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May 26, 2009

Attn: NIH Stem Cell Guidelines
MSC 7997
9000 Rockville Pike
Bethesda, MD 20892-7997

Dear Sir or Madam:

The Association of American Universities (AAU) comprises 60 leading U.S. research universities which together perform approximately 60 percent of the extramural research funded by the National Institutes of Health (NIH). I write to offer AAU's views on the Draft National Institutes of Health Guidelines for Human Stem Cell Research of April 23, 2009.

The President's Executive Order of March 9, 2009, which lifted the constraints on NIH funding for human stem cell research (hESC) established in 2001, was an inspirational moment for the biomedical research enterprise, the scientists who will pursue this promising research and, most importantly, for the patients and their families who will see its therapeutic benefits. We commend NIH for its swift issuance of draft guidelines to implement the Executive Order. Our faculty and institutions are anxious to begin new hESC research and the President's Executive Order and NIH's prompt action will enable them to pursue scientific advances this year.

Although we are supportive of the Executive Order and NIH's proposed guidelines, and look forward to working with the Administration in implementing them, we do have three major and several minor concerns with what has been proposed.

Three Major Concerns:

1. AAU's first major concern is that the proposed guidelines, as drafted, may render the hESC lines that are currently being used in NIH-supported research ineligible for future federal funding. Such lines, which were derived before August 9, 2001 and used in subsequent research according to NIH guidelines, may not meet newly proposed standards for consent, consent that, given the passage of time and the elimination of any identifiers for such cells, may now be impossible to acquire. Similarly, stem cell lines derived *after* August 9, 2001 and according to guidelines of the NIH, the National Academies or the International Society for Stem Cell Research, should also be made eligible for federally supported research.

Not only would rendering these cell lines ineligible for NIH-funded research undermine the purpose of the President's March 9, 2009 Executive Order, but the disruption—and indeed waste—of years of past and ongoing scientific research is

unthinkable. The four principles that have governed hESC research for the past eight years remain valid and require that:

- the stem cells must have been derived from an embryo that was created for reproductive purposes;
- the embryo was no longer needed for these purposes;
- informed consent must have been obtained for the donation of the embryo; and
- no financial inducements were provided for donation of the embryo.

We submit that the eligibility standards for stem cell lines of the past eight years are adequate for their continued use, and should not be subject to regulation, approval and consent processes created *de novo*. *Stem cell lines currently eligible for NIH funding, those derived after August 9, 2001 and up until the effective date of the proposed April 23, 2009 stem cell research guidelines, and according to the principles listed above, must be eligible for NIH funding.*

2. Secondly, the limitation of federally funded research to hESCs derived from surplus *in vitro fertilization* (IVF) embryos is unnecessarily narrow, and is neither scientifically, ethically nor legally justified. AAU joins with the patient advocacy and scientific communities in expressing disappointment that hESC lines derived from somatic cell nuclear transfer (SCNT), parthenogenesis and IVF embryos created for research purposes are excluded from NIH funded research.

To be sure, there is great scientific and therapeutic promise in hESC research using stem cell lines derived from surplus IVF embryos. The scientific opportunities in developmental biology; new understandings of the interplay of genetics and the environment in human development and disease genesis and progression; and, ultimately, the possibility that hESC research will lead to therapies in which diseased organs and tissues can be targeted or replaced by tissues derived from stem cells, have made this research among the most exciting and promising lines of scientific inquiry at the dawn of this new century.

However, the shortest path to all of the promise of stem cell research is through stem cell lines derived by SCNT from living patients. Such tissues will be an exact genetic match for the patient and therefore, prevent immune rejection of transplanted tissue or the need for immunosuppressive drugs that cause further stress to patients and leave them vulnerable to other infections and side effects. As the National Academies explains in the 2001 report, *Stem Cells and the Future of Regenerative Medicine*:

> A substantial obstacle to the success of transplantation of any cells, including stem cells and their derivatives, is the immune-mediated rejection of foreign tissue by the recipient's body. In current stem cell transplantation procedures with bone marrow and blood, success can hinge on obtaining a close match between donor and recipient tissues and on the use of immunosuppressive drugs, which often have severe and life-threatening side effects. To ensure that stem cell-based therapies can be broadly applicable for many conditions and individuals, new means to overcome the problem of tissue rejection must be found. Although ethically controversial, somatic cell nuclear transfer, a technique that produces a lineage of stem cells that are genetically identical to the donor, promises such an advantage. Other options for this purpose include genetic manipulation of the stem cells and the development of a very large bank of embryonic stem cell lines. In

> conjunction with research on stem cell biology and the development of stem cell therapies, research on approaches that prevent immune rejection of stem cells and stem cell-derived tissues should be actively pursued.

