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Review Article

Public Opinion About Stem Cell Research And Human Cloning - The Bioethics Of Stem Cell Research And Therapy

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Abstract

Discussion of the bioethics of human stem cell research has transitioned from controversies over the source of human embryonic stem cells to concerns about the ethical use of stem cells in basic and clinical research. Key areas in this evolving ethical discourse include the derivation and use of another human embryonic stem cell–like stem cells that have the capacity to differentiate into all types of human tissue and the use of all types of stem cells in clinical research. Each of these issues is discussed as I summarize the past, present, and future bioethical issues in stem cell research. The main bioethical issues associated with human stem cells involve their derivation and use for research. Although there are interesting ethical issues surrounding the collection and use of somatic (adult) stem cells from aborted fetuses and umbilical cord blood, the most intense controversy to date has focused on the source of human embryonic stem (hES) cells. At present, new ethical issues are beginning to emerge around the derivation and use of other hES cell-like stem cells that have the capacity to differentiate into all types of human tissue. In the near future, as the stem cell field progresses closer to the clinic, additional ethical issues are likely to arise concerning the clinical translation of basic stem cell knowledge into reasonably safe, effective, and accessible patient therapies. This Review summarizes these and other bioethical issues of the past, present, and future of stem cell research.

Keywords

stem cells; ethics; religion; human embryonic stem cells; clinic

The Past: Embryo Ethics

hES cells were first isolated and cultured in 1998 from embryos donated by couples no longer intending to use them for their own infertility treatment. From that point forward, hES cell research has been steeped in ethical controversy. Much of this controversy has been symptomatic of an ongoing public unease about the potential negative impacts of science on society. Since its inception, hES cell research has tapped into underlying dystopian fears about human cloning, the commodification of human biological material, the mixing of human and animal species, and the hubristic quest for regenerative immortality [1]. While public concerns such as these about science and its implications are

not in themselves new, hES cell research offered the opportunity for all of these inchoate worries to coalesce around a single, new scientific field.

Against this background dystopian view of science, a pro-life ideology rapidly emerged as a main driving force behind stem cell ethical debate and policy. It is safe to say that, despite a host of other concerns about where science was leading us in the future, the ethical discourse over stem cell research for the past decade has been characterized predominantly by the debate over embryo destruction. In the United States, for example, a sizable minority has objected to the fact that five days-old preimplantation human embryos are destroyed in the process of harvesting their stem cells [2]. Those who oppose embryonic stem cell research believe for religious or other personal reasons that all preimplantation embryos have a moral standing equal to all living persons, regardless of whether they are in a fertility clinic dish or in a woman's body. In this view, destroying preimplantation embryos during research is akin to murder and therefore never acceptable, no matter how noble the aims of the research may be. On the other hand, supporters of embryonic stem cell research have pointed out that not all religious traditions grant full moral standing to early-stage human embryos. According to Jewish, Islamic, Hindu, and Buddhist traditions, as well as many Western Christian views, the moral standing of human beings arrives much later in the gestation process, with some religious views maintaining that the fetus must first reach a stage of viability outside the womb [1]. Living in a pluralistic society such as ours, supporters argue, means having to tolerate differences in religious and personal convictions over such personally theoretical matters as when during the course

Other opponents of hES cell research have maintained that all preimplantation embryos have the potential to become full-fledged human beings and that it is always morally wrong to destroy this potential. In response to this potentiality argument, supporters of stem cell research have questioned whether it is true that all potential human life must be realized in every case. And even if the questionable assumption is granted that all potential life must be realized, it is simply false to claim that all early-stage embryos have the potential for complete human life, since many fertility clinic embryos are of poor quality and therefore not capable of producing a pregnancy, although they may yield stem cells. Potentiality is by no means guaranteed. For instance, developmental biologists have estimated that as many as 75%–80% of all embryos created through intercourse alone fail to implant and are naturally lost, many because of genetic abnormalities. In addition, some supporters of hES cell research have pointed out that no embryos eligible for hES cell research have an absolute, intrinsic potential for full human life since the personal choice was made to not implant these excess fertility clinic embryos in a woman's uterus. And unless this essential step is taken, the potential of a preimplantation embryo for full human life exists only in the most abstract and hypothetical sense [3].

