is morally wrong for us to prevent or delay our world-class scientists from building on this progress," he said in his opening statement. "As long as the research is conducted in an ethically validated manner, it should be allowed to go forward, and it should receive federal support."

Harkin made a point of quizzing the scientists about the distinction between an embryo or a fetus, which he said meet the legal definition of organism, and a stem cell, which he

said--quoting from a dictionary--does not. He contended that the federal ban on embryo research is intended solely to prevent research with organisms that could potentially become a human life.

All the scientists agreed that stem cells are not organisms, including Varmus. But Varmus said that despite his scientific opinion that stem cells are not organisms, he and other government officials are still "struggling" with the legal issues involved in making such a determination in order to "be sure that any actions we take are in compliance with existing law." He hopes that the administration--which has sought assistance on the matter from the National Bioethics Advisory Commission (NBAC)--will complete its review by the end of the year, he said.

The Clinton administration and Congress have variably sought to block federal support for research involving human embryos. In 1994 an NIH panel recommended that embryo research receive support as long it involves "spare" embryos; that is, embryos originally created through in vitro fertilization that have been deemed unsuitable for transplantation to the womb and donated to science.

President Clinton rejected the recommendation, and Congress has since included a "rider" to annual NIH appropriations bills forbidding expenditures in this area.

The question confronting Congress and NIH is whether the ban on embryo research precludes funding work with stem cells that have been cultured in a laboratory. Some scientists argue that even though their lineage may be ultimately traceable to the forbidden embryo, once isolated, stem cells appear to be capable of infinite propagation, and thus can end up being many generations removed from an embryo.

Richard Doerflinger, testifying on behalf of the National Conference of Catholic Bishops' Committee on Pro-Life Activities, said that one can't separate stem cells from their origins. He noted that stem cells extracted from embryos "clearly involve the creation and destruction of human embryos, which are organisms."

"One must refer here to the principles rather than to the exact letter of the law," he said. "Human embryos are destroyed precisely to obtain this tissue, and the timing and manner of destruction are tailored to obtaining this kind of tissue."

But further complicating the issue is the fact that some types of stem cells can be obtained from fetal tissue, as was the case in the stem cell isolation accomplished by Gearhart. And as long the investigator has no connection with the abortion that provides the tissue source, the work can be publicly funded (though Gearhart, while adhering to such guidelines, worked without public funds). Specter observed that there is a "curious dichotomy or inconsistency when federal funds may be used for fetal tissue research but not for human embryo research."

In other words, not only would research with stem cells obtained from aborted fetuses appear to qualify for public funding, so would the work with the fetuses themselves.

Varmus said in an interview that it is a "good question" when asked whether NIH should begin by supporting stem cell work where there is a clear legal path, i.e., funding research with cells extracted from aborted fetuses. But he said his agency would rather formulate a policy that would address all types of stem cell research--including work involving cells isolated from embryos or other means--rather than develop policy piecemeal.

For example, one of the scientists testifying Wednesday was Michael West, head of Advanced Cell Technology, which claims to have isolated human stem cells through a technique that involves fusing human tissue with portions of a cow's egg. While the work reportedly occurred several years ago, and has not been replicated or subjected to peer review, it has nonetheless complicated federal efforts to articulate a policy on stem cell

research.

Still, despite these dizzying details, what seemed to dominate Wednesday's discussions is the medical advances that stem cells could offer. While the cells have various stages of development that can narrow their potential uses, their largely "undifferentiated" state has made their isolation a prized biological achievement, given the evolving ability of medical scientists to direct such cells into becoming specific types of tissue that could perform an array of regenerative functions.

This potential has prompted a range of interests to come out this week in support of federal funding for stem cell research. For example, more than 50 disease advocates and scientific societies, representing such concerns as juvenile diabetes, blindness, Parkinson's, Down syndrome, cystic fibrosis, and cancer--sent a letter to members of Congress urging them to support federal funding for stem cell research. And the testimony at the hearing only served to re-enforce their enthusiasm for the curative powers of stem cells.

"Many diseases, such as juvenile onset diabetes mellitus and Parkinson's disease, result from the death or dysfunction of just one or a few cell types, and the replacement of those cells by transplantation could offer lifelong treatment," said Thomson, who has already grown heart tissue from stem cells he isolated from human embryos.

Thomson said heart tissue could be of immediate benefit. And Gearhart, who has coaxed stem cells into becoming neurons, predicted that within "several years," stem cells could be used to develop a treatment for Parkinson's.

Thomas Okarma, vice president for research at Geron Corporation, the company that has licensed Thomson and Gearhart's discoveries, said stem cells could also provide blood forming cells to aid cancer patients, insulin producing cells for people with diabetes and cells to line the inside of blood vessels for victims of atherosclerosis.

While there will be some applications likely to emerge absent federal support, Thomson asserted that the "number of discoveries will increase exponentially" if NIH begins funding stem cells research, particularly because NIH-funded investigators will look more closely at some of the basic science questions involved, while industry tends to focus more on immediate applications.

For Arthur Caplan, director of the Center of Bioethics at the University of Pennsylvania Health System, the moral concerns surrounding stem cell research versus its potential benefits are indicative of the kind of trade-offs that are increasingly common in a world of science, where new knowledge has made it difficult to resolve such moral issues as what constitutes life.

"I don't think we are in the realm of absolutes," he said. "I think we need judgement. I think we need virtue. That's why we need public funding, and public accountability to make the right trade-offs."

--Matthew Davis

Health - stem cell research

Total Pages: 9

LRM ID: RJP345

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

URGENT

Monday, November 30, 1998

LEGISLATIVE REFERRAL MEMORANDUM

TO: Legislative Liaison Officer - See Distribution below

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

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

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

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

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

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

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

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)**

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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:** _____

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DRAFT

Statement of

HAROLD VARMUS, M. D.

Director

National Institutes of Health

DECEMBER 2, 1998

DRAFT

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

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

What Are Stem Cells?

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

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

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

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

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

Potential Applications of Pluripotent Stem Cells

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

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

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

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

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

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

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

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

How Are Pluripotent Stem Cells Produced?

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

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about today builds on this important basic animal research.

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

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

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

The Role of the Federal Government

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

DRAFT

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.

Health - stem cell research

National Bioethics Advisory Commission

6100 Executive Blvd
Suite 5B01
Rockville, MD
20892-7508

Telephone
301-402-4242
Facsimile
301-480-6900
Website
www.bioethics.gov

November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

As a framework for our initial discussion, we found it helpful to consider three questions:

1. ***Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?***

At this time, there is insufficient scientific evidence to answer this question. What little evidence exists, based on other fusions of non-human eggs with non-human cells from a different species, suggests that a pregnancy cannot be maintained. If it were possible, however, for a child to develop from these fused cells, then profound ethical issues would be raised. An attempt to develop a child from these fused cells should not be permitted.

This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

2. ***Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?***

The common understanding of a human embryo includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being. At this time, however, there is insufficient scientific evidence to be able to say whether the combining of a human cell and the egg of a non-human animal results in an embryo in this sense. In our opinion, if this combination does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human biological material.

It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. ***If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?***

If this line of research does not give rise to human embryos, we do not believe that totally new ethical issues arise. We note that scientists routinely conduct non-controversial and highly beneficial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, lusulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro

Harold T. Shapiro
Chair

Bruce -

Did you get hard copies?

E.

Health-stem cell research

November 13, 1998

MEMORANDUM TO THE PRESIDENT

FROM: Bruce Reed and Neal Lane

SUBJECT: Attached letter

Attached is a letter to Dr. Harold Shapiro, the Chair of your Bioethics Advisory Commission, requesting that the Commission consider the ethical issues raised by a recent experiment involving the creation of an embryonic cell that is part human and part cow. The letter also asks the Commission to review issues related to other kinds of cutting edge stem cell research that have significant medical potential.

The letter is designed to make clear your serious ethical concerns about experiments that mingle human and non-human species. At the same time, the letter is intended to distinguish this very troubling research from other stem cell research, involving purely human material, that may have significant medical benefits.

We would like to get this letter to Dr. Shapiro in time for the Commission's next meeting, which will take place in Miami on Tuesday. If you approve, we will leak the letter to the *New York Times* for this Sunday's edition.

Health-stem cell research

November 14, 1998

Dr. Harold Shapiro
Chair, National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

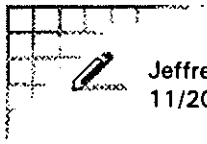
This past week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting the National Bioethics Advisory Commission to consider the implications of such research at its meeting next week, and to report back to me immediately thereafter.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting the Commission to undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Health - stem cell research



Jeffrey M. Smith
11/20/98 05:05:45 PM

Record Type: Record

To: Joseph P. Lockhart/WHO/EOP, Barry J. Toiv/WHO/EOP, Nanda Chitre/WHO/EOP, Amy Weiss/WHO/EOP

cc: See the distribution list at the bottom of this message
Subject: NBAC response

MEMO TO PRESS OFFICE:

OSTP and DPC (Chris Jennings 6-5560) would like your assistance in putting this out as promptly as possible. Harold Shapiro's letter (Chris: this is the final edited version with the words "at this time" omitted) is pasted below and should be the main focus of the release.

