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Review Series

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The bioethics of stem cell research and therapy

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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 other 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.

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-day-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 located in a fertility clinic dish or in a woman's body. In this view, destroying preimplantation embryos during the course of 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 of human biological development moral personhood first appears.

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 legislation, 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

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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 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 3/4 [*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 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



Sidebar 1

Summary of key ISSCR guidelines for the translation of stem cell research into the clinic

- Investigators involved in preclinical or clinical research involving stem cells or their direct derivatives should act within the ISSCR guidelines and other relevant policies and regulations.
- Clinical research involving stem cells or their direct derivatives should be reviewed by human subject review committees supplemented with experts in stem cell science.
- Donors and patients need to give well-informed written consent, and they should demonstrate their understanding of the involved risks.
- Scientists and regulators should work to develop common reference standards.
- Appropriate quality standards and management systems for manufacturing cells need to be developed.
- Sufficient preclinical studies in relevant animal models need to be performed.
- Cells to be used in clinical trials must be extensively tested for potential toxicities, including tumorigenicity, in vitro and in animal studies.
- Patients should be monitored for long-term health effects and adverse events reported in a timely manner.

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 go 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.

The ISSCR clinical translation guidelines stress the importance of having individuals with stem cell-specific expertise involved in the scientific and ethical review at each step along the translational research process (28). Individuals with stem cell-specific expertise are best suited to help investigators and human research review committees assess the scientific rationale of the clinical trial protocol; the in vitro and in vivo preclinical studies that form the basis of the clinical study; and the risks of abnormal cell function, proliferation, and/or tumor development. The ISSCR guidelines also

recommend that special emphasis be given to the unique risks of stem cell-based clinical research during the informed consent process. These risks include tumor formation, immunological reactions, unpredictable behavior of the cells, and long-term health effects yet unknown. Risks to future research participants may be further minimized through careful monitoring of patient-subjects and timely reporting of adverse events.

Currently, stem cell-based therapies are the clinical standard of care for a few conditions, such as hematopoietic stem cell transplants for leukemia and epithelial stem cell-based treatments for burns and corneal disorders. However, the public may not quite appreciate the many years of preclinical and clinical research that are required to establish new stem cell-based therapies. Unfortunately, there are some unscrupulous clinicians around the world exploiting the hopes of patients by purporting to provide effective stem cell therapies for large sums of money. These so-called “stem cell clinics” advance claims about their proffered stem cell therapies without credible rationale, transparency, oversight, or patient protections (29).

The administration of unproven stem cell interventions outside carefully regulated research protocols puts individual patients at risk and jeopardizes the legitimate progress of translational stem cell scientific research. Patients who travel for unproven stem cell therapies (this is colloquially referred to as “stem cell tourism”) put themselves at risk of physical and financial harm. In condemning the fraudulent practices of these so-called stem cell clinics, however, we must be very careful not to squelch simultaneously the possibility of responsible medical innovation outside the context of a clinical trial. Medically innovative patient care, in addition to regular clinical trials, can be a powerful route to the development of clinically established therapies, as has happened in other relevant areas of medicine, such as surgery (30).

Of course, it is crucial to emphasize that, given the current state of our knowledge about stem cells and their effects, patients should be advised against medical travel for unproven stem cell-based therapies at this time. In the near future, however, there will be a need to articulate a distinction between problematic stem cell tourism and legitimate attempts at medically innovative stem cell-based patient care (31). This task will become increasingly difficult, as authoritative preclinical stem



cell studies and legitimate clinical trials begin to offer promising results to the public. It is likely that the interest of the public in stem cell tourism will increase, not diminish, as stem cell science advances toward the clinic.

The ISSCR clinical translation guidelines offer a good place to begin thinking about this important problem. The guidelines allow for exceptional circumstances in which clinicians might attempt medically innovative care in a very small number of seriously ill patients, subject to stringent oversight criteria (32). These criteria include: independent peer review of the proposed innovative procedure and its scientific rationale; institutional accountability; rigorous informed consent and close patient monitoring; transparency; timely adverse event reporting; and a commitment by clinician-scientists to move to a formal clinical trial in a timely manner after experience with, at the most, a few patients. By juxtaposing the practices of current stem cell clinics against the standards outlined in the ISSCR guidelines, we can easily identify the shortcomings of some clinics and call into question the legitimacy of their purported claims of providing innovative care to patients.

By moving forward from past debates about embryo status to issues concerning the uses of all varieties of stem cells, we can begin to focus the bioethical discourse on areas that have a much broader consensus base of shared values, such as patient and research subject protections and social justice. Looking to the future development of stem cell-based diagnostics and therapeu-

tics, some commentators have wondered whether the potential for over-commercialization and restrictive patenting practices might delay or reduce the broad public benefit of stem cell research. As Patrick Taylor has forcefully argued (33), the promise of broad public benefit is one of the justifying conditions for conducting stem cell research; without the real and substantial possibility for public benefit, stem cell research loses one of its most important moral foundations. As stem cell-based clinical research advances, it is imperative that principles of social justice be taken proactively and seriously. This may include creatively reconfiguring existing models of intellectual property, licensing, product development, and public funding to encourage broad social access for stem cell-based therapies (18). Achieving social justice may also involve calling on regulatory and oversight agencies to include a greater involvement of community and patient advocates in the oversight of research. Dealing with the bioethics of *how* (rather than *whether*) to proceed with stem cell research demands that we wrestle with these and other tough questions. Much work lies ahead for the international community of researchers, clinicians, patient advocates, regulators, and bioethicists.

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