

**UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA**

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| DR. JAMES L. SHERLEY, et al. | ) |                                      |
|                              | ) |                                      |
| Plaintiffs,                  | ) | Civil Action No. 1:09-cv-01575 (RCL) |
|                              | ) |                                      |
| v.                           | ) |                                      |
|                              | ) |                                      |
| KATHLEEN SEBELIUS, et al.    | ) |                                      |
|                              | ) |                                      |
| Defendants.                  | ) |                                      |
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**DECLARATION OF STORY LANDIS**

I, Story Landis, Ph.D., pursuant to 28 U.S.C. § 1746, declare under penalty of perjury as follows:

1. I am the Director of the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH) and Chair of the NIH Stem Cell Task Force. I am responsible for helping to develop and implement stem cell policy for NIH, including the planning, development and implementation of the NIH Guidelines for Human Stem Cell Research (Guidelines), 74 Fed. Reg. 32,170 (July 7, 2009).

2. In these positions, I am familiar with the process used by NIH to review applications for research grants as well as the day to day operations of intramural scientists at NIH. I am also familiar with NIH's activities with regard to the development and publication of the draft and final Guidelines notices in the Federal Register, which establish policies and procedures under which NIH may fund human embryonic stem cell (hESC) research. I make this declaration based upon information within my personal knowledge or provided to me in my official capacity.

3. NIH funds grants, cooperative agreements, and contracts that support biomedical and behavioral research leading to the advancement of fundamental knowledge about the nature and behavior of living organisms and the application of that knowledge to the causes, diagnosis, prevention, treatment, and cure of human diseases, conditions, and injuries.

4. NIH supports research both within and outside the NIH community. Funds for research conducted by academic and other institutions not affiliated with NIH, referred to as extramural research, are provided through a competitive, peer review process operated by NIH. NIH supports both intramural and extramural human stem cell research, including hESC research. NIH has provided funds for hESC research since 2002.

#### **Development and Publication of the NIH Guidelines for Human Stem Cell Research**

5. On August 9, 2001, President George W. Bush determined that NIH funds could be used to support hESC research if the following criteria were met: (i) the derivation process (which involves the extraction of stem cells from an embryo) was initiated prior to 9 pm EDT on August 9, 2001, (ii) the stem cells were derived from an embryo that was created for reproductive purposes and no longer needed, (iii) informed consent was obtained for the donation of the embryo, and (iv) there were no financial inducements for the donation. NIH ultimately determined that there were 21 hESC lines available to investigators that satisfied President Bush's criteria and therefore were eligible for use in NIH-funded research.

6. On March 9, 2009, President Barack H. Obama issued Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells, which lifted the restrictions on hESC research that had been imposed by President Bush. In the Executive Order, President Obama stated that “[t]he purpose of this order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America’s scientists to important new discoveries and new therapies for the benefit of humankind.” Executive Order 13,505 § 1. The Executive Order directed NIH to issue new guidance on stem cell research “consistent with” the Order that would allow NIH to support and conduct responsible, scientifically worthy human stem cell research, including embryonic stem cell research, to the extent permitted by law. *Id.* §§ 2, 3.

7. Pursuant to the Executive Order, NIH began the process of developing draft guidelines describing the circumstances under which hESCs would be eligible for use in extramural NIH-funded research. As part of this process, NIH reviewed the guidelines it had issued in 2000 pertaining to pluripotent stem cells derived from human embryos, 65 Fed. Reg. 51,976 (Aug. 25, 2000). These guidelines had been promulgated after notice and comment but were later withdrawn after President Bush restricted funds on the basis of the date on which stem

cell lines were derived. NIH also reviewed a variety of guidelines promulgated by other national and international committees of scientists, bioethicists, patient advocates, physicians and other stakeholders, including the U.S. National Academy of Science, the International Society for Stem Cell Research, and others.

8. In publishing the Draft NIH Guidelines for Human Stem Cell Research (Draft Guidelines), 74 Fed. Reg. 18,578 (Apr. 23, 2009), NIH proposed that funding for hESC research only be permitted if the hESCs were derived from embryos created from in vitro fertilization (IVF) for reproductive purposes and were no longer needed for that purpose, and then, only if certain specific conditions were met, including conformity with informed consent procedures. As is well known, these embryos, if not donated, are typically destroyed, discarded, or become unusable for IVF purposes. The Draft Guidelines further noted that funding by NIH would continue to be allowed for human stem cell research using adult stem cells and induced pluripotent stem cells (iPSCs). In addition to describing research for which NIH funding would be available, the Draft Guidelines described research for which the expenditure of funds would not be permitted, including the “funding of the derivation of stem cells from human embryos ... prohibited by the annual appropriations ban on funding of human embryo research ... otherwise known as Dickey-Wicker Amendment.” 74 Fed. Reg. at 18,580. The Draft Guidelines were published on April 23, 2009, and invited written comments to be received by NIH on or before May 26, 2010.