THE WHITE HOUSE
Office of the Press Secretary

For Immediate Release **November 20, 1998**

Ethics Panel Echoes President's Views on Part Human/Part Cow Hybrid Cells

Today the National Bioethics Advisory Commission (NBAC) advised the President in a letter that they share his view that the recently reported creation of a part human and part cow embryonic stem cell "raises important ethical and potentially controversial issues that need to be considered..."

In a letter to NBAC last week, the President said that he was "deeply troubled by this news of experiments involving the mingling of human and non-human species" and requested that the Commission consider the ethical implications at their meeting in Miami this week.

The Commission further concluded that any attempt to develop a child from such hybrid cells raises the most profound ethical issues and should not be permitted.

The Commission will also address ethical, medical, and legal issues associated with human stem cell research in a later report.

The full text of the National Bioethics Advisory Commission's letter follows:

Health - stem cell research

THE WHITE HOUSE
WASHINGTON
November 23, 1998

P. I to Bruce

INFORMATION

MEMORANDUM FOR THE PRESIDENT

FROM: NEAL LANE Neal
BRUCE REED

SUBJECT: NBAC response concerning human cell/cow egg fusions

Dr. Harold Shapiro, Chair of your National Bioethics Advisory Commission (NBAC), sent you a letter on November 21 in response to your request that the Commission review the ethical, medical and legal concerns associated with fusing human cells to cow eggs. NBAC agrees with your view that this kind of research evokes serious concerns. The main points of the letter are:

- The ethical ramifications of these experiments depend heavily on whether or not the hybrid cell can become an embryo or support the development of a child.

- Because there is not yet enough scientific evidence to answer that question, NBAC discussed the ethical issues associated with three different possibilities:

  - NBAC agreed with you that any attempt to develop a **child** from these hybrid cells would raise the most profound ethical issues and should not be permitted.

  - If the hybrid cells have the capacity to develop into an **embryo**, the ethical issues that surround the creation of an embryo by any other means also apply here, and are complicated rather than simplified by the presence of non-human genetic material.

  - If the hybrid cell does not give rise to an embryo or support the development of a child, then its creation is no more controversial than other molecular engineering procedures.

Harold Varmus will be providing testimony at a Senate hearing on embryonic stem cell research, to be held on December 1 or 2. OSTP, DPC, and HHS are working together to plan a strategy for addressing this issue with Congress in the coming months.

Attachments

cc: Vice President
Chief of Staff

NATIONAL BIOETHICS ADVISORY COMMISSION

6100 Executive Blvd
Suite 5B01
Rockville, MD
20892-7508

Telephone
301-402-4242
Facsimile
301-480-6900
Website
www.bioethics.gov

November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

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This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

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It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

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We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro

Harold T. Shapiro
Chair

THE WHITE HOUSE

WASHINGTON

November 14, 1998

Dr. Harold Shapiro
Chair
National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week, and to report back to me as soon as possible.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting that the Commission undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Bill Clinton

The New York Times
THURSDAY, NOVEMBER 12, 1998

Researchers Claim Embryonic Cell Mix Of Human and Cow

By NICHOLAS WADE

Venturing deep into uncharted realms of ethics and medicine, a small biotechnology company said yesterday that its scientists had for the first time made human cells revert to the primordial, embryonic state from which all other cells develop, by fusing them with cow eggs and creating a hybrid cell.

The research comes from biologists who are well known in their field but has yet to be confirmed or published in a scientific journal. Their company, Advanced Cell Technology of Worcester, Mass., said the method could eventually be used to grow replacement body tissues of any kind from a patient's cells, sidestepping the increasing scarcity of organs available for transplant and the problems of immune rejection.

The technique is likely to concern and perplex ethicists because it would involve the creation of an embryonic cell that is part human and part cow, consisting of a human cell's nucleus in a cow egg whose own nucleus had been removed. The company said the hybrid cell quickly became more humanlike as the human nucleus took control and displaced cow proteins with human proteins. Creation of the embryonic cells is an important component of a strategy that in principle offers high medical benefits if it can overcome the high barrier to public acceptance.

The technique would involve creating an embryo of uncertain moral status, and one that crosses the barrier between humans and other species. Even though a hybrid would be in the form of cells, not a whole organism, the concept of half-human creatures arouses deep-seated anxiety, as is evident from the unfriendly powers ascribed to werewolves, centaurs, mermaids, Minotaurs and other characters of myth and folklore.

"Many people are going to be horrified by this scenario, others will say 'So what?' " said Thomas Murray, director of the center for biomedical ethics at Case Western Reserve University in Cleveland and a member of the National Bioethics Advisory Commission. "This is the sort of thing that makes me very uncomfortable," Dr. Murray said. "I think we are likely to get a very powerful reaction to it, and I would like for all of us to have a breathing space here to articulate our moral concerns."

Another serious uncertainty is the preliminary nature of Advanced Cell Technology's work. No article has yet been submitted for peer review and publication in a scientific journal, an essential touchstone of credibility. Scientists asked about the company's work said they would require much more proof before believing that human embryonic stem-like cells had been created as the company contends, and some were skeptical that the technique would work.

Announcement Tests the Waters

The company said yesterday that it had performed the work with hybrid cells two years ago. Dr. Michael D. West, Advanced Cell Technology's chief executive, said that he was announcing the work to test its public acceptability. He said the company, which is privately held, was not planning to go public or raise money now but needed to decide whether to commit money to development of the technique.

Some scientists praised Dr. West's decision to make his work public but others were critical, saying he has invited a possibly fraught public debate on a slender basis of fact.

Dr. West is the founder of Geron, a biotechnology company in Menlo Park, Calif., that has had two spectacular successes this year in research on aging. In January it developed a method for "immortalizing" human cells grown in the laboratory by making them leap the supposedly immutable barrier at which cells usually lapse into senescence. Last week two university teams sponsored by Geron said they had isolated and cultivated human embryonic stem cells, the all-purpose cells from which the fetus develops. Dr. West laid the foundations for these developments by sponsoring leading scientists in the two fields.

Researcher Uses His Own Cells

Advanced Cell Technology, which Dr. West joined in October, has focused on cloning and genetically improving cows, a technology developed by James M. Robl and colleagues at the University of Massachusetts at Amherst. Dr. West said he hoped to use the technology to further the idea on which he founded Geron, that of delving into the mystery of human aging and sidestepping some of its processes.

The work with human cells was performed in 1996 by Jose Cibelli, a colleague of Dr. Robl's at the University of Massachusetts. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Dr. Cibelli fused each one with a cow egg whose own nucleus and DNA had been removed. Most failed to thrive but one embryo grew and divided five times, generating cells resembling embryonic stem cells. Dr. Cibelli and Dr. West say the method could be made more efficient with present technology. They use cow eggs because these are far cheaper and more available than human eggs and raise no ethical problems.

Considering this work was sufficient to describe an invention, Dr. Robl and Dr. Cibelli filed a patent application and then set the research aside to focus on the more immediately practical field of cow cloning, they said. Only two others beside himself and Dr. Robl knew what had been done, Dr. Cibelli said. The patent has not yet been issued but Dr. West said he was confident of receiving "important intellectual prop-

erty" in the field. He said he is making the hybrid cell technique public now "because I want to be very open and level with everyone. We need to get the ethicists to talk about it so as to encourage a rational response to these new technologies."

Dr. Cibelli said he regarded any embryos obtained in this way as "not a separate individual, just a de-differentiated cell from a patient." Differentiation is the process whereby the all-purpose cells of the very early embryo, known as human embryonic stem cells, become committed to their roles as the various specialized tissues of the body. The process is irreversible in nature, but egg cells apparently have the ability to de-differentiate, or reset to default mode, the settings in a specialized cell's nucleus. This is presumably what happened in the experiment reported this July when mice were cloned by transferring the nucleus of an adult mouse cell into another mouse's egg cell.

Dr. Cibelli, who trained as a veterinarian in Argentina, said he and his colleagues "were the first to de-differentiate a human cell by nuclear transfer." Asked if he was concerned about destroying, in principle, potential twins of himself, he said: "I never thought about it, it's a good question. But if you use your own cells to treat a disease you may have, you are not taking cells from another person selfishly."

Dr. West and Dr. Cibelli said they had no intent of transferring the embryos to a uterus, a step considered unethical and unsafe: the embryos would be created solely for the purpose of tissue culture. "Any technology can be abused, but once the public understands how these cells can be used to treat any disease caused by loss or malfunction of cells, from Parkinson's to diabetes to heart disease, the concerns will be overshadowed," Dr. West said.

Lack of Evidence Raises Doubts

Whether Dr. West's prediction will be borne out depends on two major sets of factors, the scientific validity of the proposed method and the ethical and legal questions that related work has already raised.

From discussions with scientists, ethicists and lawyers in the past few days, these concerns have emerged.

Scientists are particularly critical of the lack of supporting evidence accompanying Advanced Cell Technology's announcement, saying in essence the claim could be true but there is no compelling reason to accept it. Even if the claim is valid, biologists note a serious uncertainty relating to an important component of the cells known as the mitochondria, which produce the energy the cell needs and are, in essence, its batteries. If the bovine mitochondria should prove incompatible with their humanized environment, the cells will not be viable.

