

# The bioethics of embryo-free stem cells

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## ABSTRACT

The use of human embryonic stem cells (hESCs) for therapy is impeded by both technical and ethical complications. The recent discovery of cellular reprogramming offers technically and ethically superior stem cells which later on can be used for therapeutic purposes in a patient-specific manner. The reprogrammed cells, called induced pluripotent stem (iPS) cells, are practically indistinguishable from hESCs according to the current established assays for pluripotency. Its therapeutic potential is obvious as it has already been demonstrated in some mouse disease models of Parkinson's, hemophilia, and sickle-cell anemia. In this paper, we revisit the human embryonic stem cell debate in light of this breakthrough and argue that the existence of the iPS technology renders obsolete embryo-associated research including hESCs. We urgently recommend the further exploration of the therapeutic potential of these cells.

Ever since the successful isolation of human embryonic stem cells (hESCs) in 1998<sup>1</sup>, stem cells have been hailed as the future of medicine. Dubbed as regenerative medicine or cell therapy<sup>2</sup>, its use in the clinic is based on the idea of replacing sick, damaged cells with new, healthy and functional ones by converting these stem cells into the specific cell types and transplanting them into the patient. It promises to cure a wide range of diseases like Parkinson's disease, diabetes, and even cancer. However bright the future may seem for these precious cells, the field of stem cell biology is plagued by controversy due to its ethical complexities, technical challenges, and even incidents of fraud and misconduct<sup>3,4</sup>. The recent discovery of cellular reprogramming has revolutionized stem cell biology as for the first time it has managed to seemingly pacify both sides of the stem cell debate, generating stem cells as pluripotent as embryonic stem cells from adult body cells without having to resort to embryo manipulation and destruction.

## The great stem cell divide

Stem cells are viewed as powerful tools in basic research and medicine because they have the capacity to give rise to various cell types, a property called pluripotency. In addition, they have a high rate of proliferation both *in vitro* (in culture) and *in vivo* (inside the living organism), another property called self-renewal. These two main properties define a stem cell<sup>5</sup>.

There are two general types of stem cells: embryonic and adult stem cells. Embryonic stem cells, located in the inner cell mass of the embryo at the blastocyst

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<sup>1</sup> Thomson et al. Embryonic stem cell lines derived from human blastocysts. *Science* (1998) vol. 282 (5391) pp. 1145-7

<sup>2</sup> Wade. Scientists cultivate cells at root of human life. *New York Times*. November 6, 1998. URL: <http://www.nytimes.com/1998/11/06/us/scientists-cultivate-cells-at-root-of-human-life.html>. Last accessed on April 2, 2009.

<sup>3</sup> Cho et al. Research conduct: lessons of the stem cell scandal. *Science* (2006) 311: pp. 614-5.

<sup>4</sup> Check. Stem cells: the hard copy. *Nature* (2007) vol. 446 (7135) pp. 485-6

<sup>5</sup> Weissman. Stem cells: units of development, units of regeneration, and units in evolution. *Cell* (2000) vol. 100 (1) pp. 157-68

stage, are considered the "gold standard of pluripotency" because they can give rise to all 220 cell types of the body including germ cells. On the other hand, adult stem cells are local stem cell populations maintained in almost every organ of the adult body (e.g., liver, hair, heart, skin, intestine, brain, etc.) in charge of maintaining its integrity and function in the organism. Compared to embryonic stem cells, adult stem cells are limited in their self-renewal and differentiation properties. Adult stem cells are less proliferative in culture and can give rise to fewer cell types within a specific lineage. For example, neural stem cells will only give rise to multiple cell types of the nervous system and not of other body systems.

From a therapeutic point of view, embryonic stem cells represent a more attractive choice as they present an unlimited source of replacement cells for all types of diseases. However, its use in therapy is bogged down by technical problems such as the patient's potential immune rejection of the transplanted cells and the uncontrolled proliferation of these cells upon transplantation which may lead to tumor formation. It is also clouded by ethical problems because it requires experimentation with human oocytes and embryos. On the other hand, although limited in their "stemness", adult stem cells, particularly bone marrow-derived hematopoietic stem cells, have already been in use in cancer therapy since the 1950s<sup>6</sup> and are recognized as a standard procedure in treatment of blood diseases today. However, their limited functions as organ-specific stem cells make them less applicable to a wide range of diseases.

Therefore, the ideal therapeutic stem cell would be a combination of the strengths of both types of stem cells: that which would not get rejected by the patient's immune system such as the adult stem cell and, at the same time, that which can give rise to a wide range of cell types like the embryonic stem cell. Thus, is there a way by which we can generate such a patient-specific pluripotent stem cell?

