REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS[1]

CEJA Report 5-A-11

Subject: Amendment to Opinion E-2.146, "Cloning for Biomedical Research"

Presented by: John W. McMahon, Sr., MD, Chair

Referred to: Reference Committee on Amendments to Constitution and Bylaws (Patricia L. Austin, MD, Chair)

Organized Medical Staff Section (OMSS) Resolutions 1, "AMA Opposition to Embryonic Stem Cell Research," and 15, "Stem Cell Research," were referred to the OMSS Governing Council (GC) for deliberation at the 2009 Annual Meeting. The OMSS GC believed that these issues would be most appropriately addressed by the Council on Ethical and Judicial Affairs (CEJA).

Both resolutions asked the American Medical Association (AMA) to support specific positions on stem cell research. OMSS Resolution 1 asked that the AMA promote the scientific truth that an embryo is not property but rather is a human being with all the attendant rights; not support embryonic stem cell research as it results in the termination of human life; seek legislative support to restore Executive Order 13455, which was revoked by the current Administration; oppose therapeutic cloning as a way of producing embryonic stem cells with a predetermined genetic patrimony in order to overcome the problem of immune system rejection; and oppose the use of stem cells for selecting the genetic characteristics of offspring.

OMSS Resolution 15 asks that the AMA support President Obama in his consideration of: the ethical issues relating to embryonic cell research; policy to restrict federal funding of research involving human cloning; policy to restrict federal funding of stem cell research that creates human embryos for the sole purpose of research.

The Council reviewed the resolutions along with AMA's related ethics policy, most relevant being Opinion E-2.146 (AMA Policy Database), "Cloning for Biomedical Research." CEJA concluded that in order to respond to both resolutions, the Opinion needed clarification and updating to reflect the current state of scientific research.

AMA POLICY

The AMA has House of Delegates policy on stem cell research. Policy H-460.915, "Cloning and Stem Cell Research," states that the AMA: (1) supports biomedical research on multipotent stem cells (including adult and cord blood stem cells); (2) supports the use of somatic cell nuclear transfer technology in biomedical research (therapeutic cloning); (3) opposes the use of somatic cell nuclear transfer technology for the specific purpose of producing a human child (reproductive

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cloning); (4) encourages strong public support of federal funding for research involving human pluripotent stem cells; and (5) will continue to monitor developments in stem cell research and the use of somatic cell nuclear transfer technology.[1]

Policy Related to Stem Cell Research

In its 2003 report on cloning for biomedical research, CEJA noted that:

> Different types of recommendations have been made to restrict research on stem cells from cloned human embryos. Some have asked that stem cell research be restricted to less controversial sources, such as adult stem cells, which have shown increasing promise. They maintain that these limits would put an end to the unjustified destruction of early forms of human life. For example, a majority on the President's Council on Bioethics (PCB) recommended a moratorium on research on stem cells derived from cloned human embryos. In the absence of specific criteria that would result in the lifting of the moratorium, this proposed suspension of research has been likened to a recommendation for a ban.
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> Others maintain that research using stem cells derived from cloned embryos should be undertaken only if no less controversial approach exists that is equally promising. In fact, given the technical difficulties that somatic cell nuclear transfer (SCNT) presents, this restriction already is a reality of laboratory life. The scientific community is using SCNT to produce embryos only for research identified as uniquely promising.
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> Several governmental bodies, including the National Bioethics Advisory Commission (NBAC) and the 1994 National Institutes of Health Human Embryo Research Panel (HERP) have proposed restrictions on federal funding of research on stem cells from human embryos deliberately created for research, including those created through SCNT. However, these restrictions would not prohibit the research itself, which could be undertaken in the private sector. In fact, NBAC's recommendation was to be reconsidered if research in the private sector showed great promise.
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> It is important to acknowledge that the recommendations of HERP, NBAC, and the PCB were never enacted into law and have been used only for advisory purposes.
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> In August 2001, President Bush announced a decision to limit federal funding to research on approximately 60 genetically diverse embryonic stem cell lines already in existence in the federal registry, which excludes any lines that were derived with private funds. In fact, currently only nine cell lines currently meet the eligibility criteria for federally funded research and are available to scientists. In addition, all of them were exposed to mouse feeder cells as part of the cultivation process, raising some of the same ethical issues as xenotransplantation. Finally, under the President's decision, federal funds could not be used to further any of the uniquely promising goals of cloning-for-biomedical-research.[2]

