REPROGRAMMED STEM CELLS AND FEDERAL FUNDING OF EMBRYO RESEARCH

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The most fundamental and widely discussed of the many important policy issues surrounding stem cell science is the question of whether it is appropriate to conduct research on human embryonic stem cell lines (hESCs) when creating these lines results in the destruction of early-stage human embryos, known as blastocysts. A closely related question is whether, because of this ethical issue, the government should refuse to fund such research or even take more aggressive action, such as prohibiting the research even if conducted with private funds.

In this short article, I evaluate whether our views on these issues should change in light of a recent technological breakthrough: the creation of induced pluripotent stem cells (iPSCs), which behave similarly to embryonic stem cells but can be produced without harming—or even using—embryos. My conclusion is that the answer depends on our precise view of the moral value of early-stage embryos. Supporters of hESC research who believe that blastocysts have no more moral value than any other clump of human tissue need not revisit their position; on the other hand, supporters who believe that blastocysts have substantial moral value, but less moral value than people, should carefully reconsider their view of the cost/benefit balance associated with embryos research.

I. THE LANDSCAPE PRIOR TO IPSCS

In 1998, James Thomson and his colleagues at the University of Wisconsin succeeded in taking cells from the inner cell mass of five-day old blastocysts and producing human embryonic stem cell lines that can proliferate in culture without differentiating into specialized cells over long periods of time.[1] For the nine years that followed,

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1. *See generally* James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCI. 1145 (1998).

most researchers in the field believed that so-called human embryonic stem cells (hESCs) have the most promise for the three goals of stem cell research: (1) understanding how degenerative diseases develop and progress, (2) creating large numbers of disease-specific cells to test potential pharmaceuticals more efficiently, and (3) ultimately creating stem-cell based treatments that could be used to replace dead or damaged cells and tissues.[2]

Adult stem cells, which exist inside all our bodies to generate replacements for the cells that routinely die every day, already have some clinical uses—a particular type, hematopoietic stem cells, are what make bone marrow transplants an effective treatment for leukemias—but they are thought by most scientists to have far less potential for a number of reasons.[3] Most importantly, adult stem cells do not live as long and replicate in culture as well as embryonic stem cells.[4] With only a few outliers, the scientific community was unified in the belief that embryonic stem cell research offered unique promise for finding cures to a range of degenerative diseases that affect, or one day will affect, nearly every family in America—from cancer, to heart disease, to Alzheimer's, to diabetes.

Notwithstanding the views of the scientific community, on August 9, 2001, President Bush ordered federal agencies to refuse to fund research on stem cell lines created through a process that entailed embryo destruction.[5] This policy implicitly rests on two assumptions, one of which finds broad support amongst the American public and the other of which is far more controversial. The first assumption is that no person's life should be intentionally sacrificed for medical research, no matter how much benefit the research may have for other members of society.[6] Although some dedicated utilitarian philosophers argue that we should be willing to intentionally sacrifice the lives of a small number of people for medical research that would cure a larger number,[7] the contrary

2. RUSSELL KOROBKIN WITH STEPHEN R. MUNZER, STEM CELL CENTURY: LAW AND POLICY FOR A BREAKTHROUGH TECHNOLOGY 18–20 (2007).

3. *Id.* at 22–23.

4. *Id.* at 23.

5. *See* President George W. Bush, Address to the Nation on Stem Cell Research from Crawford, Texas (Aug. 9, 2001), *in* 37 WKLY COMP. OF PRESIDENTIAL DOC. 1149, *available at* http://www.gpoaccess.gov/wcomp/v37no32.html [hereinafter Address to the Nation].

6. *See* Julian Savulescu, *The Embryonic Stem Cell Lottery and the Cannibalization of Human Beings*, 16 BIOETHICS 508, 512 (2002).