### **The reprogramming revolution**

In 2006, a Japanese group was able to convert adult skin cells of the mouse into embryonic stem-like cells by turning on just four genes (known to be responsible for maintaining pluripotency in embryonic stem cells) – Oct3/4, Sox2, c-Myc, and Klf4 – by viral infection<sup>7</sup>. They call this artificial process "cellular reprogramming": the adult body cell is induced to go back to its primitive embryonic pluripotent state. The resulting cell looks and behaves like an embryonic stem cell. This is considered today as one of the greatest achievements in stem cell biology. The impact of these cells on both basic science and applied medical research is enormous. For one, it goes against the common belief in developmental biology that each cell, as the developing organism matures, undergoes specialization and commits itself to one specific cell type say a skin, heart, or liver cell and stays that way performing its specific function until it eventually dies by natural death (apoptosis). This phenomenon explicitly demonstrates how the eukaryotic genome is so plastic that a cell can be tricked into changing its fate depending on which genes are turned on or off at a specific time.

These cells were named induced pluripotent stem (iPS) cells. They highly resemble embryonic stem cells in morphology, rate of proliferation in culture and pluripotency or developmental potential. They can give rise to all three cell lineages (neuroectoderm, mesoderm and endoderm) and even germ cells (sperm and oocytes). They also pass one of the most stringent tests for pluripotency as they give rise to adult

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<sup>6</sup> Thomas et al. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med* (1957) vol. 157 491-6

<sup>7</sup> Takahashi and Yamanaka. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* (2006) vol. 126 (4) pp. 663-76

mouse chimeras once injected into the mouse blastocyst of another strain of a different hair color<sup>8</sup>.

The big leap forward happened when sixteen months after the mouse iPS cells were formally announced, human iPS cells were generated by two independent groups, the same Japanese group from Kyoto University (Japan) and another from the University of Wisconsin–Madison (USA). The papers got published in two of the most important journals in science, *Cell*<sup>9</sup> and *Science*<sup>10</sup>, and cellular reprogramming was hailed as the next best thing in science<sup>11,12</sup>. The human iPS cells are highly similar to hESCs in terms of their morphology, proliferative capacity, genetic and epigenetic profiles, and developmental potential. In less than two years after these two landmark papers came out, an incredible number of papers flooded all prestigious journals in science focused on elucidating the understanding of this phenomenon, the exploration of its therapeutic potential and the improvement of the technology.

### Safer and simpler stem cells

From a clinical perspective, iPS cells are superior to embryonic stem cells.

The most important advantage of iPS cells is that they are patient-specific<sup>13</sup>. They solve the problem with embryonic stem cells of being rejected by the recipient's immune system upon transplantation. Unlike hESCs, which would have to come from different individuals, iPS cells used in therapy would be taken from the patient itself.

The technique is relatively easy and highly reproducible. Whereas human embryonic stem cell research requires human embryos or cloned human embryos by somatic cell nuclear transfer (SCNT)<sup>14</sup> and thus extensive experience with embryo culture and manipulation is necessary, generation and maintenance of iPS cells requires minimum knowledge of standard molecular biology techniques like viral infection and basic cell culture. Moreover, to generate iPS cells, the starting materials are body cells (e.g., skin fibroblasts) propagated in culture from adult individuals which is not invasive at all compared to taking cells from an embryo which later results to its death.

The therapeutic potential of iPS cells is patent as demonstrated explicitly in one study among others that corrected the sickle-cell anemia in a humanized mouse model<sup>15</sup>, foreseeing its possible application as an autologous cell transplantation

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<sup>8</sup> A chimera is the entity produced by the mixture of cells coming from two different embryos. The mouse chimera assay is used to test the capacity of pluripotent stem cells (iPS or embryonic stem cells) to give rise to tissues in the live-born organism. The stem cells are injected into the blastocyst embryo of a different mouse strain (i.e., of a different coat color) for easy validation: the embryo will give rise to a chimeric mouse with both black and white hair color indicating a positive result.

<sup>9</sup> Takahashi et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* (2007) vol. 131 (5) pp. 861–72

<sup>10</sup> Yu et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* (2007) vol. 318 (5858) pp. 1917–20

<sup>11</sup> Vogel. Breakthrough of the year. Reprogramming Cells. *Science* (2008) vol. 322 (5909) pp. 1766–7