FEDERAL & STATE POLICY

Federal regulations regarding research with embryonic stem cells are currently in flux. On March 9, 2009, President Barack Obama issued Executive Order (EO) 13505, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," which revoked President Bush's August 2001 policy.[3] EO 13505 and the subsequently released NIH Guidelines for Human Stem

Cell Research allowed for federal funding of research on newly created stem cell lines.[4] However, the other three components of the Bush policy remained intact: a cell line may be derived only from an embryo left over from the in vitro fertilization (IVF) process, there must be no financial inducements in obtaining the embryo, and informed consent must be obtained from the embryo donor. Some in the scientific community are concerned that continuing to restrict federal funding to lines created from donated embryos left over from infertility treatment significantly impedes research, given that there are other significant sources of embryos that could be used to establish disease-specific stem cell lines: parthenogenesis, SCNT, and embryos created through IVF specifically for research.[4] On August 22, 2010, the Federal District Court for the District of Columbia issued a temporary injunction halting federal spending for research involving embryonic stem cells in a lawsuit alleging that EO 13505 made it more difficult for researchers using adult stem cells to compete for federal research grants.[5]

State laws vary widely with regard to their stance on research with embryonic stem cells. The primary sources for embryonic stem cells are existing stem cell lines, aborted or miscarried embryos, embryos left over from in vitro fertilization, and cloned embryos. Individual states may permit or restrict research on cells from each of these sources.[3]

Whereas eight states have statutes that promote stem cell research, one state, South Dakota, forbids research on any embryo regardless of the origin. Likewise many states restrict research on aborted fetuses or embryos and half restrict their sale.[3] Louisiana is the only state that banned research on IVF embryos; five states prohibit research on cloned embryos. Several states limit the use of state funds for identified aspects of stem cell research, though more states have specifically authorized funding for such research.[3]

STATE OF THE SCIENCE

The National Institutes of Heath defines stem cells as “cells with the ability to divide for indefinite periods in culture and to give rise to specialized cells.”[6] There are two major categories of stem cells, adult stem cells and embryonic stem cells. Adult stem cells are sometimes referred to as nonembryonic stem cells and are “a relatively rare undifferentiated cell found in many organs and differentiated tissues with a limited capacity for both self renewal (in the laboratory) and differentiation. Such cells vary in their differentiation capacity, but it is usually limited to cell types in the organ of origin. This is an active area of investigation.”[6] Cord blood and some fetal tissues also contain adult stem cells.

Adult Stem Cells

Bone marrow (which contains a type of adult stem cells) has been in clinical use for over 40 years, mostly transplanted to treat blood disorders.[7] Similarly, cord blood stem cells have been used for the past 15–20 years.[7]

Although research with adult stem cells dates back to the 1950s, there continues to be debate in scientific community over the capabilities and limitations of these types of stem cells, particularly if stem cells found in one tissue can give rise to cell types in different tissue. There has been disagreement whether embryonic stem cells may have clinical advantages over adult stem cells; however, in recent years scientists working with adult stem cells have acknowledged that adult stem cells had limitations and could not replace embryonic stem cells in all situations.[8]

Clinical trials have explored using adult stem cells to treat ischemic heart disease, spinal cord lesions, nonunion of fractured bones, Parkinson's disease, Huntington's disease, and type 1 diabetes, among other conditions.[7] Although some trials have yielded promising results, it will likely be several years before adult stem cells will be utilized in these clinical settings.

In 2007, scientists identified techniques that would allow some specialized adult human cells to be genetically reprogrammed to assume a stem-cell-like state. Although these "induced pluripotent stem cells" (iPSCs) meet the defining criteria for pluripotent stem cells, the NIH notes that "it is not known [whether] iPSCs and embryonic stem cells differ in clinically significant ways."[9] While iPSCs have already become important tools in drug development and disease modeling, it will be years before they can be used therapeutically. Current techniques for inducing pluripotency require integration of foreign DNA, and thus transplantation of iPSCs into humans is currently not possible.[10]

Embryonic Stem Cells

The second major category of stem cells is that of embryonic stem cells. Whereas research and therapy using adult stem cells has a proven track record, that is not the case with embryonic stem cells, for which bench and clinical science lags by decades. Embryonic stem cells are defined by the NIH as "undifferentiated cells derived from a 5-day preimplantation embryo that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers."[6] Embryonic stem cells are thought to have the greatest clinical application due to their ability to differentiate and regenerate.[7,8]

