

Exhibit D



January 15, 1999

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

FROM: Harriet S. Rabb *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 treatment¹; and (2) Dr. Michael Shambloft 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. Shambloft 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

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

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

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).