Despite this diversity of religious and philosophical views, it is well known that, over the past eight years, the Bush administration took an embryo protectionist position. It consequently put in place legislature, in the form of an executive order, that restricted federal funding for hES cell research to just those hES cell lines that were in existence on August 9, 2001. Scientists were quick to point out that the hES cell lines on the federal registry were insufficient to support the full range of stem cell research since they lacked genetic diversity, were beginning to accrue genetic mutations and had been grown on mouse feeder layers (which introduce the threat of animal viruses). Scientists, therefore, believed that hES cell lines other than those on the federal registry would have to be studied. Other sources of hES cell research funding, notably state funding initiatives such as those in California, New York, and Massachusetts, began to emerge to help fill the void left by the Bush policy.

In order to bypass the ethical controversy surrounding embryo destruction and to help advance stem cell science, the President's Council on Bioethics recommended in 2005 that "alternative sources" of pluripotent stem cells be pursued that do not involve the destruction of or harm to human embryos [4]. Four such approaches were identified as worthy of serious consideration: stem cells obtained from already-deceased embryos; stem cells obtained from living embryos by nondestructive biopsy; stem cells obtained from bioengineered embryo-like artifacts; and stem cells obtained from dedifferentiated somatic cells. Each of

these approaches sought to generate the a functional equivalent of hES cells derived from living blastocyst-stage embryos — pluripotent human stem cells that are genetically stable and long-lived.

Two studies [5, 6] published soon thereafter in Nature pursued two of the President's Council's suggested alternative stem cell sources — live embryo biopsy and bioengineered embryo-like artifacts. In one of these studies [5], Robert Lanza and colleagues succeeded in deriving mouse embryonic stem cells from single blastomeres separated from eight-cell-stage mouse embryos. Since this technique sought to preserve the ability of the donor to implant and develop to birth, it theoretically could allow for the banking of autologous hES cell lines for children born from biopsied ex-corporeal embryos. In the other study [6], Alexander Meissner and Rudolf Jaenisch developed in mice a variation of somatic cell nuclear transfer (SCNT), a technique whereby the DNA of an unfertilized egg is replaced by the DNA of a somatic cell, by blocking the action of a gene (caudal type homeobox 2 [Cdx2]) that enables the developing embryo to implant into the uterus. By introducing this genetic defect in mouse somatic cells prior to nuclear transfer, they created cloned mouse embryos that generated pluripotent stem cells just before arresting developmentally.

This latter study was an early experimental realization of a concept called altered nuclear transfer (ANT), an idea that William Hurlbut had previously proposed to the President's Council [4]. Research with mouse embryos carrying a mutation in the Cdx2 gene showed that these embryos failed to form a trophectoderm and thus died at the blastocyst stage, but not before giving rise to mouse embryonic stem cells [7]. Extrapolating from this mouse study, Hurlbut reasoned that a CDX2 genetic mutation introduced into a human somatic cell prior to nuclear transfer might produce a blastocyst that could produce human pluripotent stem cells but lacked the biologic potential to develop into a complete human being [8]. Hurlbut suggested that these possible ANT products should be viewed as complex tissue cultures (i.e., bioengineered embryo-like artifacts) rather than viable human embryos because of their limited cellular systems. Leon Kass, then chair of the President's Council and a vehement opponent of hES cell research, viewed Hurlbut's proposal as an ethically attractive alternative [4].

Unfortunately, there were many uncertainties surrounding ANT as a possible source for human pluripotent stem cells. In the conclusion of their study [6], Meissner and Jaenisch acknowledged that it was unknown whether CDX2-deficient human embryos would behave just like their mouse embryo counterparts, yielding pluripotent human stem cells just before arresting at the late blastocyst stage. And even if ANT were capable of generating human pluripotent stem cells, they noted that the additional manipulation of the donor cells to eliminate CDX2 would complicate both the production and safety assessment of patient-specific stem cell lines. These scientific uncertainties called attention to the fact that ANT was motivated chiefly by political, not biomedical, utility. As George Daley and other stem cell scientists pointed out [9], determining whether ANT was feasible, efficient, and effective for research and clinical applications in humans would require significant amounts of time-consuming research and a considerable diversion of resources that could be used toward known methods for deriving hES cells.

There were also significant legal and practical challenges facing both ANT and live embryo biopsy. For instance, James Battey, then chair of the NIH Stem Cell Task Force, pointed out that these alternatives would require human embryo research at some point, either by involving live human embryo biopsy or the creation of human ANT embryos. As a result, the human equivalents of the two mouse studies just described would not be NIH-fundable under the Dickey-Wicker Amendment — a rider attached to a bill signed into law by President Clinton that prohibits federal funding for research that directly involves harm to embryos, including the derivation of new hES cell lines — which remains federal law today [10]. Moreover, some observers at the time advanced the practical point that, with regard to live embryo biopsy for stem cell research, couples who want to support stem cell science may prefer to donate the embryos remaining after their course of in vitro fertilization (IVF) rather than consenting to "nondestructive" biopsies on those precious few embryos they plan to have implanted [11].

