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Pluripotent Stem Cells: The Search for the “Perfect” Source

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Anyone who dreamed that the public controversy over human embryonic stem cell (hESC) research had begun to die down was rudely awakened by the decision in Sherley v. Sebelius. On August 23, District of Columbia District Court Judge Royce Lamberth issued a preliminary injunction halting federal funding of research using newly created hESC lines until the plaintiffs’ challenge to the 2009 liberalization of funding guidelines can be heard. On September 9, 2010, the Court of Appeals for the District of Columbia temporarily stayed Judge Lamberth’s order, and on September 28, 2010, the Court of Appeals ordered that the appeal be expedited and granted the Obama administration’s motion to permit federally

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2. Id. at 66.
funded hESC research to go forward during the appeal.4

This dispute over federal funding might seem relatively insignificant at first. Since the enactment of the Dickey-Wicker Amendment5 restricting the availability of funds for hESC research, many states have set aside funding for hESC research6—in some cases in significant amounts.7 Private funding is also available from the pharmaceutical industry and disease advocacy foundations.8 Investigators and academic medical centers have become accustomed to separating their cell lines, equipment, and activities so that there is no commingling of federally funded hESC research with hESC research that cannot receive federal support.9 And finally, there are many alternate sources of highly pluripotent stem cells, though the scientific and practical promise of these sources is, as we shall see, highly variable.

Nonetheless, this renewed focus on the Dickey-Wicker Amendment demonstrates both the sensitivity of hESC research and the complexity of the science, ethics, and policy surrounding research using all forms of human stem cells. Even the most cursory examination of this wide-ranging area of scientific progress and policy discussion illustrates the futility of searching for the “perfect” stem cell source.

I. A SHORT HISTORY

The Dickey-Wicker Amendment was initially enacted in 1996 as a rider to appropriations legislation passed by

6. See, e.g., CAL. CONST. art. XXXV (establishing the California Institute for Regenerative Medicine and the state constitutional right to conduct stem cell research); CONN. GEN. STAT. § 19a-32e (West Supp. 2010); MD. CODE ANN. ECON. DEV. § 10-434 (LexisNexis 2008).
Congress in 1995. It has been reenacted yearly since then. The amendment prohibits the Department of Health and Human Services from using appropriated funds for “(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero . . . .” The amendment defines a human embryo as any organism “derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes.”

In 2001, President George W. Bush instituted a policy permitting limited federal funding for research using hESC lines that existed as of August ninth of that year. Later, he twice vetoed legislation to expand federal financing for hESC research, and issued an Executive Order calling for further research on alternative sources of pluripotent stem cells. When Bush’s policy was instituted, the NIH estimated that 64 lines were available for use. Late in his term, however, there were only about 20 embryonic stem cell lines approved for use in federally funded studies. Many of these lines were considered to be contaminated, to lack genetic diversity, or to be otherwise insufficient for medical research. Legislation to change the date by which hESC lines must have been created to be used in federally funded research repeatedly failed in Congress during the Bush Administration.

11. Id.
12. Id.
Thus, when President Obama issued a new Executive Order permitting federal funding of research using newly created cell lines from embryos originally created for in vitro fertilization and later donated for research, the change was viewed as a simple modification of the date by which approved stem cell lines could be created. The source of embryos was considered largely uncontroversial because the embryos were not created for research and would otherwise be discarded or stored indefinitely. Concerns remained that the number of embryos available for research as a result of in vitro fertilization might not make available a sufficient number of optimally robust cell lines. Still, it was not anticipated that the interpretation of the Dickey-Wicker amendment’s language would become a source of controversy.

However the Sherley v. Sebelius litigation is ultimately resolved, it is clear that disagreement and concern about the status of embryos and divergent views among scientists and the public about morally appropriate sources of and uses for hESCs will persist. Although new sources of potentially useful stem cells are hinted at almost daily in both the scientific literature and the popular press, profound optimism about the therapeutic promise of hESCs coexists with uncertainty about when that promise will be realized, ensuring that scientists will continue their quest for better sources of pluripotent stem cells.

