PLURIPOTENT STEM CELLS: THE PROBLEM WITH BINARY POTENTIAL AND THE BENEFIT OF THE SLIPPERY SLOPE

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Stem cell researchers have been busy. Late in 2007, stem cell researchers in Wisconsin, USA,[1] and Kyoto, Japan,[2] announced that they had a new and improved pluripotent stem cell called the induced pluripotent stem cell (iPSC).[3] Unlike previous embryonic stem cells or cloned stem cells, the iPSC was not harvested from an embryo and did not use a human oocyte. Unlike previous pluripotent stem cells, researchers did not have to destroy any embryos or oocytes to get iPSCs. But like embryonic stem cells, many commentators touted the iPSC for its wonderful potential for new therapies and groundbreaking research. Charles Krauthammer welcomed the iPSCs as the "holy grail"[4] and others welcomed iPSCs as ethically clean or

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1. Junying Yu et al., Fibroblasts by Defined Factors , 131 C ELL 861, 861 (2007).

3. Pluripotent stem cells have the ability to differentiate into any cell in the body, but probably not the placenta, which is needed for implantation. A pluripotent stem cell can become a brain cell, or a kidney cell or a bone cell. The stem cells that are the subject in this essay are pluripotent stem cells, in contrast to adult stem cells, like hematopoietic stem cells, which also have the potential for differentiating into more than one type of mature or

"uncomplicated" and a solution to the "raw material problem."[5] Stem cell research, which had been a politically hot topic, is proving to be a mostly absent issue during this presidential election year of 2008, at least as of July 2008.

The second news event about stem cell research was in January 2008, when researchers at Stemagen Corporation in California published in a peer reviewed journal that they were the first to clone an early human embryo, known as a blastocyst.[6] They used a process called somatic cell nuclear transfer (SCNT), in which they combined enucleated human eggs (donated by three women from a fertility program) with the nuclear material of differentiated adult skin cells.[7] Importantly, these researchers did not isolate stem cells from the early embryos.[8] Experts say that this next step is difficult and time consuming;[9] however, several months earlier researchers at Oregon Health and Sciences University (OHSU) successfully extracted stem cells from cloned monkey embryos.[10] These researchers also used SCNT, and this was the first time researchers had cloned an animal other than a mouse, and it was not easy.[11] The investigators had started with 304 monkey eggs and ended up with two stem cell lines, one with an abnormal Y chromosome and the other apparently normal.[12]

These two recent events take us to the present state of stem cell research. There are two proven ways of acquiring human stem cells. The "traditional" method is to extract embryonic stem cells from a human blastocyst, which is a five or six day old hollow ball of cells consisting of the outer layer cells that will make up the placenta and the inner cell mass of pluripotent stem cells that will differentiate into

5. Andrew Pollack, *After Stem-Cell Breakthrough, the Work Begins*, N.Y. TIMES, Nov. 27, 2007, *available at* http://www.nytimes.com/2007/11/27/science/27stem.html.

6. Andrew J. French et al., *Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts*, 26 STEM CELLS 485, 485 (2008).

7. *Id.*

8. *Id.*

9. ABC/Reuters, *First 'Proven' Human Cloned Embryo*, ABC SCI., January 18, 2008, http://www.abc.net.au/science/articles/2008/01/18/2141478.htm.

10. Gina Kolata, *Scientists Use Monkey Clones to Extract Stem Cells*, N.Y. TIMES, Nov. 15, 2007, at A1 (reporting that OHSU researcher Shoukhrat Mitalipov cloned monkey embryos and extracted stem cells from these embryos).

11. *Id.*

12. *Id.*

2008]

	Destroy an embryo or Oocyte	Cloning	Use of oocyte	Result of fertilization	Retro-virus	Placenta[22]	Potential for born baby
Embryonic stem cell (ESC)	Yes usually	No	Yes	Yes	No	No	Yes, embryo does
Somatic cell nuclear transfer (SCNT)	Yes	Yes	Yes	No	No	No	Yes, potential for potential
Induced pluripotent stem cell (iPSC)	No	Yes	No	No	Yes	No	No/maybe potential for chimera

Are iPSCs the ethical "holy grail"? Certainly not all stem cells are alike, but how different are they? Note, that there is theoretic potential for iPSCs to become implanted into a blastocyst and grow to become a born baby.[23] Note, too, that although an embryonic stem cell is taken from a blastocyst, which has the ability of making a placenta and implanting into the uterine wall, none of the stem cells have this capability. Will looking carefully at the different categories of stem cells allow us to better understand arguments for and against stem cell research and to understand whether different kinds of stem cells should be differently funded and regulated?