The first embryonic stem cell line was established in 1998 and the first-ever human trial of a medical treatment derived from embryonic stem cells was approved in the United States in 2009 for research into the treatment of spinal cord injuries.[7,11] Potential risks are great and include spontaneous and uncontrolled cellular differentiation, tumorogenesis and the potential for transmission of genetic abnormalties.[8] Other risks include immunological reaction or rejection, unpredictable cell behavior, and unknown long-term health effects.[12] Although clinical trials are underway to examine tolerability of therapy using embryonic stem cells, if these trials are successful it will likely be many more years before therapies are available outside of the research setting.[13]

ETHICAL ISSUES

Ethical concern has often focused solely on the source of stem cells. Much of the controversy surrounding biomedical research with stem cells in generated by the use of human embryonic stem cells and the plurality of views in our society regarding the moral status of early embryos. Concern is exacerbated by the fact the current techniques for retrieving stem cells require that the embryo be disaggregated or destroyed. This question of moral status cannot be answered by science and decades of moral debate have not yielded consensus.

Whether it is ethical to create embryos for research purposes by means of IVF or SCNT has also been hotly debated. SCNT, also known as cloning-for-biologic-research, involves introducing nuclear material from a somatic cell into an enucleated oocyte. This process yields an embryo that is genetically nearly identical to the donor of the somatic cell: its nuclear DNA is contributed by the nucleus donor, while its cytoplasmic DNA is contributed by the oocyte donor. Current NIH guidelines restrict research to the use of stem cells derived from donated surplus IVF embryos.

Even absent the NIH guidelines, the availability of cloned embryos as sources of stem cells is constrained by the fact that to date human embryos have not been derived through SCNT due to difficulties in initiating human embryo development. Moreover it has been difficult to convince women to undergo the process of oocyte donation, with its associated dangers, discomforts, and psychosocial risks, without compensation. At present, the National Academy of Sciences recommends against compensating egg donors and two states have outlawed the practice. One state, however, allows compensation commensurate with what a woman would receive for donating eggs for IVF in treatment of infertility.[3]

The use of adult stem cells and induced pluripotent stem cells derived from somatic cells does not pose questions about the moral status of the embryo. However, stem cell research poses other ethical challenges, regardless of the source of stem cells. As with any research involving human biological materials, stem cell research requires a robust process of informed consent. The emerging consensus about the core components of consent for research with biological specimens requires that donors be informed about the specific procedures involved and their risks; what will be done with the biological specimen—in the case of stem cell research; whether an embryo will be created and then destroyed, the intention to derive immortal cell lines for subsequent use in research and, possibly, therapeutic contexts; and primary and secondary uses (when known) of specimens. Informed consent should also address donors' rights to restrict use of their biological materials to only specified purposes, what will happen should they withdraw their consent, potential recontact, and donors' "reach through" rights with respect to commercial products that may be developed through use of their biological materials.[12]

Clinical research involving stem cells poses further ethical challenges. As noted above, questions remain about the safety of therapeutic uses of stem cells or stem cell products, particularly embryonic stem cells. Risks include spontaneous and uncontrolled cell differentiation and tumorigenesis and immunological reactions or tissue rejection, the severity and likelihood of which are uncertain, as well as potential unknown long-term health effects.[12]

RECOMMENDATION

The Council on Ethical and Judicial Affairs recommends that Opinion E-2.146, "Cloning for Biomedical Research" (Appendix) be amended by substitution as follows and that the remainder of this report be filed:

> Opinion 2.146 – Research with Stem Cells
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> Human stem cells are widely seen as offering a source of potential treatment for a range of diseases and are thus the subject of much research. Clinical studies have validated the use of adult stem cells in a limited number of therapies, but have yet to confirm the utility of embryonic stem cells.
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> Physicians who conduct research using stem cells obtained from any source (established tissue, umbilical cord blood, or embryos) must, at a minimum:
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> (a) adhere to institutional review board (IRB) requirements;
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> (b) ensure that the research is carried out with appropriate oversight and monitoring: and

(c) ensure that the research is carried out with appropriate informed consent. In addition to disclosure of research risks and potential benefits, at minimum, the consent disclosure should address:

(i) for a donor of cells to be used in stem cell research:

(a) the process by which stem cells will be obtained;

(b) what specifically will be done with the stem cells;

(c) whether an immortal cell line will result; and

(d) the primary and anticipated secondary uses of donated embryos and/or derived stem cells, including potential commercial uses.