With the alternative strategies suggested by the

President's Council for moving stem cell science forward stalled at the starting gate, and with limited federal funding for hES cell research, it was left to individual states and philanthropic organizations to rally behind stem cell progress for the duration of President Bush's tenure in office.

The Present: Beyond The Embryo

While the controversy over embryo destruction remains far from settled, two recent developments have helped reduce much of the heat behind the public debate over hES cell research. The first is the advent of human induced pluripotent stem (iPS) cells — dermal fibroblasts genetically engineered to behave like hES cells. The second is the far friendlier stance of the Obama administration toward hES cell research. At present, the main bioethical considerations tend to lean more toward how stem cell research ought to be conducted, rather than whether it ought to be conducted.

The iPS cell technique was pioneered in 2006 by Kazutoshi Takahashi and Shinya Yamanaka, in Kyoto, Japan [12]. Using retroviruses to insert four stem cell-associated genes (Octamer ¾ [Oct3/4], SRY-box containing gene 2 [Sox2], Myc, and Kruppel-like factor 4 (gut) [Klf4]) into mouse dermal fibroblasts, they showed that these ordinary cells could be reprogrammed to behave like mouse embryonic stem cells and termed these reprogrammed cells induced pluripotent stem cells (iPS cells) [12]. Later, Yamanaka's laboratory and an independent team of researchers were both able to show that human iPS cells could be created and that they behaved very much like hES cells [13, 14].

Predictably, opponents of hES cell research heralded the iPS cell revolution as marking the end of embryonic stem cells. However, most stem cell scientists do not believe that iPS cells (or indeed any other "alternative source" of stem cells) can obviate the need for ongoing hES cell research [15]. For one thing, hES cells must be used as controls to assess the behavior and full scientific potential of iPS cells. In order to carry out these comparisons at the highest levels, scientists' knowledge of hES cells must continue to move forward. Furthermore, iPS cells may not be able to answer important questions about early human development; hES cells would have to be used in these studies instead. In addition, safety is a major issue for iPS cell research aimed at clinical applications, since the methods used in the process of generating iPS cells could cause harmful mutations later in the resulting cells. In light of these and other concerns, iPS cells may perhaps prove to be most useful in their potential to expand our overall understanding of stem cell biology, the net effect of which will provide the best hope of discovering new therapies for patients. The relative ease with which new iPS cell lines can be derived means that new entrants into the stem cell field are now likely to emerge. However, while iPS cells do not require the use and manipulation of donated human embryos for their derivation, it would be a mistake to conclude that iPS cell researchers are free of their own set of ethical concerns. Unlike hES cells, iPS cells can be derived from the somatic tissues of a wide variety of living donors. Therefore, the prospect of having an iPS cell line derived from a living donor entails that familiar ethical issues come into play regarding, for example, the re-contacting and tracking of donors, what to do with incidental findings that may impact a living donor's health, and the extent and scope of donors' reach-through rights to the downstream research uses and commercial benefits of their genetically matched iPS cell lines [16, 17]. The intersection of iPS cell research and these ongoing ethical questions in genetic and tissue research has yet to be fully explored [18]. So, rather than avoiding ethical controversy altogether, researchers working with iPS cells will be effectively trading one set of ethical concerns for another.

Despite becoming connected to ongoing controversies in the biomedical sciences, the stem cell research field in the United States as a whole is likely to become much more active than it has ever been with the arrival of iPS cells and with expanded federal funding for hES cell research under the Obama administration. Perhaps the most important applications of stem cell research today lie in the areas of disease research and targeted drug development. By deriving and studying stem cells that are genetically matched to diseases such as Parkinson disease and juvenile diabetes, researchers hope to map out the developmental course of complex medical conditions to understand how, when, and why diseased specialized cells fail to function properly in patients. Such "disease-in-a-dish" model systems would provide researchers with a powerful new way to study genetic diseases not possible through animal research alone

or by observing patients. Furthermore, researchers can aggressively test the safety and efficacy of new, targeted drug interventions on tissue cultures of living human cells derived from disease-specific hES cells and iPS cells, thus reducing the risks associated with research on human subjects.

To date, stem cell scientists have succeeded in producing a few disease-specific hES cell lines using unwanted fertility clinic embryos that had tested positive for serious genetic diseases, such as cystic fibrosis and fragile X syndrome [19, 20]. However, no embryo genetic screening methods exist for complex diseases such as amyotrophic lateral sclerosis (also known as Lou Gehrig's disease) and Alzheimer disease; thus scientists have been using, with great success, the iPS cell a technique to create disease-specific stem cell lines for these and many other diseases they wish to study [21].