19. See generally National Institutes of Health Guidelines for Human Stem Cell Research, supra note 9, at 32,173.
22. Lyerly & Faden, supra note 17, at 46–47.
II. hESCs IN BRIEF

In 1981, pluripotent cells were found in the inner cell mass of the mouse embryo, and the term “embryonic stem cell” was coined.\textsuperscript{25} The ability to retrieve human embryonic stem cells was described in 1998.\textsuperscript{26} These cells are able to differentiate into all cells of the human body, excluding placental cells (only cells from the morula are totipotent; that is, able to develop into all cells of the human body). Human embryonic stem cells are highly versatile, able to give rise to all types of cells and to be “immortalized,” or perpetually propagated in a cell line.\textsuperscript{27} Their versatility makes them valuable for research and treatment. However, they also have the intrinsic property of forming teratoma tumors.\textsuperscript{28}

Ethical and policy arguments about the legal and moral status of the embryo and preembryo are so familiar to most of us that they no longer engage the intellect, but only serve to harden apparently irreconcilable viewpoints. Each new alternative source of highly multipotent stem cells seems to alter the balance of arguments only slightly, exchanging some concerns for others but never changing the moral landscape enough to change minds.\textsuperscript{29}

Opponents of hESC research posit that all human zygotes and embryos deserve significant protections because of their potential for human development, regardless of whether that potential will ever be realized.\textsuperscript{30} While each cell in a zygote, or very early embryo, is totipotent, that is, fully able to develop into a complete embryo, the cells and cell lines derived from human embryos are instead pluripotent: highly versatile but not able to become new embryos. For this reason, contemporary


\textsuperscript{29} See generally Cohen, supra note 23.

arguments in opposition to hESC research focus on the destruction of embryos capable of developing into adult humans, rather than on the moral status of the hESCs themselves.31

In contrast, proponents of hESC research employ a range of deontological and consequentialist arguments, from the proposition that human embryos should be viewed as biological property, afforded no special protection, to holding that human embryos should be afforded an intermediate moral status with some special protections, but not a status equivalent to that of a living infant or adult human.32 Terms like ‘spare,’ ‘extra,’ ‘leftover,’ ‘discarded,’ ‘abandoned,’ and ‘unwanted’ are used to characterize human embryos created for assisted reproduction but frozen and unused. A utilitarian calculus is often employed to justify using these embryos—the most commonly discussed potential source of new hESC lines, and the source referenced in President Obama’s Executive Order and the revised 2009 Guidelines—in research. Many couples who have attempted in vitro fertilization have expressed willingness to donate frozen embryos for this purpose.33

III. ALTERNATIVE SOURCES

Sherley v. Sebelius has now redoubled attention to deriving highly pluripotent stem cell lines in ways that do not destroy human embryos. These methods can be organized into several categories: (1) somatic cell reprogramming; (2) other non-embryonic sources; (3) employing artificial and asexual methods to create embryos; and (4) extracting hESCs from embryos without embryo destruction. Each method shows considerable promise, and each raises scientific, ethical, and policy questions of its own.

A. SOMATIC CELL REPROGRAMMING: INDUCED PLURIPOTENT STEM CELLS

The newest and, to many, the most exciting alternative to hESC research is the development of pluripotent cells through somatic stem cell reprogramming. In this process, either

31. See generally COHEN, supra note 23.
33. Lyerly & Faden, supra note 17, at 46–47.
somatic cells or determined stem cells are stimulated by the introduction of genetic material to evolve backward to a state of pluripotency. The resulting induced pluripotent stem cells (iPSCs) can then be grown into cell lines. This process mimics the limb regeneration capacities of some amphibians. The most significant moral concern that has been raised about this research is that the process could be pursued beyond pluripotency to totipotency. This concern appears, however, to be entirely speculative.