(ii) for a recipient of stem cells in clinical research:

(a) the types of tissue from which the stem cells derive (e.g., established tissue, umbilical cord blood, or embryos); and

(b) unique risks posed by investigational stem cell products (when applicable), such as tumorigenesis, immunological reactions, unpredictable behavior of cells, and unknown long-term health effects.

The professional community as well as the public remains divided about the use of embryonic stem cells for either research or therapeutic purposes. The conflict regarding research with embryonic stem cells centers on the moral status of embryos, a question that divides ethical opinion and that cannot be resolved by medical science. Regardless whether they are obtained from embryos donated by individuals or couples undergoing in vitro fertilization, or from cloned embryos created by somatic cell nuclear transfer (SCNT), use of embryonic stem cells currently requires the destruction of the human embryo from which the stem cells derive.

The pluralism of moral visions that underlies this debate must be respected. Participation in research involving embryonic stem cells requires respect for embryos, research participants, donors, and recipients. Embryonic stem cell research does not violate the ethical standards of the profession. Every physician remains free to decide whether to participate in stem cell research or to use its products. Physicians should continue to be guided by their commitment to the welfare of patients and the advancement of medical science.

Physicians who conduct research using embryonic stem cells should be able to justify greater risks for subjects, and the greater respect due embryos than stem cells from other sources, based on expectations that the research offers substantial promise of contributing significantly to scientific or therapeutic knowledge.

(Modify HOD/CEJA Policy)

Fiscal Note: Staff cost estimated at less than $500 to implement.

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APPENDIX

E-2.146 Cloning for Biomedical Research

Stem cells derived from cloned human embryos resulting from somatic cell nuclear transfer technology are promising as a potential source of treatment in a wide range of diseases. However, much controversy arises from the necessity to destroy embryos in order to extract their stem cells for use in biomedical research. The conflict centers on the moral status of embryos, a question that divides ethical opinion and that cannot be resolved by medical science.

(1) While the pluralism of moral visions that underlie this debate must be respected, physicians collectively must continue to be guided by their paramount obligation to the welfare of their patients. In this light, cloning-for-biomedical-research is consistent with medical ethics. Every physician remains free to decide whether to participate in stem cell research or to use its products.

(2) Cloning-for-biomedical-research requires appropriate oversight and monitoring. At a minimum, not only is the oversight of an institutional review board required, but also that of a regulatory body, such as the Office for Human Research Protections, to monitor progress in the field, assist in developing relevant guidelines, and ensure that the technique of cloning-for-biomedical-research is used only if uniquely promising.

(3) Informed consent by subjects participating in cloning-for-biomedical-research is governed by standard principles: voluntary participation and disclosure of all relevant risks and benefits to subjects. Disclosure to the donor of the oocyte and the donor of the somatic cell also must include:

   (a) Description of the procurement procedures specific to the donor

   (b) Statement of the intention to create a cloned human embryo through introduction of the somatic cell's nucleus into the enucleated egg for research purposes (and not for transfer to a woman's uterus)

   (c) Acknowledgment that the extraction of stem cells will require the cloned embryo's destruction

   (d) The intention to derive immortal cell lines from the stem cells to be used in research and possibly in therapeutic contexts; primary and secondary uses should be disclosed and individuals should be free to refuse the use of their biological materials for specified purposes

   (e) Potential commercial uses and patent or ownership issues (as described in Opinion E-2.08, "Commercial Use of Human Tissue")

(4) The informed consent process for potential recipients of stem cells derived from cloned embryos should conform with ethical standards outlined in the Council on Ethical and Judicial

Affairs' Opinion E-2.07, "Clinical Investigation," and address additional disclosures including provenance of stem cells.

(5) Due to the possibilities of contamination by infectious agents from other species and damage to DNA during growth of new tissues and organs, products of cloning-for-biomedical-research raise ethical concerns similar to those surrounding xenotransplantation. Therefore, the informed consent process for potential recipients of these products also should conform to Opinion E-2.169, "The Ethical Implications of Xenotransplantation." (V)

Issued December 2003 based on the report "Cloning-for-Biomedical-Research," adopted June 2003.