Ethicists said the mixing of species was likely to trouble the public severely, at least at first. Lawyers who specialize in issues of human reproduction note that the moral and legal status of the human embryo is undecided in American law, a fact pointed up by the isolation of the human embryonic stem cells announced last week. The new entity adds further complexity.

If Advanced Cell Technology can produce viable hybrid cells, they would offer a new route to growing new tissues for transplant. This is the same goal held by the scientists who announced last week that they had grown human embryonic stem cells in the laboratory. It is widely accepted in principle that embryonic stem cells can be directed to develop into any desired tissue, with enormous potential for medicine, though this has yet to be achieved in practice.

Dr. West said the advantage of the Advanced Cell Technology method is that embryonic cells derived from the patient being treated would generate entirely compatible tissues. The two methods reported last week, by Dr. James A. Thomson of the University of Wisconsin and Dr. John Gearhart of the Johns Hopkins University, derive stem cells from human embryos or fetuses. Tissues made from these cells would be incompatible with the patient, a problem that has not been resolved.

In support of its claim, Advanced Cell Technology supplied a patent application and a photograph taken of its embryonic cells under a microscope. The patent application describes how the cells are made but provides no proof that they possess the properties to be expected of human embryonic stem cells. Dr. Robl said his laboratory was not set up to perform the required tests at the time the hybrid cells were made.

Shown the photograph of the purported hybrid cells, Dr. John Gearhart of Johns Hopkins, author of one of the two methods reported last week, said that "they certainly could be embryonic stem cells" but that no scientific journal would publish the result without further proof. "It's not that I don't believe this biologically, I just think they could have given a little bit more assurance as to what was done here."

Dr. Roger Pedersen of the University of California, San Francisco, who also works on human embryonic stem cells, said he doubted any hybrid cells would last long enough to develop into useful tissue because of their cow-derived mitochondria. The mitochondria of chimpanzees and gorillas work well enough in human cells but those of primate species that diverged more than 10 million years ago from the human line, do not work.

Because cows and humans last shared an ancestor so long ago, cow mitochondria are very unlikely to work well with a human nucleus, in Dr. Pedersen's view, and as most of the mitochondria in the hybrid cells are contributed by the cow egg, the cells would probably not remain viable for long. "It's hard to say this is a total sham, but I smell a sham here," he said.

Citing the same data, Dr. Gearhart said the mitochondria in the hybrid cell had clearly carried it through its first few divisions but might not sustain it in further development, unless the few human mitochondria that were also present somehow took over.

Dr. Pedersen said Advanced Cell Technology should be held to a high standard of proof "because of what the implications are for upsetting people unnecessarily — if you cry fire in a crowded auditorium you may be liable if it's a false alarm."

New Frontiers For Medical Ethics

The human embryonic stem cells announced last week have already pushed against the frontiers of ethical acceptance. Experts in biomedical ethics say the public is likely to be alarmed by the new technique, particularly because of the mingling of species. Dr. Murray of Case Western Reserve University in Cleveland said that the hybrid embryo "escapes our usual categories." When biologists first learned to transfer genes from one species to another, "The idea of human-animal hybrids was often raised as the kind of monstrosity that no morally perceptive person would ever create," he said.

"Even if it's only to create tissue, the minute you start mixing species you raise all kinds of red flags in people's minds," said Barnie Steinbock, a moral philosopher at the State University of New York in Albany. But she noted that pig valves are now seen as acceptable replacements in human hearts.

Rebecca Dresser, a law professor at Washington University in St. Louis, noted, as did several biologists, that distinctions between humans and other animals are less clear in nature than they are in people's minds. "Biologically a lot of this research is showing us similarities and the upshot in a hundred years may be that the lines between humans and nonhumans will be viewed as a little bit grayer," Professor Dresser said.

A perplexing feature of the hybrid embryo would be that it would start mostly bovine, then become mostly yet not entirely human. But some legal experts have no doubt that any hybrid should be regarded from the start as a human embryo. "It doesn't matter that the mitochondria come from a cow, it also has human mitochondria and so has all the potentials of a human embryo," said Lori Andrews, a professor at the Chicago-Kent College of Law in Chicago.

"Once it's gone through that first division it has gone from being a somatic cell to a thing with potential life," Dr. Andrews said, referring by somatic to the ordinary specialized cells of the human body. If transferred to a woman's uterus the embryos might or might not come to term, "but under state laws it doesn't matter whether the fetus is going to be born or not — it doesn't make them less human."

The human body consists of 100 billion cells. Should embryos created from them by the cow egg method be regarded as having special status when they can be made so easily and plentifully? Dr. Andrews said that human embryos are not so hard to make the usual way, and the fact that an embryo is easily made, by whatever means, is irrelevant to arguments about its status.

The moral status of the human embryo "is not clearly established in U.S. law," Dr. Dresser said. The embryo can be regarded as mere property, as a person, or as something in between but deserving of special respect. Congress, in banning the use of Federal money for research on human embryos, has favored the view that they are in the category of people. But in custody battles over fertilized embryos, courts have favored the special respect status. Dr. Dresser said the hybrid cells could be seen as between the property and special respect status.

The company said the hybrid cells were made by Dr. Cibelli in Dr. Robl's laboratory in the University of Massachusetts at Amherst. Michael Weinberg, executive secretary of the university's human subjects committee, said the experiment was given administrative approval, without review by the committee or major discussion. Dr. Cibelli was using his own cells, not experimenting on other people, and self-experimentation does not require special consent. "If someone wants to inoculate themselves they can do that," Dr. Weinberg said.

The New York Times
THURSDAY, NOVEMBER 12, 1998

2/2

November 18, 1998

Human-Cow Hybrid Cells Are Topic of Ethics Panel

Forum

- Join a Discussion on Beyond Dolly: The Future of Cloning

By NICHOLAS WADE

At the request of President Clinton, the ethical implications of creating hybrid human-cow cells were discussed by the National Bioethics Advisory Commission at its meeting Tuesday in Miami, but at least in the public portion of their discussion, none of the commissioners voiced concern about the creation of the hybrid cells.

Clinton requested the discussion last week in a letter to the commission's chairman, Dr. Harold Shapiro of Princeton University. Clinton said he was "deeply troubled" by news that Advanced Cell Technology, a small biotechnology company in Worcester, Mass., had created the hybrid cells. The company proposes to use the technique to take any body cell from a patient, return it to its embryonic form and use it to grow any of a variety of body tissues for possible transplant back into the patient.

One advantage of the technique is that the patient would receive tissues made from his own cells. Another is that no cells would be taken from human embryos or fetuses.

Noting that scientists had been fusing together cells of different origin for years, Dr. David R. Cox of Stanford University, a member of the commission, said, "We should tell the President there is nothing new in cells fused from different eggs."

The hybrid cow-human cells consist of the nucleus of a human cell inserted into a cow egg whose own nucleus has been removed. Factors in the cow egg are thought to make the human cell nucleus revert to its embryonic form. Because the proteins of a cell turn over rapidly, the cow proteins are expected to be rapidly replaced by human proteins. The mitochondria of the cell, however, are likely to remain cowlike, giving rise at least initially to cells that are not wholly

human.

An outside expert who spoke to the commission by telephone, Ralph Brinster, a physiologist at the University of Pennsylvania, said of the cow-human hybrid cell, "Most scientists would not regard it as a chimera." Chimeras are animals made from the cells of two different individuals by injecting the embryonic cells of one into the embryo of another.

Making human chimeras is widely regarded as unethical.

Dr. Michael West, the president of Advanced Cell Technology, attended the commission's meeting and was invited speak. In response to questions, he said he did not believe the cells formed in his procedure, called embryonic stem cells, were capable of forming a fetus if transferred to a uterus, something he said he had no intention of doing.

Asked how he would prevent the technique from being misused, such as in cloning a person, he suggested that the cloning of humans should be made a crime.

The commission members said they would draft a reply to Clinton.

Ethics Panel Is Guarded About Hybrid Of Cow Cells

By NICHOLAS WADE

Struggling to respond to President Clinton's request for immediate advice on the hybrid cow-human cell announced earlier this month, the National Bioethics Advisory Commission has delivered a guarded and somewhat tentative reply, based on the few facts available to it.

The chairman of the commission, Dr. Harold T. Shapiro, the president of Princeton University, said in a letter to Mr. Clinton that the news raised "concerns about crossing species boundaries and exercising excessive control over nature."

The proposed use of the hybrid cells to grow human tissues for transplant into a patient would or would not raise new ethical issues, depending on the nature of the cells, Dr. Shapiro said.

The cells are obtained by fusing a human skin or blood cell with a cow egg whose own nucleus has been removed. The cow egg is thought to make the nucleus of the human cell revert to the embryonic state. The human nucleus then takes over control of the cell, displacing most of the cow proteins with human proteins, and the cell divides into a cluster of embryonic stemlike cells, said Dr. Michael West, president of Advanced Cell Technology, who announced the technique earlier this month.