However, questions still linger over whether iPS cells are absolutely identical to stem cells harvested from early-stage embryos. Another possible way of deriving disease-specific stem cells is through SCNT, otherwise known as "research cloning." Using this approach, researchers may be able to produce hES cells that are genetically matched to the patient and his or her particular disease. SCNT has worked recently in non-human primates to produce cell donor–matched primate stem cells, suggesting that human SCNT for disease research is, in principle, possible [22]. However, two realities appear to undermine the feasibility of SCNT as a widespread methodology in stem cell research. The first is that recently drafted NIH guidelines [23] only allow federal funds to be used for research on stem cell lines derived from excess IVF embryos, not embryos created specifically for research purposes (which includes those created via SCNT). The second is that, to date, women have been unwilling to donate their eggs for SCNT without any compensation for their efforts. Egg donor compensation for research is against the law in California and
Massachusetts and is not recommended by the National Academy of Sciences' Guidelines for human embryonic stem cell research [24]. The chief concern has been that compensation would undermine a woman's voluntary choice by creating an undue inducement to undergo hormonal induction to provide eggs for research [25]. Bucking this trend, however, the State of New York has recently announced that it will allow donor compensation for providing eggs for research commensurate with what women typically earn for providing their eggs for infertility treatment. Varying state and national stem cell research funding policies threaten to complicate attempts by researchers to collaborate across research locales, both nationally and internationally. For example, in the United States, the individual states have dramatically differing policies regarding the derivation and use of new hES cell lines, including divergent policies on the procurement of gametes, embryos, and other cells from donors [26]. Some countries, such as Germany and Italy, permit hES cell research only with imported lines and prohibit the derivation of new hES cell lines from excess IVF embryos and SCNT. Other countries, such as Canada and Denmark, permit hES cell research and the derivation of new hES cell lines from donated IVF embryos but prohibit SCNT. Many other nations have no explicit laws governing hES cell research [27]. Efforts to harmonize disparate standards have been undertaken by groups such as the Interstate Alliance on Stem Cell Research (IASCR) and the International Society for Stem Cell Research (ISSCR) and may blunt some of the potential sharp differences in research policies both in the United States and abroad.

Over the past few years, there has also evolved a new system of research oversight in stem cell research locales. Following professional guidelines issued by the National Academies and the ISSCR, all privately and publicly funded researchers working with pluripotent stem cells today are encouraged (and in most institutions required) to have their research proposals approved by a Stem Cell Research Oversight (SCRO) committee. SCRO committees include basic scientists, physicians, ethicists, legal experts, and community members and are designed to look at stem cell–specific issues relating to the proposed research. SCRO committees also work with local ethics review boards to ensure that the donors of embryos and other human materials are treated fairly and have given their voluntary, informed consent to stem cell research teams. Informed consent is especially important for somatic cell donors in iPS cell and SCNT studies since the individuals represent a living genetic

source of the resulting genetically matched stem cell lines. It is also crucial for patients donating somatic cells for disease-specific stem cell studies, as they might otherwise donate under a false expectation that they will benefit directly from eventual medical applications of their patient-specific stem cells.

The Future: Toward The Clinic

Perhaps the most exciting and vexing set of bioethical issues arising today involves the process of transitioning bench knowledge to the bedside. Emerging ethical issues of this clinical translational stage of stem cell research goes far beyond the embryo debate since they encompass all stem cell types, not just hES cells, and because they involve human subjects, who, despite what one may think about the moral status of embryos, are unequivocally moral persons with rights and interests that may be harmed.

Until very recently, there existed no professional guidance for researchers wanting to translate basic stem cell research into effective clinical applications for patients. This past year, the ISSCR released a set of international guidelines to fill this void [28]; these are summarized in Sidebar 1. Moving from the bench to the bedside will involve many complex steps, many of which are quite scientifically technical. All of these aspects, however, are relevant in a bioethical sense, since they affect directly the risk/benefit ratio that must be assessed before clinical research with patients can be ethically allowed. For example, uniform standards for cell processing and manufacture must be agreed upon by the international community of researchers, stem cell banks, and regulators. Standards for preclinical testing using animal models must be clarified before first-in-human clinical trials can begin, and fair procedures for enrolling human subjects in early stem cell-based clinical trials must be articulated.