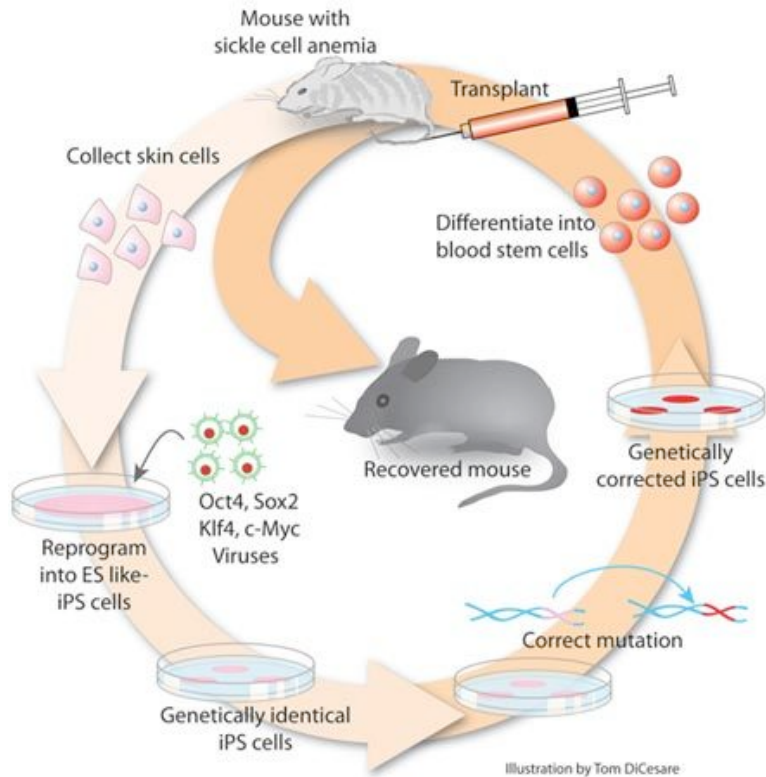
<sup>12</sup> Kolata. Scientists bypass need for embryo to get stem cells. *New York Times*. November 21, 2007. URL: <http://www.nytimes.com/2007/11/21/science/21stem.html>. Last accessed on April 2, 2009.

<sup>13</sup> Yamanaka. Strategies and new developments in the generation of patient-specific pluripotent stem cells. *Cell Stem Cell* (2007) vol. 1 (1) pp. 39–49

<sup>14</sup> Somatic cell nuclear transfer is the same technique used by Ian Wilmut and colleagues when the first cloned mammal (Dolly) was created: Wilmut et al. Viable offspring derived from fetal and adult mammalian cells. *Nature* (1997) vol. 385 (6619) pp. 810–3

<sup>15</sup> Hanna et al. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. *Science* (2007) vol. 318 (5858) pp. 1920–3

strategy<sup>16</sup> (See figure). Other studies also focused on the possibility of using iPS cells to cure or study the following diseases: Parkinson's<sup>17</sup>, hemophilia<sup>18</sup>, spinal muscular atrophy<sup>19</sup>, amyloid lateral sclerosis<sup>20</sup>, and a host of other diseases<sup>21</sup>. This brings us to the crux of the whole matter: are human embryos still necessary to obtain pluripotent stem cells when iPS cells can be made without the ethical guilt?



An iPS-based autologous cell transplantation strategy adapted from Hanna et al. *Science* (2007) vol. 318 (5858) pp. 1920-3

## New, old bioethics

This takes us back to that "age-old" debate on hESCs. Human embryonic stem cell research is controversial because it makes use of and destroys human embryos in order to establish such pluripotent cell lines. At the heart of the stem cell debate are two big issues: the moral status of the embryo and the justification of its manipulation and destruction for therapeutic and research purposes.

<sup>16</sup> Higgs. A new dawn for stem-cell therapy. *N Engl J Med* (2008) vol. 358 (9) pp. 964-6

<sup>17</sup> Wernig et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *Proc Natl Acad Sci USA* (2008) vol. 105 (15) pp. 5856-61

<sup>18</sup> Xu et al. Phenotypic correction of murine hemophilia A using an iPS cell-based therapy. *Proc Natl Acad Sci USA* (2009) vol. 106 (3) pp. 808-813

<sup>19</sup> Ebert et al. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* (2008) pp.

<sup>20</sup> Dimos et al. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science* (2008) vol. 321 (5893) pp. 1218-21

<sup>21</sup> Park et al. Disease-specific induced pluripotent stem cells. *Cell* (2008) vol. 134 (5) pp. 877-86

The first argument divides scientists and ethicists alike: is that "clump of cells" that we call an embryo a human being?

At conception, when the sperm fertilizes the oocyte, a single cell called the zygote is formed endowed with its own complete genome, a cross between the DNA of the father and the mother. This means that an entirely different individual is created. The new cell is only one of its kind as each and every living organism is unique by function of its genetic individuality. Moreover, the fertilized cell is a viable entity separate from the mother albeit dependent on her for his early growth and development. It is important to underline that it is the zygote which really grows and develops and not just some part or cell of the mother. Through time, the zygote gives rise to other cells and this agglomeration of cells is called the embryo. The embryo then becomes more and more complex in its organization as its cells further give rise to other cells and as these other cells later specialize and acquire functionality and make up the even more complex human body. From purely scientific logic, we conclude that every cell and part of our body came from that primordial cell. Is the zygote then a person? Yes, it is a person at its first stages of development. After all, we were all zygotes in the beginning.