As embryonic stem cells have the potential to develop into any tissue of the body, Dr. West's company hopes to grow whatever replacement tissues a patient might need from his or her own cells.

Dr. Shapiro's letter pointed to the ambiguous nature of the cells apparently created in the technique. If the embryonic cells that result from the human cell-cow egg fusion are capable of developing into a fetus when transferred to a uterus, then they raise the same "important ethical concerns" as any other research on human embryos.

But if the embryonic cells are not capable of developing into an embryo, then "we do not believe that totally new ethical issues arise," Dr. Shapiro said.

His letter implies that the only issue raised in this case would be that of mingling human and animal cells, noting that this is routinely done for certain medical purposes.

The ability of the embryonic cells to grow into an infant cannot at present be determined. The original experiments were taken only to a very preliminary stage, and no scientific tests were performed on the cells that resulted.

Other experts said they would need more evidence to know if human embryonic, stemlike cells had indeed been produced, as the company asserted, although one expert, Dr. John Gearhart of Johns Hopkins University, said when shown a photograph of the cells that they could be embryonic stem cells.

Dr. West said previously that his company had no intention of transferring the embryonic cells created in this way to a person's womb and that it would be wrong to do so. Dr. Shapiro said the commission also held this view. Thus, it seems unlikely that the potential of the cells to become a person will be tested directly.

In his letter to the commission a week ago, Mr. Clinton said he was "deeply troubled" by news of the cow-human hybrid cells. In interviews, several commission members expressed a somewhat lesser level of alarm while saying they understood the reasons for the President's concerns.

Dr. Carol W. Greider, a biologist at Johns Hopkins, said that the thought that someone might transfer to a uterus the embryonic cells created by the hybrid technique was deeply troubling, but that she had fewer problems with the company's stated purpose of making transplantable tissues.

"I think there are some ethical issues there but they are much less worrisome," Dr. Greider said.

The commission plans in a later report to address a second issue that Mr. Clinton raised, the ethical problems and medical benefits of research on human embryonic stem cells derived from human tissue. Earlier this month two groups of university scientists isolated embryonic stem cells from embryos and from aborted fetuses, the first time that these primordial cells had cultured in the laboratory.

The company that sponsored the research, the Geron Corporation of Menlo Park, Calif., also plans to use the cells to grow transplantable tissues.

NYT SATURDAY, NOVEMBER 21, 1998

Ethics and Embryos

THE PRESIDENT has asked the National Bioethics Advisory Panel to take a careful look at recent breakthroughs in embryo research. The request follows reports that two research labs have succeeded in producing human embryonic stem cells—the primitive "super cells" that can develop into any cell type or organ—and that a third lab, in experiments two years ago, had produced similar stem-like cells by merging human genetic material with the egg cell of a cow.

Discoveries such as these offer not just moral issues but a fair measure of goose bumps. The cow-human cell experiment ranks extremely high on the goose-bump index; the president, in his letter, stressed the dangers of techniques that could lead to the horrible scenario of fused human-animal creatures.

But set aside whether these cells actually would constitute a fusion of genetic material from two species. (The researchers involved say they do not, that the cow cell is merely a container for the human cell nucleus.) The notion that the cow cell experiments pose a more immediate moral danger than the better-documented breakthroughs on embryonic stem cells may be a function less of scientific reality than of simple publicity spin.

News of the cow cell experiments was released two years late, in the wake of the stem cell announcements, without any indication that the cow cell experiments had been published or otherwise confirmed scientifically. Questions as to how they passed through ethics screening at that initial phase have yet to be answered. As more biotech labs, academic and entrepreneurial, begin to converge on this area, their jostling for position will become just one more factor to be weighed by the many official and unofficial bodies that will be considering the issues involved.

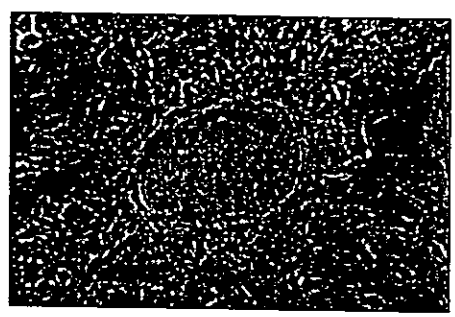
The government's ethics advisory panel needs to keep its eye on a few overriding questions. Which of the many apparent routes to the creation of embryonic stem cell material are morally defensible? Which ones seem actually in reach? Which of the many beckoning uses for that magical material can be deemed acceptable by the whole society?

Washington Post
Nov. 21, 1998

BIOTECHNOLOGY

Claim of Human-Cow Embryo Greeted With Skepticism

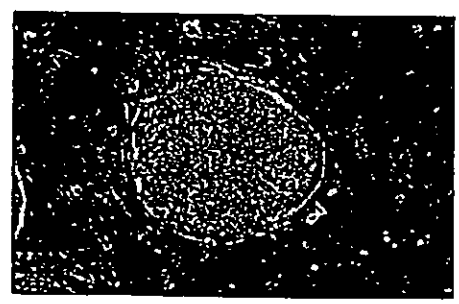
A small, privately held company in Worcester, Massachusetts—Advanced Cell Technology Inc.—startled the scientific world last week by announcing that it had fused human DNA with a cow's egg to create a new type of human cell. Company leaders say that a colony of these fused cells—created in 1996, kept alive for 2 weeks, and discarded—looked like a cluster of human embryo cells. On this basis, the company declared that it had "successfully developed a method for producing primitive human embryonic stem cells."



The claim, announced in a front-page news story in *The New York Times* on 12 November, came just 6 days after two groups of researchers reported in *Science* and the *Proceedings of the National Academy of Sciences* that they had used traditional techniques to culture human embryonic stem cells—"undifferentiated" cells that have the potential to grow into any cell type (*Science*, 6 November, pp. 1014 and 1145). It added to the concerns already raised among ethicists and government officials. On 14 November, President Clinton sent a letter to Harold Shapiro, chair of the National Bioethics Advisory Commission (NBAC), saying he is "deeply troubled" by news of the "mingling of human and nonhuman species." The president asked NBAC to give him "as soon as possible ... a thorough review" of the medical and ethical considerations of attempts to develop human stem cells. And a Senate committee may review the company's claim at a hearing on stem cell technology planned for 1 December.

Scientists, however, were startled for another reason: They were amazed that Advanced Cell Technology (ACT) broadcast its claim so widely with so little evidence to support it. Some were puzzled that the company had tried to fuse human DNA and cow eggs without first publishing data on the fusion of DNA and eggs of experimental animals. Many doubted that ACT's scientists had created viable human embryonic stem cells. And most were left wondering why the company chose to go public now with this old experiment.

The company had inserted DNA from adult human cells into cow's eggs using a nuclear transfer technique similar to the one used to clone Dolly, the first mammal cloned from an adult cell. ACT's top researcher and co-founder—developmental biologist James Robl of the University of Massachusetts, Amherst—says an early version of the experiment was performed in his UMass lab "around 1990." A student carrying out nuclear DNA transfer in rabbits had run out of donor cells, Robl recalls, and, almost as a lark, took cheek cells from a technician and transferred their DNA into rabbit oocytes. "I didn't even know about it," Robl says. To everyone's surprise, the cells began to divide and look like embryos. "I got very nervous" on learning about it, Robl says, and shut down the experiment.



Scant evidence. Experts question whether the cells in ACT's circular colony *(top)* are really human embryonic stem cells, like those from James Thomson's lab *(bottom)*.

Robl and his former postdoc Jose Cibelli, now a staffer at ACT, returned to this line of experimentation in 1995 to '96, when they were working with cow embryos on other projects. They remembered that the human DNA–animal oocyte combination worked before, and "we thought, 'Maybe we can get a cell line' " this way. Cibelli transferred nuclear DNA from 34 of his own cheek cells and 18 lymphocyte cells into cow oocytes from which the nuclei had been removed. Six colonies grew through four divisions, according to Cibelli, but only one cheek cell colony grew beyond that stage—reaching 16 to 400 cells. Robl says they didn't follow up on the work because "we had about 15 other things we were doing," and developing human stem cells was not at the top of the list. But the university did file for a patent on the technique, granting an exclusive license to ACT.

Robl concedes that the experiment did not yield publishable data. He says he classified the cells as human stem cells based on his experience of "look[ing] at hundreds and hundreds" of cell colonies. But Robl offered no other data to support this conclusion.

Other researchers agree that the cells may have had human qualities, because they continued to divide after the cow's nuclear DNA had been replaced with human DNA. But Robl and Cibelli didn't do any of the tests normally done to show that these cells were human or that they were stem cells, such as looking for expression of human proteins or growth of specialized tissues. James Thomson of the University of Wisconsin, Madison, lead author of the *Science* paper, says that ACT's cells "meet none of the criteria" for embryonic stem cells. And Gary Anderson of the University of California, Davis, who has isolated a line of embryonic pig cells, comments: "Just because someone says they're embryonic stem cells doesn't mean they are."