22. A blastocyst's outer cell layer gives rise to the placenta, but none of the stem cells used for research have a capacity yet to give rise to a placenta. Nicholas Agar argues that it unimplanted embryos can ethically be used for research because they lack a "functional relationship with a womb" and the important question is whether IVF and SCNT embryos have the "morally relevant potential for sentience." Nicholas Agar, *Embryonic Potential and Stem Cells*, 21 BIOETHICS 198, 198–207 (2007) (discussing unimplanted embryos used for research).

23. Kazutoshi Takahashiand & Shinya Yamanaka, *Introduction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 673 (2006) (inducing pluripotent stem cells injected into mouse blastocyts and contributing to mouse embryonic development).

No federal laws prohibit stem cell research on any kind of stem cells, including embryonic stem cells.[24] Most states do not prohibit stem cell research, but some, like South Dakota, make it a misdemeanor[25] and others limit funding. This uneven landscape is important to keep in mind, as are the polling results that consistently show that a majority of Americans support stem cell research.[26] To this extent, there is yet no "winner" in the stem cell debate. President George W. Bush limited federal funding to research using only stem cell lines created before August 2001, which, although frustrating to

position that the fertilized human egg is the same as a born baby,[31] and these constitutional issues are beyond the scope of this article. Part IV concludes that iPSCs are not distinctly different from other types of stem cells when focusing on the idea of potential as a continuum, and that the lessons of *Roe v. Wade*[32] instruct us to hold back on picking a stem cell winner.

I. THE IDEA OF POTENTIAL AS THE BASIS FOR OPPOSITION TO STEM CELL RESEARCH

A. The Conceptionalists and the Potentialists

The basis of most arguments opposed to embryonic stem cell research is that obtaining the stem cells requires destroying an embryo. In other words, the objection is not to the stem cell research but to the destruction of an embryo. Father Kevin Wildes explains: "[I]f there were a way to conduct stem cell research without destroying human life, either embryonic or fetal, I do not think Roman Catholic tradition would have a principled opposition to such research."[33] Viewing embryonic stem cell research as unavoidably paradoxical led President George W. Bush to his compromised restriction of federal stem cell funding, which only allows federal funding for stem cell lines existing before August 2001. President Bush explained: "Embryonic stem cell research offers both great promise and great peril, so I have decided we must proceed with great care."[34] His policy has enjoyed broad criticism for many reasons.[35]

31. *See* Pope John Paul II, *Evangelium Vitae*, ¶ 58–63 (1995), *available at* http://www.vatican.va/holy_father/john_paul_ii/encyclicals/documents/hf_jp-ii_enc_25031995_evangelium-vitae_en.html. Pope John Paul II believed that human life begins at fertilization, stating: "[T]he use of human embryos or fetuses as an object of experimentation constitutes a crime against their dignity as human beings who

easy to devalue a human life. Although the argument presumes its conclusion that valuable life begins at conception (it is circular), it has rhetorical appeal. Researchers might arbitrarily designate some of us as "pre-embryos" with devastating results. Ex-chair of the President's Council on Bioethics, Edmund Pellegrino explains:

> Terms such as "pre-embryo" or "pre-implantation embryo" seem to be contrivances rather than biological or ontological realities. Also rejected are socially constructed models that leave moral status to definition by social convention. In this view, moral status may be conferred at different times, or taken away, depending on social norms. This is a particularly perilous model for the most vulnerable among us: fetuses, embryos, the mentally retarded, or those in permanent vegetative states. The horrors of genocide in current events force us to recognize how distorted social convention can become, even in presumably civilized societies.[38]

For Pellegrino, destroying "pre-implantation embryos" is immoral because we all are humans deserving of full moral respect, whether we are embryos, in a permanent vegetative state, or at work writing essays. Social norms typically value these different places differently, but social norms for Pellegrino are arbitrary, ever changing, inherently misleading, and dangerous. Indeed, as Jeb Rubenfeld reminds us, "the concept of 'person' is ineluctably normative; it is not given by facts or by definition alone, but by a normative judgment operating definitively on certain sets of facts."[39]

Similarly, although Father Demopulos of the Orthodox Catholic Church recognizes that there may be a continuum in how close to "authentic human personhood" we may get, he emphasizes that every human, whether born or a blastocyst, should be given the same chance to reach authentic human personhood.[40] "Unborn human life is entitled to the same protection and the same opportunity to grow in the image and likeness of God as are those already born."[41]

This first argument maintains that a newly fertilized embryo is the moral equivalent to a born baby because, in part, there is no particular point to draw the line. In other words, conceptionalists

38. *See* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 33, at F-1, F-3 (testimony of Edmund D. Pellegrino).