A corollary of such argument is the debate of whether the embryo is entitled to the same rights as any other human being. If we recognize that embryos are persons and adults in potential, they have the same right to life and should be protected from any harm or abuse.

The second issue revolves around the "ends and means" argument. Finding cures for the most debilitating of human diseases is a most noble pursuit; however, does it justify the manipulation and sacrifice of other human beings? Do embryos have the same human dignity as these people who are suffering and in need of therapeutic stem cells? If yes, then they cannot be used neither for therapy nor for research. As the adage goes, the end no matter how good or noble never justifies the most evil of means, such as killing a human being in order to save another. Human dignity is a concept that governs the inherent respect for human life common to all human beings the world over. It is something that every human being is endowed with and never is something granted by other human beings to a select few. By merely existing, we have earned human dignity and thus the right to live. Otherwise, that kind of "human dignity" would be a farce.

The advantages that iPS cells offer also render unnecessary other alternatives that have been put forward in order to circumvent the present problems of hESCs such as human-animal "cybrids"<sup>22</sup> in order to address the high demand for human oocytes and embryos and the derivation of single blastomere-derived hESCs<sup>23</sup> without embryo destruction. Since all these techniques involve the production of new embryos of human nature (in the case of cybrids, *mostly* of human nature) and using it as mere means to advance another human being's ends, they treat human embryos (and oocytes) as

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<sup>22</sup> Human-animal "cybrids" are the result of the transfer of human nuclear DNA into enucleated (i.e., their nucleus taken out) mammalian oocytes giving rise to an embryo that has the full set of genes from the donated human nucleus, along with the cytoplasmic mitochondrial genes of the animal egg. However, these created entities have not been shown to develop beyond the 16-cell stage, just short of the blastocyst phase of development, probably due to the incompatibility between animal mitochondrial and human genes. (Chen et al. Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes. *Cell Res* (2003) vol. 13 pp. 251-63)

<sup>23</sup> Chung et al. Human embryonic stem cell lines generated without embryo destruction. *Cell Stem Cell* (2008) vol. 2 (2) pp. 113-7

fungible raw material promoting a dehumanizing and utilitarian attitude towards human reproduction<sup>24</sup> and thus, are immoral and unacceptable.

It is clear that the direction of the current stem cell research is to determine if human iPS cells can indeed replace hESCs in therapeutic schemes. The majority of scientists at the moment believes that both human iPS and hESC research should go in parallel and further recommends the continued research on hESCs and derivation of new hESC lines<sup>25</sup>. They also highlight that human iPS cells and hESCs have significant, albeit minor, differences that may have a pronounced effect on the developmental and therapeutic potential of human iPS cells.

We agree that human iPS cells are not hESCs. However, we argue that human iPS cells, after having been proven highly similar, albeit not identical to hESCs according to the established tests for pluripotency, should stand out on its own and need not be always meticulously compared to hESCs given the already patent differences in their origin, derivation and ontology. In theory, based on the results to date, human iPS cells are capable of whatever hESCs are capable of according to their capacities for self-renewal and developmental potency. This also means that there is no need to create more hESC lines despite recent interventions at the level of law and politics<sup>26</sup>. We think that continuous comparison of human iPS cells with hESCs would be rather detrimental to the progress of the field as the potential of iPS cells would always be measured in relation to hESCs. We further argue that human iPS cells should be studied for what they are and not for what they should be.

It is true that the iPS cell era has just begun and it's still too soon to tell if they will indeed replace hESCs as the most versatile pluripotent stem cells for therapy and basic research. Many parameters in the technology still need to be improved in order for it to be sufficiently safe for the clinic like the replacement of viruses and DNA manipulation as methods of induction. We have yet to see iPS cells generated by inserting proteins<sup>27</sup> instead of genes which would be a step closer to using them in the clinic. The foremost advantages of iPS cells both on ethical and technical grounds make it an irrefutable substitute to hESCs in the near future.

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<sup>24</sup> Meyer. The significance of induced pluripotent stem cells for basic research and clinical therapy. *Journal of medical ethics* (2008) vol. 34 (12) pp. 849–51

<sup>25</sup> Hyun et al. New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells. *Cell Stem Cell* (2007) vol. 1 (4) pp. 367–368

<sup>26</sup> Stolberg. Obama lifts Bush's strict limits on stem cell research. *New York Times*. March 9, 2009. URL: <http://www.nytimes.com/2009/03/10/us/politics/10stem.html>. Last accessed on April 2, 2009.

<sup>27</sup> Authors' note: Shortly a month after having written this paper, induction of pluripotency in mouse skin cells by recombinant proteins had already been demonstrated (Zhou et al. Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins. *Cell Stem Cell* (2009) doi: 10.1016/j.stem.2009.04.005).