A few researchers—including Robert Wall, a geneticist at the U.S. Department of Agriculture in Beltsville, Maryland—were willing to suspend their disbelief, however, if only because they respect Robl. He is "a top-notch, very solid scientist," says Wall, who adds that anyone who has examined a large number of embryonic cells can distinguish real ones from impostors.

But others are less charitable. "This may be another Dr. Seed episode," says Brigid Hogan, an embryologist at Vanderbilt University in Nashville, Tennessee, referring to Chicago physicist Richard Seed, who caused a furor early this year when he announced that he planned to clone humans. Although Seed didn't have the means to carry out his

CREDITS (TOP) ACT, (BOTTOM) J. THOMSON ET AL.

project, Congress quickly drafted a criminal ban on many types of cloning research. Congress set that debate aside last spring but indicated it might take it up again later (*Science*, 16 January, p. 315 and 20 February, p. 1123). Hogan, a member of a 1994 National Institutes of Health (NIH) panel that proposed guidelines for human embryo research, agrees that "it's theoretically possible" to do what ACT claims to have done. But the company's announcement reminds her of the Seed case because "it smells to me of sensationalism" and seems "likely to inflame an uninformed debate."

Why did ACT publicize this experiment now? Some observers think the company wanted to ride the PR bandwagon created by the 6 November announcements by the labs that had isolated human embryonic stem cells using more traditional culture techniques. One group, led by developmental geneticist John Gearhart at The Johns Hopkins University, extracted primordial germ line cells from fetal tissue and kept them growing through 20 passages (transfers from one plate to another) for more than 9 months. The other group, led by Thomson at the University of Wisconsin, established a culture of stem cells derived from early human embryos. Thomson, whose cell line has survived 32 passages over 8 months, published molecular data suggesting that the cells may continue dividing "indefinitely."

Michael West, president and chief executive officer of ACT since October, says it is "pure coincidence" that ACT's news came out within a week of these announcements. West—noting that ACT won't benefit immediately, for it doesn't sell public stock—says that after becoming ACT's CEO last month, "I learned about the work that had been done in 1996 ... and I wanted to develop this technology." But he says he "didn't feel comfortable" moving ahead with nuclear DNA transfer experiments without getting a reading on how future U.S. laws and regulations might affect the field. "So I decided, 'Let's talk about the preliminary results,' " says West. "Let's get NBAC to help clear the air."

West notes that some information on ACT's mixing of human and cow cells was already public. In February, the World Intellectual Property Organization in Geneva had published Robl's application for a patent on "Embryonic or Stem-like Cell Lines Produced by Cross Species Nuclear Transplantation" (WO 98/07841). It describes the Robl-Cibelli experiment of 1996 and stakes broad claims to stem cell technology based on transferring human or animal DNA into an animal oocyte. After being approached by the staff of CBS's news show *48 Hours*, West says, he arranged to discuss the research in exclusive but simultaneous releases to *The New York Times* and CBS. The CBS report aired on 12 November.

Robl confirms it was West, and not the scientific staff at ACT, who initiated the announcements. "I wouldn't have had the guts to do it," Robl says, although he agrees it is important to debate ethical concerns that might impede the technology.

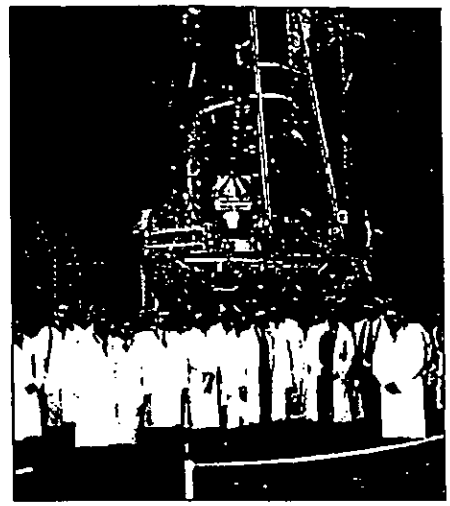
These ethical concerns may get an airing next month. Senator Arlen Specter (R–PA), chair of the appropriations subcommittee that approves the budget for NIH, is planning a hearing on 1 December. There, NIH director Harold Varmus and developers of new human cell technologies are expected to testify about federal restrictions on the use of embryonic and fetal tissue and their impact on biomedical research. That discussion may now be expanded to include questions about ACT's single experiment. –ELIOT MARSHALL

With reporting by Elizabeth Pennisi.

RUSSIAN SPACE SCIENCE

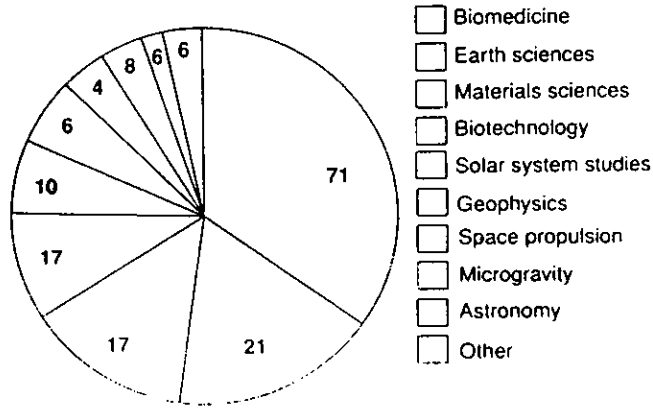
Station Launch Hides Lingering Woes

MOSCOW—Valery Bogomolov welcomes the scheduled launch today of the first piece of the international space station as a sign of the world's commitment to space exploration. But the launch is also a bitter reminder to Bogomolov, deputy director of Russia's premier space biology facility, the Institute for Biomedical Problems (IBMP), of his country's recent decision to sell NASA thousands of hours of station time earmarked for research by Russian cosmonauts for the $60 million needed to complete a key station component (*Science*, 9 October, p. 206). "It was very sad for us, and for Russian science," says Bogomolov, whose institute is scrambling to plan experiments on the ground that were meant to be done in space. "We had no warning."



Still grounded. Managers hope to get the Spectrum-X-Gamma mission into orbit by 2001.

As the rest of the space community readies its payloads for the $50 billion international space station, Bogomolov and his Russian colleagues must resign themselves to a limited role until at least 2003, when they will vie for a share of research time aboard the completed station. And the lost opportunity is only one of several continuing crises for Russian space science. The launch of the Russian-backed Spectrum-X-Gamma spacecraft, a $500 million international effort to study x-rays, is running almost a decade behind schedule. Even a last-ditch effort to postpone the dismantlement of the Mir space station, allowing some biology



Miraculous results. Biomedicine got the largest slice of Russia's $20 million of research on Mir, both in dollars and number of projects (in blue).

CREDIT: (TOP) SPACE RESEARCH INSTITUTE, RAS. SOURCE: (BOTTOM) ANSER

Health - Stem cell research

Statement of

HAROLD VARMUS, M. D.

Director

National Institutes of Health

before

the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies

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. John 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 close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization (IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types--endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more

specialized function. There is a hierarchy of stem cell types. Some stem cells are more committed than others. Some stems cells - the pluripotent stem cell we are discussing today - have the ability to become many, but not all, of the cells types in the human body.

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

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

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. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, 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 uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different kinds of cells. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor

many types of stem cells responsible for the body's ability to repair some but not all tissues. 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, important to 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. 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. Technological

challenges remain before these discoveries can be incorporated into clinical practice. 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. The techniques they used were initially developed using mice. Dr. Thomson first made 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, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human 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

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for infertility treatment. 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 may be 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 department may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue, as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

Ethical Issues

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells were produced from embryos and fetal tissue raises a number of ethical concerns including, for example, the need to ensure that stem cell research not encourage the creation of embryos or the termination of pregnancies for research purposes. In strict accordance with the President's 1994 directive, no NIH funds will be used for the creation of human embryos for research purposes. We also will continue to abide by relevant statutes.

The ethical and social issues associated with stem cell research are complex and controversial and require thoughtful discourse in public fora to reach resolution. To this end, the President has asked the National Bioethics Advisory Commission to undertake a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations.

Summary

The development of cell lines that may produce almost every tissue of the human 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.

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.

Health - stem cell research

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Page 6

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The legality of using Federal funds to support research using pluripotent stem cells is a question to be determined by DHHS lawyers.