First created in 2007, iPSCs hold great promise as an alternative to hESCs. To create them, pluripotency is induced in a somatic cell (or sometimes in a so-called “adult stem cell,” which can generate a single cell type) by genetically reprogramming it to dedifferentiate into a pluripotent state. In a clinical setting, this method could facilitate the growth of compatible cells, tissues, or organs from a patient’s own cells. In a research setting, iPSC lines could facilitate the close study of many genetic disorders and the genetic contributions to common complex disorders. This technique thus has potential uses very similar to those of somatic cell nuclear transfer, without the need for oocytes.

Several scientific obstacles must be overcome, however, before iPSCs can be demonstrated to be as useful as hESCs. Safety is a key consideration in the process of generating

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36. Yoshinori Yoshida & Shinya Yamanaka, Recent Stem Cell Advances: Induced Pluripotent Stem Cells for Disease Modeling and Stem Cell-Based Regeneration, 122 Circulation 80, 80 (2010).


38. See infra Part III.C.1.
iPSCs. Most current methods of iPSC creation require the introduction of genetic material into the cell. This is often achieved by using viral vectors, as in gene transfer research, and thus introduces comparable risks, including the possibility of inducing cancers through insertional mutagenesis.\(^{39}\) Uses of non-integrating vectors or removable viral vectors, non-viral vectors, and non-genetic means of reprogramming cells to a pluripotent state are in development in many laboratories.\(^{40}\) In a recent development, the use of non-integrating synthetic messenger RNA for cell reprogramming appears potentially safe and efficient.\(^{41}\) The intrinsic propensity of iPSCs, like hESCs, to form teratoma tumors, however, may still pose a risk.\(^{42}\) Some recent experiments show potential for circumventing these issues, but any risk of tumorigenicity remains a challenge.\(^{43}\)

Finally, because decades of research have established hESCs as the researcher’s gold standard, even as iPSCs are increasingly studied, hESCs will continue to be necessary in research, particularly as controls. Accordingly, the ethical concerns attending the use of hESCs are likely to accompany much iPSC research for the time being. Many uncertainties about the safety, effectiveness and cost of iPSC development and use in research are yet to be determined.

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\(^{40}\) See Rudolf Jaenisch & Richard Young, Stem Cells, the Molecular Circuitry of Pluripotency and Nuclear Reprogramming, 132 CELL 567, 576 (2008); Lengner, supra note 37, at 40; Wenlin Li et al., Generation of Rat and Human Induced Pluripotent Stem Cells by Combining Genetic Reprogramming and Chemical Inhibitors, 4 CELL STEM CELL 16, 18–19 (2009); Keisuke Okita et al., Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors, 322 SCIENCE 949, 949–52 (2008); Takashi Tada, Genetic Modification-Free Reprogramming to Induced Pluripotent Cells: Fantasy or Reality?, 3 CELL STEM CELL 121–22 (2008).

\(^{41}\) Luigi Warren et al., Highly Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA, 7 CELL STEM CELL 1, 6–7 (2010).


\(^{43}\) See Lengner, supra note 37, at 39.
B. NON-EMBRYONIC SOURCES: AMNIOTIC FLUID AND PLACENTAL CHORIONIC VILLI

Scientists have also discovered that broadly multipotent stem cells capable of extensive expansion in laboratory culture have been isolated from what are often considered biological waste products: amniotic fluid and placental chorionic villi, and the stromal tissue of umbilical cord. The discovery that amniotic fluid and placental tissue yields stem cells that are neither derived from nor capable of developing into a human embryo, yet are far more malleable and versatile than determined stem cells, is an exciting research prospect. The derivation of useful cell lines from non-embryonic sources does not, however, eliminate all ethical issues attendant upon this research. For example, concern exists that the desire to capture and store amniotic fluid stem cells will result in an increase in amniocentesis, which carries small but well-recognized risks of morbidity. However, similar cells can be obtained from the placenta, which is more readily accessible after birth and is also usually discarded.