References

1. Cohen CB. Renewing the Stuff of Life: Stem Cells, Ethics, and Public Policy. New York, NY; Oxford University Press; 2007.
2. Nisbet MC. Public opinion about stem cell research and human cloning. Public Opin Q. 2004;68(1):131–154.
3. Hyun I, Jung KW. Human research cloning, embryos, and embryo-like artifacts. Hastings Cent Rep. 2006;36(5):34–41.
4. The President's Council on Bioethics. White Paper: Alternative Sources of Human Pluripotent Stem Cells. Washington, DC: National Academic Press; 2005.
5. Chung L, et al. Embryonic and extraembryonic stem cell lines derived from single mouse blastomeres. Nature. 2006;439(7073):216–219.
6. Meissner A, Jaenisch R. Generation of nuclear transfer-derived pluripotent ES cells from cloned Cdx2-deficient blastocysts. Nature. 2006;439(7073):212–215.
7. Chawengsaksophak K, de Graff W, Rossant J, et al. Cdx2 is essential for axial elongation in mouse development. Proc Natl Acad Sci U S A. 2004;101(20):7641–7645.
8. Hurlbut W. Altered nuclear transfer as a morally acceptable means for the procurement of human embryonic stem cells. Perspect Biol Med. 2005;48(2):211–228.
9. Melton DA, Daley GQ, Jennings CG. Altered nuclear transfer in stem cell research: a flawed proposal. N Engl J Med. 2004;351(27):2791–2792.
10. Alternative Methods for Deriving Stem Cells: Hearing before a Subcommittee of the Committee on Appropriations, United States Senate, 109th Cong, 1st Sess (2005) (testimony of James Battey, MD, PhD).
11. Alternative Methods for Deriving Stem Cells: Hearing before a Subcommittee of the Committee on Appropriations, United States Senate, 109th Cong, 1st Sess (2005) (testimony of George Q. Daley, MD, PhD).
12. Takahashi K, Yamanaka S. Induction of plurip-

otent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–676.

13. Takahashi K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–872.
14. Yu J, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858):1917–1920.
15. Hyun I, Hochedlinger K, Jaenisch R, Yamanaka S. New advances in iPS cell research do not obviate the need for human embryonic stem cells. Cell Stem Cell. 2007;1(1):367–368.
16. Aalto-Setala K, Conklin B, Lo B. Obtaining consent for future research with induced pluripotent cells: opportunities and challenges. PLoS Biol. 2009;7(2): e42.
17. Wolf S, et al. Managing incidental findings in human subject's research: analysis and recommendations. J Law Med Ethics. 2008;36(2):219–248.
18. Hyun I. Stem cells from skin cells: the ethical questions. Hastings Cent Rep. 2008;38(1):20–22.
19. Pickering SJ, et al. Generation of a human embryonic stem cell line encoding the cystic fibrosis mutation deltaF508, using preimplantation genetic diagnosis. Reprod Biomed Online. 2005;10(3):390–397.
20. Eiges R, et al. Developmental study of fragile X syndrome using human embryonic stem cells derived from preimplantation genetically diagnosed embryos. Cell Stem Cell. 2007;1(5):568–577.
21. Park IH, et al. Disease-specific induced pluripotent stem cells. Cell. 2008;134(5):877–886.
22. Byrne JA, et al. Producing primate embryonic stem cells by somatic cell nuclear transfer. Nature. 2007;450(7169):497–502.
23. National Institutes of Health. Guidelines on Human Stem Cell Research. Stem Cell Information August 25, 2009.
24. National Research Council. Guidelines for Human Embryonic Stem Cell Research. Washington, DC: The National Academies Press; 2005.
25. Hyun I. Fair payment or undue inducement? Nature. 2006;442(7103):629–630.
26. Stayn S. A guide to state laws on hESC research and a call for interstate dialogue. Medical Research Law & Policy Report. 2006; 5:718–725.
27. Caulfield T, et al. The stem cell research environment: a patchwork of patchworks. Stem Cell Rev Rep. 2009;5(2):82–88.
28. ISSCR Task Force for the Clinical Translation of Stem Cells. Guidelines for the Clinical Translation of Stem Cells. December 3, 2008.
29. Lau D, et al. Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. Cell Stem Cell. 2008;3(6):591–594.
30. Cosgrove DM. Ethics in surgical innovation: vigorous discussion will foster future progress. Cleve Clin J Med. 2008;75(suppl 6): S6.
31. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. Science. 2009;324(5935):1664–1665.
32. Hyun I, et al. New ISSCR guidelines underscore major principles for responsible translational stem cell research. Cell Stem Cell. 2008;3(6):607–609.
33. Taylor PL. Research sharing, ethics and public benefit. Nat Biotechnol. 2007;25(4):398–401.