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b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Health - stem cell research

Holly L. Gwin
11/18/98 08:57:38 AM

Record Type: Record

To: Jeffrey M. Smith/OSTP/EOP
cc: Christopher C. Jennings/OPD/EOP, Elena Kagan/OPD/EOP, Neal Lane/OSTP/EOP, Clifford J. Gabriel/OSTP/EOP
bcc:
Subject: Re: NBAC response to stem cell query

Rachel just called to say that Harold Shapiro announced during the meeting that the Commission would consider the draft response this morning but that he expected it would take longer, i.e., the next couple of days, to finalize the language of the response. She expects the letter to be completed before the end of the week, but not this morning. She expects the conclusions of the Commission will be clear by this morning and that finalizing the letter will only be a matter of wordsmithing, but can't be certain of that at this point.
Jeffrey M. Smith

Jeffrey M. Smith
11/18/98 08:10:41 AM

Record Type: Record

To: Christopher C. Jennings/OPD/EOP, Elena Kagan/OPD/EOP
cc: Neal Lane/OSTP/EOP, Clifford J. Gabriel/OSTP/EOP, Holly L. Gwin/OSTP/EOP
Subject: NBAC response to stem cell query

Chris, Elena -- At 8:00 a.m. this morning, we spoke with Rachel Levinson, who is at the NBAC meeting in Miami. She reports that the Commission will discuss the draft of their response to the President on the stem cell issue this morning; she expects to fax a copy to us very shortly -- perhaps by 10:00 a.m. As soon as we have something in hand, we'll pass it along to you right away. Should you need to reach Rachel in the meantime, her pager number is P6/(b)(6)

health - stem cell research

November 19, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

The Commission clearly shares your view that combining a human cell with a cow egg raises important ethical issues that need to be considered. In particular, we believe that any attempt to create a child by combining a human cell and a non-human egg would raise profound ethical concerns and should not be permitted. This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "... at this time it is morally unacceptable for anyone in the public or private sector, whether it a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning"

We reached our conclusions after consultation with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania and Dr. Michael West, of Advanced Cell Technology, Inc., the company that reported having fused a human cell with a cow egg.

As you know, the design and results of the human cell-cow egg experiment are not yet publicly available and, as a consequence, we are unable to evaluate fully its implications. Nonetheless, if this recent research does result in the production of embryos, it raises many potentially controversial issues, including those associated with cloning as well as those associated with crossing human/non-human species boundaries, which need further careful examination.

The common understanding of a human "embryo" includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a child. The little evidence that exists from previous experimentation involving combining early developmental cells from more than one species suggest that the hybrid cells that result do *not* have this potential, hence are not embryos. At this time, however, there is insufficient scientific evidence to be able to say whether combining of a human cell and an animal egg results in an embryo in this sense. In our opinion, if this *is* an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human genetic material.

It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

If this line of research does not give rise to embryos, and therefore cannot be used to produce a child, we do not believe that totally new issues arise. We note that scientists routinely conduct non-controversial research that involves combining material from human and other species. This research has led to such useful therapies as insulin for diabetes, blood clotting factor for hemophilia, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

Health - stem cell research

THE WHITE HOUSE

WASHINGTON

November 14, 1998

Dr. Harold Shapiro
Chair
National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week, and to report back to me as soon as possible.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting that the Commission undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Bill Clinton

Health - stem cell research

0&V‡? ¾üüÊ:~ November 18, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:
These changes are suggested to simplify the draft by changing references to "fusions" to hybrid cells

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of combining a human cell with a cow egg to produce a hybrid cell. I would also not however, that since the design and results of this experiment are not yet publicly available, we are unable to evaluate fully its implications. Nevertheless, the Commission clearly shares your view that this development raises important ethical issues that need to be considered. In particular, we believe that any attempt to create a child through the fusion of by combining a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

Moreover, this newly recently reported research raises many new and potentially controversial issues, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product hybrid cell resulting from the fusion of combining a human cell and the with an egg from a non-human animal is transferred into a woman's uterus, and as well as, in a different manner, if the fusion products are hybrid cell is an embryos even if no attempt is made to bring them to termcreate a child.

We devoted time at our meeting to discuss this issue in public, benefiting in particular from consultation (via phone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members.

We found it helpful to consider three questions:

Can the product of fusing hybrid cell that results from combining a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?

At this time there is insufficient scientific evidence to answer this question. However, if it were possible, the Commission believes that any attempt to create a child in this manner would raise profound ethical concerns, and should not be permitted. This objection is consistent with our views expressed in Cloning Human Beings, in which we concluded that:

"... at this time it is morally unacceptable for anyone in the public or private sector, whether it a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning"

Does the fusion of Is the hybrid cell that results from combining a human cell and an egg from a non-human animal result in a human embryo?

The common understanding of an a human "embryo" includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living beingchild. The little evidence that exists from previous experimentation involving combining early developmental cells from more than one species suggest that the products of such fusions hybrid cells that result do not have this potential, hence are not embryos. At this time, however, there is insufficient scientific evidence to be able to say whether the fusion combining of a human cell and an animal egg results in an embryo in this sense. In our opinion, if this fusion does result

in if this is an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these fusion products hybrid cells will contain both human and non-human genetic material.

It is worth noting that these fusion products hybrid cells should not be confused with human embryonic stem cells. Embryonic stem cells, while derived from embryos, are not themselves capable of developing into organismschildren. The use of embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

If the fusion of hybrid cell that results from combining a human cell and an animal egg does not result in is not an embryo with the potential to develop into a child, what ethical, medical or scientific issues remain?

If there is not attempt to create children or an embryolf this line of research does not give rise to embryos, and therefore cannot be used to produce a child, we do not believe that totally now issues arise. We note that scientists routinely conduct non-controversial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, crythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

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Health - stem cell research

Jeffrey M. Smith
11/19/98 08:53:51 AM

Record Type: Record

To: Clifford J. Gabriel/OSTP/EOP, Rachel E. Levinson/OSTP/EOP

cc: Christopher C. Jennings/OPD/EOP, Elena Kagan/OPD/EOP
Subject: redrafting the NBAC letter

Cliff/Rachel -- I am at PCAST for the better part of the day. Can you please work with DPC on this letter?

Attached are some suggested changes Rachel phoned in yesterday. I'm also passing along a hard copy of some edits Chris Jennings made last night. More to come. Elena indicated at senior staff this morning that we might consider releasing this letter in 24 hours after Shapiro has had an opportunity to consider some redrafted language, which would initially be worked with OSTP/DPC and Eric at NBAC's Bethesda office. Tact, of course, is necessary, but clarity is crucial.

This morning Neal said he would like to proceed in gathering all hands from all relevant quarters on this issue next Monday, November 23rd. Chris and Elena both agree
---------- Forwarded by Jeffrey M. Smith/OSTP/EOP on 11/19/98 08:32 AM ----------

Jeffrey M. Smith
11/19/98 08:25:02 AM

Record Type: Record

To: Rachel E. Levinson/OSTP/EOP

cc:
Subject: NBAC letter

Attac NOVEMB~1.Dhed is the NBAC letter with your changes recorded. Page me if you need anything. -- David Stevens

health - stem cell research

CONFIDENTIAL DRAFT

November 18, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg. I would also note however, that since the design and results of this experiment are not yet publicly available, we are unable to evaluate fully its implications. Nevertheless, the Commission clearly shares your view that this development raises important ethical issues that need to be considered. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

Moreover, this newly reported research raises many new and potentially controversial issues, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term.

We devoted time at our meeting to discuss this issue in public, benefiting in particular from consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members.

We found it helpful to consider three questions:

1. *Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?*

At this time there is insufficient scientific evidence to answer this question. However, if it *were* possible, the Commission believes that any attempt to create a child in this manner would raise profound ethical concerns, and should not be permitted. This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning"

2. *Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?*

The common understanding of an "embryo" includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living being. The little evidence that exists from previous experimentation involving combining early developmental cells from more than one species suggests that the products of such fusions do not have this potential, hence are not embryos. At this time, however, there is insufficient scientific

evidence to be able to say whether the fusion of a human cell and an animal egg results in an embryo in this sense. In our opinion, if this fusion does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these fusion products will contain both human and non-human genetic material.

It is worth noting that these fusion products should not be confused with human embryonic stem cells. Embryonic stem cells, while derived from embryos, are not themselves capable of developing into organisms. The use of embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. *If the fusion of a human cell and an animal egg does not result in an embryo with the potential to develop into a child, what ethical, medical or scientific issues remain?*

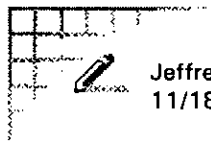
If there is no attempt to create children or an embryo, we do not believe that totally new issues arise. We note that scientists routinely conduct non-controversial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

Health - stem cell research



Jeffrey M. Smith
11/18/98 09:09:56 AM

Record Type: Record

To: See the distribution list at the bottom of this message

cc:
Subject: FYI -- Senate stem cell heaings

From 11/18/98 Washington Fax:

SENATE SET FOR HEARINGS ON BREAKTHROUGH STEM CELL RESEARCH
BIOETHICS COMMISSION WILL ALSO DELIBERATE THE ISSUES

The Senate Appropriations Labor, Health and Human Services, Education and Related Agencies (L/HHS) subcommittee plans to hold a hearing the first week in December to examine issues raised by recent research breakthroughs in which scientists have reported success in using human embryos and fetal tissue to isolate and grow human stem cells.

Witnesses at the hearing, tentatively scheduled for either December 1 or 2, are expected to include the two scientists who headed teams that, working independently of each other and entirely with private funds, recently reported that they had isolated and then grown stem cells in the laboratory: James Thomson of the University of Wisconsin, who obtained stem cells from donated embryos, and John Gearhart of Johns Hopkins University School of Medicine, who extracted stem cells from aborted fetuses.

Others likely to testify include Harold Varmus, director of the National Institutes of Health, representatives of Geron Corp., a California biotechnology company that owns the commercial license for Thomson's and Gearhart's discoveries, and biomedical ethicists.