7. *E.g.*, *id.*

position garners near unanimous support in our society. Even if dissecting my brain could save a dozen terminally ill individuals, I have little fear that the government, or any Institutional Research Board, will approve my involuntary death sentence for the good of my fellow citizens. The second, more controversial, assumption is that human blastocysts have moral value equivalent to that of persons, which in turn suggests that researchers should not do to blastocysts anything that they would not do to a person like you or me. As a compromise of sorts, President Bush agreed to permit funding on the small number of such cell lines already in existence on the date of his pronouncement (August 9, 2001), reasoning that, the embryos from which those cell lines were derived had had already been destroyed, and so science might as well benefit from them to the extent possible.[8]

The Bush policy initially received widespread public support,[9] but as scientists made the case for the potential unique benefits of embryonic stem cell research, the policy soon became, and remained, broadly unpopular. Numerous polls show public support for embryonic stem cell research in the mid-decade ranging from 50%–65%, with the President's policy receiving support from a decided minority of Americans.[10] During 2005–2006 and again in 2007, both houses of Congress passed the Stem Cell Research Enhancement Act by comfortable majorities,[11] which, had it not been met with two presidential vetoes that Congress failed to override,[12] would have substantially expanded federal funding of this exciting area of research. The main conclusion to be drawn by the opposition of the public and two Congresses (the first with Republican majorities in both houses, the second with Democratic majorities) to the Bush policy is that most Americans do not accept the President's premise

8. Address to the Nation, *supra* note 5.

9. Matthew C. Nisbet, *Public Opinion About Stem Cell Research and Human Cloning*, 68 PUB. OPINION Q. 131, 137, 149 tbl.17 (2004).

10. KOROBKIN, *supra* note 2, at 56–57 (summarizing poll results).

11. Stem Cell Research Enhancement Act of 2007, S. 5, 110th Cong. (2007); Stem Cell Research Enhancement Act of 2005, H.R. 810, 109th Cong. (2005).

12. President George W. Bush, Message to the Senate Returning Without Approval the "Stem Cell Research Enhancement Act of 2007" (June 20, 2007), *in* 43 WKLY COMP. OF PRESIDENTIAL DOC. 833, *available at* http://www.gpoaccess.gov/wcomp/v43no25.html; President George W. Bush, Message to the House of Representatives Returning Without Approval the "Stem Cell Research Enhancement Act of 2005" (July 19, 2006), *in* 42 WKLY COMP. OF PRESIDENTIAL DOC. 1365, *available at* http://www.gpoaccess.gov/wcomp/v42no29.html.

of equivalent moral worth between blastocysts and persons. Most people in this group reason that, since people are more important than blastocysts, medical research that has unique potential to save and improve the lives of people must take precedence over the well-being of blastocysts.

II. THE iPSC BREAKTHROUGH

The consensus that embryonic stem cells have unique potential was brought into question in June 2007, when Japanese researcher Shinya Yamanaka and his colleagues published a paper showing that they had reprogrammed skin cells from the tail of mice to behave like embryonic stem cells by using retroviruses to insert four genes into the cells.[13] While tantalizing, this result begged the obvious question of whether the same could be accomplished using human cells; many promising scientific breakthroughs in mice fail to transfer across species.

Surprisingly, it took less than six months for two groups of scientists to accomplish the same feat using human cells, with Yamanaka's lab and Thomson's lab publishing their results on the same day in November, ending the race in a virtual tie.[14] The new cells are known as induced pluripotent stem cells (iPSCs): "pluripotent," because, like embryonic stem cells, they can generate a range of different specialized cells; "induced" because, unlike embryonic stem cells, they must be genetically reprogrammed to do so.

III. IMPLICATIONS FOR EMBRYO RESEARCH

Supporters of President Bush's policy immediately hailed the creation of iPSCs as vindicating the President's policy and proving that we now can enjoy all the benefits of embryonic stem cell research without harming embryos.[15] The conservative bioethicist and former

13. Keisuke Okita, Tomoko Ichisaka, & Shinya Yamanaka, *Generation of Germline-Competent Induced Pluripotent Stem Cells*, 448 NATURE 313 (2007).

14. Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861 (2007); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCI. 1917 (2007) (both articles published online Nov. 20, 2007).

15. *See, e.g.*, Ryan T. Anderson, *The End of the Stem-Cell Wars*, WKLY STANDARD, Dec. 3, 2007, at 22; Charles Krauthammer, Editorial, *Stem Cell Vindication*, WASH. POST, Nov. 30, 2007, at A23; Michael Levenson, *Romney Camp is Buoyed by Skin Cell News, Feels Affirmed in View Against Embryo Work*, BOSTON GLOBE, Nov. 21, 2007, at A8; *Stem Cell*

chair of the President's Council on Bioethics, Leon Kass, wrote: "Why work to derive new stem cell lines from frozen embryos . . . when one can work with iPSCs . . . ?"[16] This reasoning jumps ahead of the science, and cannot be supported in its strong form—at least at the moment.