39. Jed Rubenfeld, *On the Legal Status of the Proposition that "Life Begins at Conception,"* 43 Stan. L. Rev. 599, 619 (1991).

40. *See* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 33, at B-1, B-3 (testimony of Demetrios Demopulos explaining that the Eastern Orthodox view does not see the continuum as ending at birth, but as a life-long struggle toward theosis).

41. *Id.*

believe that either nature, God, or our moral code gives value to the newly fertilized egg, and there is no subsequent point that allows one to distinguish between the newly fertilized egg and a born baby. As the 2004 report by the President's Council on Bioethics put it, there is "no discrete point in time or development [that] would seem to give any justification for assuming that the embryo in question was one thing at one point and then suddenly became something different (turning, for example, from non-human to human or from non-person to person)."[42]

The second argument is based on potential and is a central topic of this article. Potentialists, like the conceptionalists, give equal protection to the implanted embryo and a blastocyst in a Petri dish; both are worthy, but for different reasons. Whereas conceptionalists draw no distinctions between the newly fertilized egg and a born baby, potentialists do discriminate between the blastocyst's microscopic ball of cells and the born human. The President's Council on Bioethics, which has advanced arguments from both conceptionalist and potentialist viewpoints, wrote: "An embryo is, by definition and by its nature, potentially a fully developed human person; its potential for maturation is a characteristic it *actually* has, and from the start."[43] Similar to the conceptionalist approach, the quote reflects the belief that the embryo's value does not change during gestation; the "potential for maturation" to a "fully developed human person" is from conception. It does not progress incrementally. Similar, too, is the appeal to nature. The embryo is "by its nature" a potential "fully developed human person." Different, however, is that the embryo's value is based on potential of becoming that which has full moral and legal worth and protection, the fully developed human.

Responding to critics who claim that a pre-implanted blastocyst is different from an implanted embryo because the later is further on its way to becoming a viable human, the President's Council on Bioethics analogized the pre-implanted, Petri dish bound blastocyst with a caged bird:

42. MONITORING STEM CELL R

people who believed that abortion should always be illegal also opposed stem cell research.[51] The percent of people opposed to stem cell research dropped to about 50% among those who wanted abortion to be illegal but who made exceptions for certain situations.[52] Of course, results are influenced by how the questions are phrased. For example, two different polls reported seemingly-significant different results. One found 70% opposed to destroying "live embryos" for undefined "experiments," whereas another found 77% in favor of using "excess fertilized eggs" to treat "deadly diseases."[53] Perhaps these differences are partly explained by what people place on the risk/benefit scale: research vs. treatment and, embryos vs. excess fertilized eggs. The results also likely reflect public thinking that stem cell research or treatment should be undertaken with respect and seriousness, but that people view the issue in terms of balancing risks and benefits.[54]

Interestingly, President George W. Bush, known for his pro-life stance in the abortion debate, employed a risk/benefit analysis when he explained his compromise on federal funding for stem cell research.[55] Like many citizens, his religious views powerfully influenced his policy toward stem cell research, [56] but it was not the only consideration. He has stated, "I'm a strong supporter of science

51. Gary Langer, *Public Backs Stem Cell Research: Most Say Government Should Fund Use of Embryos*

the state would have a compelling interest and the ability to prohibit abortion were it to grant the fetus personhood.[64] However, the decision in *Roe*

life no longer had gradations of value. Instead, the potential at conception had the same value as potential at viability. Chief Justice Rehnquist, writing for the plurality, stated: "[W]e do not see why the State's interest in protecting potential human life should come into existence only at the point of viability, and that there should therefore be a rigid line allowing state regulation after viability but prohibiting it before viability."[71] Endorsing the dissenting opinions of Justices White and O'Connor in *Thornburgh v. American College of Obstetricians and Gynecologists*,[72] the *Webster* plurality shifted the state's compelling interest in protecting human life to "throughout pregnancy."[73]