Thomson and Gearhart's achievements are considered a major advance. Stem cells are human cells at their earliest stage of development. The ability to isolate and grow them in the laboratory could, theoretically, allow them be manipulated to perform a variety of regenerative activities, such as replacing tissue in a defective heart or repairing the neurological damage suffered by Parkinson's patients.

But other potential uses--and the techniques required for their isolation--raise questions in some of the most ethically sensitive areas of biology: research involving human embryos and fetal tissue, cloning, and genetic manipulation.

In addition, the ramifications of Thomson and Gearhart's work were further clouded by reports from company called Advanced Cell Technology that its scientists have isolated human stem cells by fusing human cells with a cow egg. (Some scientists have criticized the announcement as unnecessarily complicating the issue since the reported discovery happened almost three years ago, was never published in a scientific journal and the scientists did not offer conclusive proof that they created stem cells.)

An aide to Sen. Tom Harkin, D-IA, the L/HHS panel's highest ranking Democrat, said the hearing is mainly aimed at learning more about stem cell research and its implications. He said Harkin, in particular, wants to "send a signal that we should not just shut the door on research because some view it as controversial, since that is not always in the best interest of public policy or good health."

Lawyers at the National Institutes of Health are already reviewing whether the ban on federal funding for research involving human embryos prohibits scientists from studying stem cells derived from embryos. A key issue is whether the ban was intended to stop federal funding for research on something with the potential to grow into a human. Some scientists argue that stem cells don't have that potential.

Rep. Jay Dickey, R-AR, one of the authors of the ban, has said that the restriction should apply to work involving stem cells.

Varmus, speaking last week to the Ad Hoc Group for Medical Research Funding, said he hoped to have a legal opinion on the issue by the time of the hearings.

While he has not taken a position on whether stem cell research should be eligible for federal funds, Varmus, responding to a reporter's question, did say that it was "extremely important that the larger scientific community be engaged in the process" and that "we are looking at the legalities of whether we can do that."

Varmus also noted that while many scientific problems must be resolved before stem cells can be used in practical applications, "the prospect of having human cells that can be grown in large numbers (and) differentiated into specific tissues that might be used for a wide variety of diseases

represents, to me, a remarkable advance."

President Clinton has responded to the discoveries by asking his National Bioethics Advisory Commission (NBAC) to review the implications of the research. The commission discussed the issue yesterday at a previously scheduled meeting in Miami.

NBAC Chairman Harold Shapiro described the President's request during a press conference as two-part. First, Clinton wants an immediate response on the issue of the appropriateness of "human and non-human species intermingling." Shapiro said the commission may respond to that request as early as today: "I think we may be able to come to at least a temporary conclusion on this."

But the second part, looking at the controversy surrounding stem cell research in general, may take some six months, Shapiro predicted. He said the commission will be discussing today how to mobilize that study. Meanwhile, Congressional involvement in the debate--should it lead to legislation--is something that makes the biotech industry uneasy, said Carol Feldbaum, president of the Biotechnology Industry Organization (BIO).

"We have absolutely no reservations when it comes to talking about the implications of these developments," said Feldbaum, who had urged Clinton to refer the issue to his bioethics panel. "What happens next is fraught with some trepidations and some difficulty. Once rules and regulations get into the legislative arena, the fact is that anything can happen. Many members of Congress are not well versed in science and the kind of precision these developments need may not always be there when legislative language is drafted."

--Matthew Davis

Compiled and Published by: WASHINGTON FAX: AN INFORMATION SERVICE
Publisher: Bradie Metheny
Executive Editor: Shirley Haley
Phone: 508-999-6097 Fax: 508-994-9366
E-mail: subscriptions@washington-fax.com

THE PRESIDENT HAS SEEN
11-17-98

Health - stem cell research

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20502

'98 NOV 13 PM5:40

November 13, 1998

Copied
Lane
Podesta
Sperling (pgl)
Reed

MEMORANDUM FOR THE PRESIDENT

FROM: NEAL LANE

CC: JOHN PODESTA

SUBJECT: OSTP WEEKLY REPORT

Information Technology (IT) Initiative

The public debate over FY 2000 spending on IT is heating up. Members of your Information Technology Advisory Committee (PITAC) fear you may commit resources only to DOE's Strategic Simulation Program (SSP) -- designed to buy supercomputers for application to mission needs -- in lieu of the programs they have recommended at NSF, DARPA and other agencies that will address IT research in software, high-end computing, and other research needed to ensure IT continues to grow our economy. As you know, I favor a balanced program of IT research and applications in the mission agencies, and I remain hopeful that we will find the resources to cover all of our needs in this vital area. But in a tight budget, I favor a balanced investment in IT research, as recommended by PITAC. I have initiated discussions with Jack Lew and Gene Sperling concerning my detailed recommendations for an IT initiative. Members of their staff have been very helpful in developing a good plan.

Human Embryo Stem Cell Research

Last week, two groups of privately-funded researchers reported advances in isolating and growing human stem cells. In these reports, stem cells were derived from two sources; embryos left over from successful in vitro fertilization cycles and aborted fetuses. Several newspaper articles noted the absence of Federal funding and regulation of embryo research. Your 1994 ban on using Federal funds to create human embryos for research purposes was not violated by either group. The 1995 Congressional ban on NIH embryo research funding would have been violated by the group using embryos, had they received public money. HHS General Counsel is reviewing the language of the Congressional ban to determine if NIH-supported scientists can *use* the stem cells already growing in the laboratory. Even if such use is does not fall under the ban, a policy decision as to whether or not to allow such use remains an open question. Harold Varmus would very much like to allow public sector scientists to use these promising cells for basic biological research.

In a front page story in yesterday's (11/12/98) NYT, a Massachusetts biotechnology company, Advanced Cell Technology (ACT), announced it has applied for a patent on technology resulting in the creation of human stem cells derived from fusing a human cell with a cow egg that had its

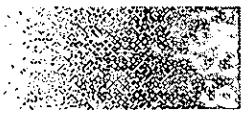
nucleus removed. This technique is similar to that used to produce Dolly, but in this case the intent was to produce human stem cells, not cloned offspring. Human stem cells have enormous potential to treat many diseases such as diabetes and Parkinson's. The human cell/cow egg hybrids, which result in what the company calls "embryonic stem cell-like" cells, add to the growing list of ethical issues resulting from recent advancements in biomedical research. Until this research is published in peer reviewed literature, many scientists will remain skeptical of the veracity of this claim. ACT's report links cloning with other new methods for obtaining human embryonic stem cells.

Late yesterday, the biotechnology trade organization issued a statement urging you to ask your National Bioethics Advisory Commission (NBAC) to consider issues raised by stem cell research. I am currently working with DPC, COS and NIH to prepare a letter for your signature to NBAC requesting that they review the ethical, social and legal issues raised by these two developments.

PCAST To Meet Next Week

Your Committee of Advisors on Science and Technology (PCAST) will next meet on Thursday, November 19 at the White House Conference Center. John Podesta and Secretary Richardson will meet with PCAST members in the morning for informal discussions. During the afternoon public session John Yochelson, President of the Council on Competitiveness, and Director Lew will discuss the S&T budget outlook for the 21st Century.

Goal the - stem cell research



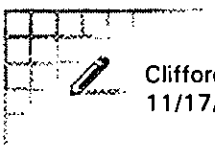
Jerold R. Mande

11/17/98 10:36:17 AM

Record Type: Record

To: Clifford J. Gabriel/OSTP/EOP
cc: See the distribution list at the bottom of this message
bcc:
Subject: Re: Stem cell research

I agree. My point wasn't that the use of embryo was incorrect in the Shapiro letter, but that strategically we should seek to draw a bright line between an embryo that is the product of conception, and a totipotent cell that is derived from and is genetically identical to a somatic cell. The Shapiro letter was an opportunity to do that. Educating the public about the difference is critical to winning public support for federally funding totipotent cell research, which should be one of our goals.
Clifford J. Gabriel



Clifford J. Gabriel
11/17/98 08:46:22 AM

Record Type: Record

To: Jerold R. Mande/OSTP/EOP
cc: See the distribution list at the bottom of this message
Subject: Re: Stem cell research

Jerry: I don't believe the use of the term embryo in the Shapiro letter is incorrect. Cultured stem cells were derived from embryos and fetuses, which clearly triggers the Congressional ban on embryo research. The cow egg/human somatic cell fusion product was reported to generate embryonic stem cell-like cells. Perhaps the letter could have put more distance between the cow egg/human fusion and the creation of embryos (i.e., the ethical issues are the same as those associated with xenotransplantation), but we know so little about their results. I suspect this will be an issue NBAC will address. I agree that we should not equate a totipotent cell with an embryo.
Cliff

Message Copied To:

Elena Kagan/OPD/EOP
Neal Lane/OSTP/EOP
Christopher C. Jennings/OPD/EOP
Sarah A. Bianchi/OPD/EOP
Rachel E. Levinson/OSTP/EOP

Message Copied To:

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Clinton Library

DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
002. email	Jeffrey M. Smith to Christopher c. Jennings. Pager Number (Partial). (1 page)	11/17/1998	P6/b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elena Kagan
OA/Box Number: 14363

FOLDER TITLE:
Health - Stem Cell Research

2009-1006-F
ab810

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

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RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
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b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

health - stem cell research

Jeffrey M. Smith
11/17/98 09:04:31 AM

Record Type: Record

To: Christopher C. Jennings/OPD/EOP, Elena Kagan/OPD/EOP

cc:
Subject: Schedule for NBAC deliberations

Chris -- pasted below is self-explanatory. Elena and I touched upon this briefly this morning, and she mentioned it at senior staff. As it stands now, any NBAC statement will not come today, but rather on Wednesday. We'll keep you posted and in the loop from our end... please let us know if you hear anything. Thanks.