It is important to recognize that the new iPSCs are not identical to embryonic stem cells. Here, there are two important points. First, the process used, at least to this point, to reprogram ordinary cells into iPSCs employs retroviruses to insert the required genes—a process which can cause cancer.[17] Scientists agree that this makes the current iPSCs unsuitable to ever use as the basis for stem cell treatments. Researchers hope to create alternative techniques to engineer iPSCs without retroviruses. Many think that this is a hurdle that can be overcome quickly, and perhaps it can. In February 2008, a private company claimed to have done so, but it has declined to demonstrate it in a peer reviewed publication, thus producing a skeptical response from the research community.[18] In June 2008, a group of researchers using a type of adult stem cell from mice demonstrated success in using a synthetic molecule to activate the genes necessary for pluripotency, avoiding the need to use retroviruses to insert copies of the genes.[19]

More importantly, because iPSCs are not in fact embryonic stem cells—they merely behave in much the same way as embryonic stem cells—scientists just don't know whether they have properties that will make them an adequate substitute for all the purposes to which hESCs might be put.[20] Early results have been promising: MIT scientists recently succeeded in using iPSCs differentiated into dopamine neurons to reduce symptoms of Parkinson's disease in

Breakthrough Could Benefit GOP, MSNBC, Nov. 21, 2007, http://www.msnbc.msn.com/id/21914276/.

16. Leon R. Kass, *Defending Life and Dignity: How, Finally, to Ban Human Cloning*, WKLY STANDARD, Feb. 25, 2008, at 30.

17. *See* Gina Kolata, *Scientists Bypass Need for Embryo to Get Stem Cells*, N.Y. TIMES, Nov. 21, 2007, at A1.

18. Marie McCullough, *PrimeGen Biotech: Stem-Cell Progress*, PHIL. INQUIRER, Feb. 28, 2008, at A1.

19. *See generally* Yan Shi et al., Correspondence, *A Combined Chemical and Genetic Approach for the Generation of Induced Pluripotent Stem Cells*, 2 CELL STEM CELL 525 (2008).

20. *Accord* Insoo Hyun, *Stem Cells from Skin Cells: The Ethical Questions*, 38 HASTINGS CTR. REP., Jan.–Feb. 2008, at 20.

rats.[21] Still, it will probably take years of study before scientists fully understand the potential and limitations of these cells.

Ultimately, iPSCs might prove to be perfect substitutes for hESCs, or they might even prove to be better than hESCs because they can more easily be used as the basis of patient-specific treatments. On the other hand, it is possible that they will also prove to be less useful than hESCs, or at least less useful for some purposes. As of today, it is fair to say both that iPSCs offer tremendous potential and that a good deal of uncertainty remains concerning their potential efficacy. The California Institute for Regenerative Medicine, charged with distributing three billion dollars in taxpayer funding of stem cell research, is currently funding both research paths. "To ensure that research moves forward," its president, Alan Trounson, recently proclaimed that a set of grants the agency will soon award, "will fund the derivation of new cell [lines] from both the well-established means of human embryonic stem cells, which remain the gold standard for research into pluripotent cells, as well as new technologies."[22] Those whose concern is solely with maximizing the likelihood that stem cell research will lead to treatments or cures for as many diseases as possible as soon as possible should favor continued hESC research and a lifting of the constraints on federal funding. As one commentator put the point: "The idea that iPS cell research can (and should) proceed by itself is not a hope that makes much *scientific* sense."[23]

Nonetheless, the explosion of iPSCs onto the stem cell research scene challenges those who support hESC research to assess the moral worth of blastocysts more carefully than was necessary even six months ago. Many Americans intuitively assume that blastocysts have significant moral worth, deserving of special treatment and care, although less than the moral worth of persons. As a consequence of this "special respect" or "intermediate moral value" view, blastocysts

21. Colin Nickerson, *Blank Stem Cells Showing Promise: Could Quiet Debate on Embryos*, BOSTON GLOBE, April 8, 2008, at 1A.

22. Press Release, Cal. Inst. for Regenerative Med., Fifty Applications Received for CIRM's New Cell Lines Awards (Feb. 8, 2008), *available at* http://www.cirm.ca.gov/press/pdf/2008/02-08-08.pdf.