However promising stem cell lines from surplus IVF embryos may be, the scientific and therapeutic promise of cell lines from SCNT, parthenogenesis and IVR embryos created for research purposes is far greater. NIH and federally supported scientists must be able to work with stem cell lines that have been derived from sources other than IVF embryos, lines in which the genomes of such cell lines can be selected or, as appropriate and ethical, designed. The greatest scientific opportunity arises from the ability of scientists to work with stem cell lines that can model the earliest stages of human development and disease development and progression. As was explained in the 2002 National Academies report *Scientific and Medical Aspects of Human Reproductive Cloning*:

> In addition to possible uses in therapeutic transplantation, embryonic stem cells and cell lines derived by nuclear transplantation could be valuable tools for both fundamental and applied medical and biological research. This research would begin with the transfer of genetically defined donor nuclei from normal and diseased tissues. The resulting cell lines could be used to study how inherited and acquired alterations of genetic components might contribute to disease processes. The properties of the cell lines could be studied directly, or the embryonic stem cells could be studied as they differentiate into other cell types. For example, the way in which cells derived by nuclear transplantation from an Alzheimer's disease patient acted while differentiating into brain cells, compared with those derived from a normal patient, might yield new clues about Alzheimer's disease. Such cell lines could also be used to ensure that research covers a more genetically diverse human population than that represented in the blastocysts stored in IVF clinics, promoting studies of the causes and consequences of genetic diseases by allowing researchers to study how embryonic stem cells with different genetic endowments differ in the way that they form cell types and tissues. Finally, studies of genetic reprogramming and genetic imprinting will be substantially enhanced through the use of stem cells derived by nuclear transplantation, compared with studies with stem cells derived from other sources.

AAU's member presidents and chancellors have long been committed to the derivation of stem cells through SCNT, as the AAU Statement on Human Cloning, adopted by the AAU Membership on April 23, 2002 attests:

> AAU therefore supports nuclear transplantation to produce stem cells, also known as somatic cell nuclear transfer, as nonreproductive cloning, and as therapeutic cloning. AAU concurs with the NAS that nuclear transplantation to produce stem cells has considerable potential for advancing our fundamental knowledge and developing new medical therapies to treat debilitating diseases. Continuing the investigation of stem cells produced by nuclear transplantation is the only way to assure that the value of this nascent technology is realized. Before applications to humans should be considered, we need further study of cells derived from the process of nuclear transplantation, subject to federal safeguards.

AAU understands that NIH-funded scientists must adhere to the legal limitations imposed by the Dickey Wicker Amendment, prohibiting federal funding for any research in which a human embryo is created or destroyed for such research. But, the draft guidelines put the situation best: "Although human embryonic stem cells are derived from embryos, such stem cells are not themselves human embryos."

Although SCNT is only a theoretical possibility at this point, the technical barriers to its successful use are falling away rapidly, and it will likely become widely available—and used in the private sector and in privately-supported research—in coming months or years. Furthermore, as SCNT is one of only three methods of deriving stem cells, along with derivation from IVF embryos and derivation using iPSC, it would be unwise to exclude this method from those available to the scientific community for research of benefit to human health. This work can be done in full compliance with ethical and legal considerations**.** *If we are to realize the full therapeutic and scientific potential of human embryonic stem cell research, cell lines derived by SCNT and other methods must be eligible for federal funding.*

3. AAU's final major concern is that the use and sharing of approved cell lines might be hindered by omissions or a lack of clarity in the draft guidelines about eligibility standards, and how and under what terms such research use and sharing occurs. NIH's intent to require institutional assurances that cell lines have been derived according to the guidelines is the correct approach. Institutions have an obligation to implement policies according to the guidelines and maintain the appropriate documentation to demonstrate compliance. Institutions will likely address these requirements by negotiating standard materials transfer agreements that include the documentation and consents upon which such assurances are based.

The necessity of assurances that cell lines have been derived and transmitted according to regulation provides yet another argument for NIH to continue to maintain the existing stem cell registry. Such a registry would assist institutions in meeting the guidelines and streamline the identification and certification of approved cell lines.

NIH has not mandated that IRBs review hESC lines and should not mandate such review going forward. At present, IRBs are required only to review those studies involving research in which cell lines are derived, or in which cell lines are used in humans or if the cells' donors can be identified, but not studies that only involve the use of cell lines *in vitro* or in animals. We think it is entirely appropriate to require and rely on IRB review when human participants are involved as recipients of treatment or can be identified as cell donors. We do not feel that *additional* review should be required. The proposed guidelines do not mandate IRB review for any non-human subject research, but they do impose more stringent restrictions regarding informed consent than those required by the Common Rule. We believe that the consent form requirements in the Common Rule (45 CFR 46) are sufficient. As in other types of research using human tissues, continued IRB review is necessary only in cases where cell lines have identifiable information.

NIH should rely upon existing methods, such as standardized material transfer agreements and institutional assurances, to govern the exchange of stem cell lines. IRB review of such lines should not be mandated, except as called for under existing regulation.

Additional, secondary concerns:

- The title of the regulation should be modified to say that the guidelines govern **federal funding** for human stem cell research.

- The Administration is urged to ensure that standards governing federal support for stem cell research are applied government-wide, not just at NIH.

- Regarding IVF embryo donor consent, it is only proper that donors retain the right to withdraw an embryo up until the moment the research begins. Similarly, such a right to withdraw should be retained up to the moment that the tissue is anonymized for research purposes.

- As stated in the Executive Order and in the draft guidelines, and given the great promise and the potential for rapid progress offered by stem cells, NIH should review the stem cell research guidelines on a regular basis. At a minimum, NIH should state when the next review of these guidelines will occur.

In conclusion, and notwithstanding the concerns raised above, AAU supports the guidelines and looks forward to working with NIH and the Administration in implementing them. The draft guidelines will, in the words of the President's Executive Order "expand NIH support for the exploration of human stem cell research, and in so doing . . . enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind."

Sincerely,

Robert M. Berdahl
President