The discovery of new sources of highly multipotent cells in potentially abundant biological waste materials like amniotic fluid and placenta presents the real possibility of creating publicly accessible stem cell banks which, by virtue of their size and completeness, could quickly amass stem cells in sufficient number and diversity to provide very good (albeit not perfect) matches for almost all of the human population. Building on the arguments for pooling and sharing stored umbilical cord blood, the creation of a cord blood and amniotic fluid stem cell bank would have great promise for research and, eventually,

44. M. Minhaj Siddiqui & Anthony Atala, Amniotic Fluid-Derived Pluripotent Cells, in 2 HANDBOOK OF STEM CELLS 175, 178–79 (Robert Lanza et al. eds., 2004); Ming-Song Tsai et al., Clonal Amniotic-Fluid Derived Stem Cells Express Characteristics of Both Mesenchymal and Neural Stem Cells, 74 BIOLOGY REPROD. 545, 550 (2006).
46. Paolo De Coppi et al., Isolation of Amniotic Stem Cell Lines with Potential for Therapy, 25 NATURE BIOTECH. 100, 100–06 (2007).
48. De Coppi et al., supra note 46.
49. Faden et al., supra note 17, at 13.
for treatment, without traditional ethical concerns. Traditional objections, however, may simply be replaced by concerns about stem cell banking, including questions about collection protocols, consent for collection, and the development, maintenance, and sharing of banked cells. Much work is needed to ensure the appropriate establishment and operation of amniotic fluid and placental stem cell banks. Systems for the collection, storage, and use of stem cells of different types are still in the early stages, both technologically and from a policy standpoint. Scientific, practical, and ethical issues raised include ensuring the broad availability of matches for those in need, determining access for research and for therapeutic uses, refining consent forms, information, and procedures, and developing robust systems for confidentially labeling biospecimens and linking them to the information needed for research and treatment. These issues have been well-rehearsed in cord blood banking but have not been solved or settled. Future extensions to highly multipotent stem cells from amniotic fluid and placenta may be easier in some respects—for instance, the cells can be perpetuated and thus will not be used up when samples are taken for a particular use. Other issues may be more difficult. For example, the processing cost for amniotic fluid stem cells may be nontrivial. In addition, since amniotic fluid stem cells are expected to have a broader range of potential uses, the desired scope of consent could be controversially broad.

C. ASEXUAL METHODS USING OOCYTES: SOMATIC CELL NUCLEAR TRANSFER, ALTERED NUCLEAR TRANSFER, AND PARTHENOGENESIS

1. Somatic Cell Nuclear Transfer

Artificial and asexual methods of stimulating the human oocyte to act like an embryo are yielding promising results. For

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example, in somatic cell nuclear transfer (SCNT), the nucleus
of an oocyte is removed, replaced with a cell from another
donor, and stimulated to engage in cell differentiation. After
sufficient cell division, stem cells are extracted that are a
genetic match to the donor, thus making this process, like iPSC
creation, useful to study certain genetic diseases or to grow
tissues and organs that will not be rejected. Concerns about
the use of SCNT include the need to use large numbers of
oocytes in order to produce a viable and stable stem cell line, along with the issues of understanding, consent, and voluntariness that accompany oocyte procurement. This method, moreover, uses the same principles as reproductive cloning, giving rise to a slippery slope problem for some opponents. The possibility of using non-human oocytes could resolve concerns about oocyte procurement, but raises other questions of feasibility and the ethics of this type of chimera creation.

2. Altered Nuclear Transfer

Scientists are therefore looking for ways to make reproduction impossible from cloned embryos. With this technology, called altered nuclear transfer (ANT), a gene that helps with implantation is deactivated during the growth of the blastocyst, but reactivated after harvesting stem cells in order


56. Korobkin, supra note 30, at 171.

to create normal stem cell lines.\textsuperscript{58} ANT is a variation of SCNT in which a genetically modified nucleus from a somatic cell is transferred into a human oocyte. This embryo, which contains a deliberate genetic defect, is capable of developing into a blastocyst, but the induced defect prevents the blastocyst from implanting in the uterus. This process has the potential to generate customized hESCs from the blastocyst stage.\textsuperscript{59} Human embryos with this genetic defect might lack the capacity to develop into viable fetuses, as a result of their inability to implant, thus providing a source of stem cells without destroying viable embryos. Proof of concept was obtained in mice by Meissner and Jaenisch using embryos lacking the \textit{Cdx2} homeobox gene.\textsuperscript{60}