23. Hyun, *supra* note 20, at 20 (emphasis added).

should be treated more deferentially than adult cells and tissues but not as deferentially as persons.[24]

The congressional alternative to President Bush's policy, the Stem Cell Research Enhancement Act, implicitly adopts this view. Had it become law, that bill would have authorized federal funding of research conducted on embryonic stem cell lines only if they were derived from excess embryos from IVF clinics[25] and not if the embryos were created for the purpose of stem cell research. Futher, the Act would not have lifted the Dickey Amendment, an annually-renewed twelve-year old congressional ban on the funding of any experiments that directly destroy embryos or subject them to significant risk of harm.[26] Because it would limit funding to research on embryos already slated for destruction, and because it distinguishes between research that actually destroys embryos and research that uses cell lines derived from previously destroyed embryos, the congressional policy suggests a far greater reluctance to use blastocysts for research than ordinary adult cells or tissues.

Before the development of iPSCs, most Americans who assumed that embryos have intermediate moral worth supported embryonic stem cell research because no other technology appeared to even approximate its medical promise for people suffering from a range of fatal or debilitating degenerative diseases. But if iPSCs offer a promising alternative to embryo research, it is not clear that an intermediate moral worth view should translate into support for embryonic stem cell research any longer. At a minimum, the balance between the potential benefits of embryo research and the costs of embryo destruction is less clear cut. Public support for hESC research has not yet declined in the wake of the new iPSC technology, but as an understanding of this technology permeates the public consciousness, it is likely that support for hESC research will decline, as some reluctant supporters of embryo research determine that iPSCs provide an acceptable substitute.

I continue to believe that research should be pursued and funded based solely on its scientific potential, with no weight given to

24. *See, e.g.*, PRESIDENT'S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH 82–84 (2004), *available at* http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

25. Stem Cell Research Enhancement Act of 2005, H.R. 810, 109th Cong. §2 (2005).

26. This limitation, known as the Dickey Amendment, has been included in appropriations bills every year since 1996. *See, e.g.*, Balanced Budget Downpayment Act of 1996, Pub. L. No. 104-99, § 128, 110 Stat. 26, 34 (1996).

whether or not particular research requires the destruction of blastocysts, and no consideration given to how or for what purpose the blastocysts were brought into being. It is important to emphasize, however, that my conclusion relies on the premise that there is no logically defensible basis for viewing human embryos as possessing any moral value similar to that of people. Blastocysts have none of the attributes that give persons unique moral worth. They lack even the most rudimentary neurological function; they lack sentience, the ability to feel pain, consciousness, and the ability to imagine the future. Blastocysts are certainly human, in the sense that they possess an entire complement of human DNA, but this is true of every type of cell, and no one opposes research on ordinary adult tissues (assuming informed consent is obtained) or grieves at the millions of cells we shed naturally every day.[27]

It is sometimes argued that it is their *potential* to become persons that provides blastocysts with heightened moral value, but this argument threatens to prove too much. An embryo created in a dish indeed could become a person if someone implants it into a womb and it defies the odds by successfully implanting, but the route to personhood is neither direct nor assured; even most embryos created the "old fashioned" way fail to implant and develop into a person.[28] If every cell that could potentially become a person with considerable external assistance and luck were treated like one, we would have to afford personhood status to every egg and sperm cell. The development of iPSCs suggests that it might be possible to reprogram any type of cell into an egg or sperm cell (if not a zygote), rendering the argument for providing personhood status to every single adult cell, based on potential to be transformed into a person, just as strong as the argument for treating blastocysts like persons.

This is not to say that the fact that embryos have the potential to become people is completely irrelevant to the way we ought to treat them. Because of the relationship between blastocysts and people—that is, every person was once a blastocyst—we should treat the former with a level of care and respect. But, crucially, this is because the treatment of blastocysts indirectly represents the respect we accord to people, not because blastocysts qua blastocysts have moral

27. This argument is made in KOROBKIN, *supra* note 2, at 29–33. For a counterargument, see ROBERT P. GEORGE & CHRISTOPHER TOLLEFSON, EMBRYO 112–43 (2008).

28. *See, e.g.*, Stephen S. Hall, *The Good Egg*, DISCOVER, May 2004, at 30, 34.

worth themselves.[29] Using blastocysts in medical research to try to find cures for disease shows deep respect for people, not disrespect, so the endeavor is morally appropriate, whether or not other avenues for progress in medical research also exist.

29. *Cf.* John A. Robertson, *Symbolic Issues in Embryo Research*, 25 HASTINGS CTR. REP., Jan.–Feb. 1995, at 37–38.