Planned Parenthood v. Casey[74] confirmed the view adopted in *Webster* that potential fetal life begins "from the outset" of pregnancy.[75] *Casey* made no attempt to recognize a continuum or gradation of either value or status between different age pre-viability fetuses. If the fertilized egg is potential life, not quite the same as the newborn baby or post-viable fetus, but indistinguishable from a twelve week old fetus, then it should be protected in the same way as any other pre-viability fetus. The determining difference between the five day old fertilized egg and the twelve week old fetus became the level of the burden to the mother, rather than where on a continuum of potentiality the fetus may lie. The *Casey* joint opinion stated, "the State has legitimate interests from the outset of the pregnancy in . . . the life of the fetus that may become a child."[76] In this structure, stem cell research cannot be allowed if it means destroying any fetus, or perhaps any cell with human DNA with the potential to become a human person (e.g. iPSCs), because there is no countervailing constitutionally recognized interest as there is in the setting of abortion.

The blame for this shift, according to Professor Jed Rubenfeld, is at least partially on *Roe*. He writes, "It was *Roe* that recognized a compelling state interest in protecting *potential* human life, and if there can ever be such an interest, then the *Webster* plurality is quite right to question why it should be marked at viability rather than at

71. *Id.* at 519.

conception."[77] *Roe* and Rubenfeld's comments illustrate the vagueness of potential and the problems with relying on it. One might argue that *Roe* distinguished between potential at viability and potential at conception, or potential with a high likelihood of actuality and potential with a low degree of actuality, respectively. But *Roe* failed to explicitly state this. Justice Blackmun viewed the trimester framework[78] as an artificial construct placed on a biological continuum, but a continuum means that the points on it are not identical. *Roe* is a pragmatic approach that uses a risk/benefit framework, with tipping points translating into a trimester framework, but it relies on an idea of potential as a continuum.

Having examined the idea of potential in the abortion cases and the idea of potential in the stem cell debate, one may ask whether the abortion cases are relevant to stem cell research.[79] The *Casey* fetus is in utero, and specifically described as one "that may become a child," implying that there are others, perhaps not in utero, that are not en route to becoming a child. At issue in the abortion cases is an implanted fetus, which has a much better chance of becoming a born baby than a yet to be implanted five or six day old blastocyst. In the abortion debate, the underlying state interest might be best characterized as promoting family values and healthy children.[80] It has not been framed to discuss the balancing of state interest in protecting a woman's privacy or reproductive right against the state interest in protecting the fetus. Rather, the woman's interests are private interests, albeit constitutionally protected.

One advantage to the *Casey* approach, which focuses upon the undue burden on the mother, is that it returns to a continuum, instead of the binary notion of potential at work in *Webster* and *Thornburgh.* Some burdens to the mother are reasonable, whereas others are

77. Rubenfeld, *supra* note 39, at 607.

78. Justice Blackmun adopted the trimester framework from the medical profession. The following passage from *Roe v. Wade* illustrates this:

> With respect to the State's important and legitimate interest in the health of the mother, the 'compelling' point, in the light of present medical knowledge, is at approximately the end of the first trimester. This is so because of the now-established medical fact [ ] that until the end of the first trimester mortality in abortion may be less than mortality in normal childbirth.

Roe v. Wade, 410 U.S. 113, 161 (1973).

79. *See generally* Dolgin, *supra* note 30 (The abortion debate and stem cell debate are fundamentally different because the first is about preservation of nineteenth century ideas regarding family and strict gender roles, while the later is about personhood.).

80. *Id.*

unconstitutional. There is an implicit continuum. In the stem cell research setting, in contrast, there may or may not be a state interest in promoting stem cell research. States lack uniformity in what they view as their state interest in stem cell research. Some states, like South Dakota, prohibit using stem cells, and others, like California, promote it. The same dichotomy does not exist in the abortion setting. Certainly, some states make it more difficult for women to get abortions than other states, but all share the basic equation, in part, because it has become a federal issue. On one side is the woman's privacy right. Stem cell research, on the other hand, does not have the constitutional aspects of a woman's right with which it must contend. Instead, the state interest, which either favors research (and its "potential" benefits) or favors the potential life of a five day old blastocyst, will set the state's policy.