The viability of human embryos lacking the \textit{Cdx2} gene is unclear, as is whether this mutation restricts human developmental potential into certain lineages. While much research must be done before therapeutic strategies based on this technique could ever enter the clinic, at this time hESCs derived from ANT can provide opportunities to study pluripotency in hESCs, without the need for destruction of viable embryos. The exact effects of \textit{Cdx2} gene knockout on the development of human embryos are not well known. Opponents contend, however, that using ANT does not overcome moral objections to this methodology.\textsuperscript{61}

3. Parthenogenesis

Another method that focuses on oocyte stimulation and development is parthenogenesis, or “virgin birth.”\textsuperscript{62} This is the reproduction method of certain amphibians, and has been used to induce pregnancy artificially in mice. Here, an oocyte is chemically stimulated to undergo several rounds of cell division, as if it had been fertilized. The oocyte retains all 46

\begin{itemize}
  \item \textsuperscript{58} Alexander Meissner & Rudolf Jaenisch, \textit{Generation of Nuclear Transfer-Derived Pluripotent ES Cells from Cloned Cdx2-Deficient Blastocysts}, 439 \textit{NATURE} 212, 214 (2006).
  \item \textsuperscript{59} WB Hurlbut, \textit{Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells}, 48 \textit{PERSP. BIOLOGY & MED.} 211, 222–26 (2005).
  \item \textsuperscript{60} See Meissner & Jaenisch, \textit{supra} note 58, at 212–14.
  \item \textsuperscript{61} Hall, \textit{supra} note 17, at 16–22; Korobkin, \textit{supra} note 30, at 161, 171.
  \item \textsuperscript{62} Kent Vrana et al., \textit{Nonhuman Primate Parthenogenetic Stem Cells}, 100 \textit{PROC. NAT’L ACAD. SCI. U.S.} 11911, 11911, 11916 (2003).
\end{itemize}
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chromosomes, and appears to lack developmental capacity beyond the blastocyst stage. It is uncertain whether a line obtained by this means would be stable or whether issues related to its parthenogenetic origin may limit its usefulness. Moreover, the Dickey-Wicker Amendment includes research on human parthenogenesis in its list of federal funding prohibitions.

D. HESC WITHOUT EMBRYO DESTRUCTION: EXTRACTION AND “DEAD” EMBRYOS

1. Extraction

Using blastomere extraction, it may be possible to extract a single cell from embryos created for purposes of IVF, as is done for preimplantation genetic diagnosis (PGD). In 2006, Chung et al. were the first authors to report the generation of mouse embryonic stem cell lines in this manner. Cells were taken from eight-cell blastomeres rather than from blastocysts. The remaining four to six cells continue to divide and multiply as normal. The cells differentiated into derivatives of all three embryonic germ layers in vitro, as well as into teratomas in vivo. In addition, the mouse embryos that resulted from the biopsied blastomeres developed to term without a reduction in their developmental potential. In PGD, the removed cells are biopsied so that genetic testing can be performed. With blastomere extraction, the removed cells are cultured on feeder cells, from which stem cells can be derived.

Preimplantation genetic diagnosis now commonly accompanies IVF, particularly when there is concern about

63. Id. at 11912. See generally GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH, supra note 34.
69. See Young Chung et al., Human Embryonic Stem Cell Lines Generated Without Embryo Destruction, 2 CELL STEM CELL 113, 113 (2008).
inheritable disease. While some have raised concerns that the removal of a single cell from the developing embryo for PGD could pose significant risks to its development, so far it appears not to have adverse effects on embryos that are later implanted and progress to live birth. Moreover, if it is clearly shown to be safe to remove more than one cell from an embryo, in order to use one for PGD and one for development of a stem cell line—or, more probably, if it is reasonable to remove one cell, grow it overnight into a blastocyst, and use one of those cells for PGD and the rest for cell line development—then embryos need not be destroyed to pursue hESC research. This source of pluripotent stem cells, however, may require development to the blastocyst stage. If blastocysts are thought to deserve protection as future persons, then this source may be unacceptable to hESC research opponents.