---------- Forwarded by Jeffrey M. Smith/OSTP/EOP on 11/17/98 09:00 AM ----------

Holly L. Gwin
11/17/98 08:30:37 AM

Record Type: Record

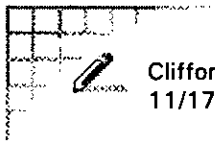
To: Neal Lane/OSTP/EOP, Jeffrey M. Smith/OSTP/EOP

cc: Betty J. Fountain/OSTP/EOP
Subject: Schedule for NBAC deliberations

According to Rachel (8 AM 11/17), NBAC will discuss mingling of human and nonhuman species today during their afternoon session, write something overnight, and make its decision about a statement mid-morning tomorrow (11/18). Rachel will fax the statement to Jeff/me at 6-6021. She will call us if the schedule changes. Rachel's pager number is P6/(b)(6) (it's registered with Signal).

Jeff: would you please notify Chris Jennings?

health - stem cell research



Clifford J. Gabriel
11/17/98 08:46:22 AM

Record Type: Record

To: Jerold R. Mande/OSTP/EOP

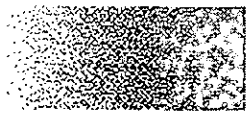
cc: See the distribution list at the bottom of this message
Subject: Re: Stem cell research

Jerry: I don't believe the use of the term embryo in the Shapiro letter is incorrect. Cultured stem cells were derived from embryos and fetuses, which clearly triggers the Congressional ban on embryo research. The cow egg/human somatic cell fusion product was reported to generate embryonic stem cell-like cells. Perhaps the letter could have put more distance between the cow egg/human fusion and the creation of embryos (i.e., the ethical issues are the same as those associated with xenotransplantation), but we know so little about their results. I suspect this will be an issue NBAC will address. I agree that we should not equate a totipotent cell with an embryo. Cliff

Message Copied To:

Elena Kagan/OPD/EOP
Neal Lane/OSTP/EOP
Christopher C. Jennings/OPD/EOP
Sarah A. Bianchi/OPD/EOP
Rachel E. Levinson/OSTP/EOP

Health - stem cell research



Jerold R. Mande

11/16/98 06:34:05 PM

Record Type: Record

To: Elena Kagan/OPD/EOP, Neal Lane/OSTP/EOP, Christopher C. Jennings/OPD/EOP

cc: Sarah A. Bianchi/OPD/EOP, Clifford J. Gabriel/OSTP/EOP, Rachel E. Levinson/OSTP/EOP

Subject: Stem cell research

I want to urge that we try to redefine the stem cell/cloning debate. The term "embryo" is being used too broadly, to the advantage of our right-to-life opponents, and to the harm of patients who could benefit from prohibited research. The letter Potus sent Shapiro implies embryos are being created where they are not. We should seek consensus that remodeling (turning back on all of the genes) of DNA from a human somatic cell does not produce an embryo (even when scientists fuse a somatic cell with what was once an egg -- "once" because with its nucleus removed the egg is merely a chemical factory that is being used to turn on genes). Embryo in this debate should be reserved for "the prefetal product of human conception (Webster's II)." For there to be an embryo there must be conception -- creation of a potential human being. Despite Dolly, it is only a theory that the DNA in a human somatic cell can be remodeled to produce a human being. We should state without reservation that we oppose human cloning, but we should not ban various techniques and processes because such techniques and processes might make cloning more likely. We should stop affixing the term embryo to reactivating an individual's DNA for the purposes of producing cell lines or tissue for therapeutic uses. I recognize redefining the debate at this stage will be difficult. Sensational coverage of cloning has created a powerful lens through which the public views the stem cell debate. Too many experts have fallen into the trap of labeling remodeled somatic cells as embryos. But it is possible to draw a bright line between conception and reactivating somatic cells even when it involves components from eggs.

Health - stem cell research

HUMAN STEM CELL RESEARCH USING COW EGGS
November 12, 1998

Context
In a front page story in today's (11/12/98) NYT, Nicholas Wade reports on an announcement by a Massachusetts biotechnology company, Advanced Cell Technology, that they have applied for a patent on technology resulting in the creation of human stem cells derived from fusing a human cell with a cow egg that had its nucleus removed. This technique is similar to that used to produce Dolly, but in this case the intent was to produce human stem cells, not cloned offspring. Human stem cells have enormous potential to treat many diseases such as diabetes and Parkinson's. The human cell/cow egg hybrids, which result in what the company calls "embryonic stem cell-like"cells, add to the growing list of ethical issues resulting from recent advancements in biomedical research. Until this research is published in peer reviewed literature, many scientists will remain skeptical of the veracity of this claim.

General
This report, as did last week's report on the isolation and culture of human embryonic stem cells, has highlighted the serious ethical issues that still remain unresolved with regard to embryo research.

These techniques offer great promise in advancing biomedical research for a large number of devastating conditions, including diabetes, cardiovascular disease, neurodegenerative disorders, burns and spinal cord injuries, and cancer.

While this science is clearly preliminary, all of these issues deserve serious attention and review by the scientific and medical ethics communities. The President's Science Advisor is developing a strategy to address this issue, in consultation with the nation's scientific and ethical experts in the areas of biomedical research and human development.

Q. What does the Administration plan to do about regulating these kinds of experiments?

A. The President's Science Advisor is developing a strategy to address this issue in consultation with the experts on biomedical research and human ethical issues, to protect the sanctity of the human being while preserving our ability to pursue avenues of research that can improve the human condition. This includes whether it is appropriate or necessary to refer this type of research to the National Bioethics Advisory Commission. The company whose work was reported today has declared that it will take a time-out on this research and has asked that the President facilitate a national review of the ethical issues raised by new advances in human developmental biology. The President believes we should strive to achieve the appropriate balance of encouraging research that can have a positive contribution to treating and preventing diseases that plague our nation and the world with serious and real ethical concerns. The President has stated unequivocally that he is opposed to producing human beings using cloning. As he stated last year at Morgan State, we have to be sure that our ethics are as good as our science.

Q. Was public funding used to support this research?

A. The research that was reported in today's NYT, as well as that reported last week on embryonic stem cells, was privately funded, and approved by the institutions' review boards.

Q. Are we closer now to being able to clone humans?

A. It is far too premature to draw that conclusion. The experiments described in today's news did not result in the production of a viable embryo. There is no substantiating evidence that the hybrid cells that were generated had the properties of embryonic stem cells or the capacity to survive beyond a few days in the laboratory. Many scientists are highly skeptical that these kinds of hybrids can survive, given the incompatibility of the genetic material in the nucleus with that in the cytoplasm.

Health - stem cell research

Elena - Copy of final

November 14, 1998

Dr. Harold Shapiro
Chair, National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

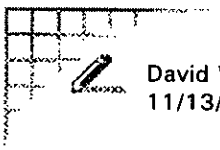
This past week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting the National Bioethics Advisory Commission to consider the implications of such research at its meeting next week, and to report back to me immediately thereafter.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting the Commission to undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Health - stem cell research



David W. Beier @ OVP
11/13/98 07:22:07 PM

Record Type: Record

To: Neal Lane/OSTP/EOP, Elena Kagan/OPD/EOP, Rachel E. Levinson/OSTP/EOP

cc:

Subject: Letter from the President to the NBAC

I received a copy of the draft letter which is proposed to be sent by the President to the NBAC. I offer one important editorial suggestion. In the second sentence reference is made to "mingling of species". This reference is likely to be more problematic than helpful. During the debate about transgenic animal research this type of rhetoric was used by biotech opponent Jeremy Rifkin. As a subsequent OTA report correctly pointed out this notion is not scientifically relevant in the context of animal breeding (or plant breeding).

As most of the NBAC witnesses who testified in the cloning hearings the "special status" of certain cellular material is what is at issue. In the published reports some of the research involved concerned cellular material that could not become a fetus that could be brought to term. Thus, it is important to correctly idenify the exact nature of the experiments which are to be addressed.

I think there are better ways to get this point across (see below). It is also important to separate the types of experiments involved here. There were legitimate and published work done on stem stems by Geron. There, on the other hand, have been press reports about work about claims from Dr. West. It would be mistake to dignify the later claims with the former peer reviewed work. Having said that, it is important to clarify which experiments are to be examined. Is the intention to look at both of the published experiments and those claimed by Dr. West. If so, that should be stated.

My suggested amendment to the letter would be to state"

"...experiments involving stems cells, and other research on material related to embryos".

I hope that this helps.