The binary theory of potential, whether in the context of the abortion or stem cell debate, forces the discussion into one about a controversial and overarching view. Opinion poll results repeatedly confirm that people have a complex view about both issues.[81] The polling shows that people have what may be summarized as a reluctant or cautious support of embryonic stem cell research; most people support it as long as it is undertaken with respect and awareness. To reduce the debate to only the single issue of whether a in proeq(doesu0 l)fC, da6sal i t]TJis aJ0 -1.1302 TD0.2349 Tw[(promot)6.5al, whe7(t]TJiso)-5ce th

potential cannot incorporate the risk/benefit, pragmatic approach supported by the American public, and it hinders open and fruitful political debate because it fosters a controversial and overarching view. Focus on the slippery slope, in contrast, helps define the arguments and give them greater substance. Admittedly, I am rejecting the idea that there is in fact, or that an overwhelming majority of people draw a bright line at, the instant of conception. Recall, too, that many opposed to embryonic stem cell research do not draw a bright line at conception, as did Pope John Paul II, who wrote that the fertilized egg is the same as a newborn.

blastocyst) and B (i.e. a second trimester fetus) and C (a born baby). They must evaluate A based on B. Potential, for example, values A because of its potential to become B and C. The slippery slope approach evaluates doing something to or for A on the basis of doing the same thing to or for B or C. For example, the wisdom of allowing the destruction of A to do stem cell research should be evaluated on

benefits. The slippery slope approach allows a consideration of risks and benefits in a way that discussing potential does not. This is an important difference, because a risk/benefit discussion allows for a debate about what to put on the scale and opens a way for political compromise.[86]

Many slippery slope arguments apply to the pluripotent stem cell debate, and each brings with it other political issues. Applied to the

economically and politically advantageous. This is the "cost and bureaucracy argument."

4. Allowing stem cell research will give political momentum to anti-abortionists. It has similarities with some of the other slippery slope arguments listed, but emphasizes the political aspects. Perhaps we would see Supreme Court nominees having to address a stem cell research support litmus test. This is the "political momentum argument."

5. Allowing stem cell research will undermine respect for God and humanity. Even if the just fertilized egg is not the same as a viable fetus, there is value in respecting the argument that it is and respecting views of the people that believe it. One would weigh the advantages of this against the advantages of doing stem cell research. This is similar, but not identical, to the first two slippery slope arguments. It is the "broad umbrella of God and humanity argument" and introduces an aspect of tolerance and diversity.

6. Allowing stem cell research will reinforce our misguided emphasis on concierge medicine that focuses on ridiculously expensive therapies for the select few, instead of simpler, cost effective therapies for many. In other words, there is nothing wrong with stem cell research, except that it makes it more likely that we will continue to have problems with under-funding more routine health care for the economically disadvantaged. This is the "distributive justice argument" and introduces many issues to the debate.

There are undoubtedly many more slippery slope arguments, and my descriptions of those above could be more comprehensive. Nonetheless, the advantage of these arguments is that they expand the discussion to one that is more complete and nuanced.

IV. CONCLUSION

of potential is also reflected in the Supreme Court cases, like *Webster* and *Casey*. However, even iPSCs have the potential to become born human babies, although admittedly, the potential is very small right now. Scientists have placed iPSC derived stem cells into mouse blastocytes and these iPSCs have contributed to embryonic development. The potential of iPSCs and embryonic stem cells to become a born baby is different, but potential as a binary idea (it either is or is not) cannot distinguish between the two types. One can distinguish between ESCs and iPSCs if one views potential as a continuum, but this is not the view of potential held by many who support iPSCs as the "holy grail" and see potential as a binary notion.

An alternative approach is needed because the binary idea of potential has lead to a debate about stem cell research that fails to incorporate a risk/benefit approach, which is the approach supported by most Americans. The binary potential approach leads to a debate that focuses on only a single overarching view that maintains the blastocyst is like a born human because it has a particular kind of potential. In contrast, an approach based on the slippery slope allows a broad consideration of risks and benefits and a more substantive discussion.

slope approach allows for a better discussion than the current debate based on binary potential. Recall that iPSCs have the theoretical potential of becoming born human babies, but the potential is very small. Nonetheless, there is a House of Representatives bill pending that declares "the life of each human being begins with fertilization, cloning, or its functional equivalent, irrespective of . . . stage of biological development . . . at which time every human being shall have all the legal and constitutional attributes and privileges of personhood."[88] Although unlikely to get anywhere, the bill captures the logic of a binary notion of potential and may treat iPSCs as functional equivalents of cloning.

It may be that the debate between iPSCs and embryonic stem cells returns us to debating about varying degrees of potential, and that this idea of potential as a continuum will cross over into other debates about stem cells, the value of blastocysts, and even abortion.