2. Dead Embryos

Another possible way to obtain pluripotent stem cells without intentionally destroying the embryo would be to use only those spare IVF embryos that, after achieving the four-to-eight cell division, undergo “cleavage arrest” or death. During IVF, only a small proportion of zygotes produced will develop successfully to the morula and blastocyst stages. Over half the embryos stop dividing, and are therefore considered dead embryos. Such embryos have unequal or fragmented cells and blastomeres and are usually discarded. While some of these embryos show chromosomal anomalies, others appear to be normally developed embryos from which stem cells can be extracted. Some researchers claim that there are reliable methods for determining whether or not the embryo has a normal chromosome complement, while others are skeptical about the viability of hESC lines derived from such embryos. Advocates note that hESC lines derived from this method may have broad therapeutic application for genetic conditions. Some opponents of this method raise informed consent issues, as well

70. See Klimanskaya et al., supra note 66, at 481–84.
72. Id.
73. Xin Zhang et al., Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos, 24 STEM CELLS 2669, 2670 (2006).
as ethical concerns over whether and when death actually occurs in embryos.

IV. FUTURE PERFECT?

Those who follow the stem cell debate are familiar with its rhythm: rapid proliferation of press information about possible new sources of pluripotent stem cells, followed by reflexive moral pronouncements, followed by questions about the science, followed by clarifications, qualifications, and additional expert views, followed by policy discussions (“Maybe we don’t need new legislation now after all . . .”), followed by the next round of new science. Unfortunately, the only dance that seems to fit this rhythm is “one step forward, two steps back.” We are not the first to argue that progress can only be made if all reasonable lines of research are pursued as science develops.\(^\text{74}\) Waiting for the perfect source serves simply to make the best the enemy of the good.

But there are other reasons not to await the perfect source. Here is one reason that is not usually offered: as we have seen even in this brief review, a prime requirement for a “perfect” source of pluripotent stem cells is that it have no “ethical baggage.”\(^\text{75}\) Physicians and scientists facing ethical issues arising in biomedicine and research often reason that if they wait for certainty—more facts, more information, more data—the ethical issues will go away, having been answered by the science.

They don’t. They never do. Science itself has values, as do scientists. Ethics and science are always intertwined. Waiting for perfection is a moral choice, and should be acknowledged as such. What it means for a source of pluripotent stem cells to be “free of ethical baggage” should be a subject of discussion. Since all ethical issues can never disappear from scientific and medical research, public discourse must continue as science advances.

Research using pluripotent stem cells unquestionably strives to alleviate significant disease burdens, and the search

\(^{74}\) This scientific truism has been invoked many times. With respect to stem cells, see, for example, Jennifer Hipp & Anthony Atala, *Sources of Stem Cells for Regenerative Medicine*, 4 STEM CELL REV. & REP. 3, 9 (2008); Zachary J. Kastenberg & Jon S. Odorico, *Alternative Sources of Pluripotency: Science, Ethics, and Stem Cells*, 22 TRANSPLANTATION REV 215, 221 (2008).

for pluripotent stem cell-based therapies continues to show great promise, but the realization of effective therapies is still far in the future; thus, it is important not to overestimate the potential for benefit at this stage. As is the case for many new biotechnologies, however, the development of pluripotent stem cell science seeks a careful balance of scientific altruism and commercial interests. It is worth noting that underlying the arguments on all sides of the stem cell debate is some degree of concern about the potential for commodification, either of the person resulting from biotechnological advances or of the human biological products that permit desired designs to be realized. Only by acknowledging, critically examining, and discussing the concerns that may arise from pluripotent stem cell research can we hope to minimize its ethical and social risks. Ultimately, science and society must face the ethical issues openly, in order to move forward while searching for ever more perfect sources.