9. NIH received approximately 49,000 comments from patient advocacy groups, scientists and scientific societies, academic institutions, medical organizations, religious organizations, members of Congress and private citizens. All of the comments were reviewed and categorized. Many comments opposed hESC research, expressing moral and ethical concerns and, in most cases, citing a belief that adult stem cell research categorically yielded better results for clinical applications. Other comments expressed support for hESC research, including many that urged NIH to broaden the guidelines to grandfather existing cell lines without any further review and/or to permit NIH funding for research using hESC lines derived from the product of somatic nuclear cell transfer or parthenogenesis. A small number of comments were identified as entirely non-responsive or offensive. Comments were classified as non-responsive if they did not address stem cell research at all or if they were self-contradictory or too vague to reasonably determine a position. Comments were also marked non-responsive if

they only contained reference information. All were publicly posted except for those that contained offensive material.

10. Further analysis of the comments received indicated that about one-half of all comments consisted of “form” comments, boilerplate objections to hESC research, or standard talking points that particular organizations had urged members of the public to submit. For example, more than 10,000 nearly identical comments were submitted at the behest of the National Committee for Human Life Amendment and the Susan B. Anthony List, expressing the categorical view that hESC research destroys human life and should not be subsidized with federal funds.

11. Comments opposing hESC research as a categorical matter were all reviewed and considered, but they were deemed to fall outside the scope of the issues to be decided in promulgating the Guidelines. By Executive Order, NIH had been directed to issue guidelines for the funding of stem cell research, including hESC research, following the President’s removal of existing limitations on that research. The purpose of the Guidelines was to outline how NIH would implement the Executive Order, not whether it would implement the Executive Order. A large number of comments contained no recommendations related to the specific requirements for eligibility for NIH funding presented in the Draft Guidelines. Even where NIH determined that comments did not address matters within the scope of the Guidelines, NIH did not “ignore” those comments but simply deemed them not relevant to the issues to be resolved and therefore not appropriate for discussion in the final Guidelines. As a general matter, comments voiced two types of categorical objections to hESC research: moral and scientific.

12. NIH received numerous comments that categorically opposed hESC research for moral or ethical reasons. NIH considered these comments but deemed them not relevant to the promulgation of the final Guidelines. Having “remove[d] [the] limitations” on stem cell research imposed by the previous Administration, the President directed NIH to develop guidelines for the funding of “responsible” hESC research. The scope of the Guidelines was thus limited to establishing how to determine which hESC lines were derived in an ethical manner and appropriate for use in NIH-funded research. NIH responded to comments that were relevant to the inquiry for which comments had been requested. For instance, in response to concerns raised by commenters, NIH revised the Guidelines to provide that donors of embryos should be informed of the point in time at which their donation decision would become irrevocable. 74

Fed. Reg. 32,173, 32,174. NIH did not respond to comments that went beyond the scope of the rulemaking, such as those containing no recommendations for how to determine which hESC lines were derived in an ethical manner and appropriate for use in NIH-funded research, including comments that categorically opposed hESC research on moral or ethical grounds.

13. NIH also received numerous comments asserting that hESC research is lacking in scientific merit as a categorical matter, in particular when compared to adult stem cell and induced pluripotent stem cell (iPSC) research. These comments were reviewed, but it was determined that they also did not bear on the issues that were being decided in the rulemaking. The Guidelines did not purport to decide the relative merits of different forms of stem cell research or express an agency-wide preference for one scientific methodology over another. Rather, the Guidelines were premised on the understanding that the scientific merit of any research for which funding was sought, including hESC research, would be evaluated separately on a case-by-case basis through NIH's statutorily-mandated peer review process. *See* 42 U.S.C. §§ 282(b)(9), 284(a)(3), 289a; *see also* Declaration of Sally Rockey ¶¶ 8-17. Peer review allows experts to assess the scientific merit of research proposals in a manner far superior than would be available through the rulemaking process. The Guidelines did not alter the way NIH evaluates the quality or scientific merit of grant applications as part of that peer review process. Nor did the Guidelines assign any preference to hESC research over other forms of stem cell research. Accordingly, NIH did not address comments that, in contravention of the President's Executive Order, sought a blanket ban on federal funding for research involving hESCs.

14. Since July of 2009, NIH has approved 75 stem cell lines for use in NIH-funded research, having determined that they were consistent with the Guidelines. A handful of these 75 lines were used in research approved under the Bush Administration, but the vast majority were developed during the period from 2001 until 2009 when no federal funding was available for research that used any new lines. Of the approved lines, 73 were derived from embryos donated prior to the issuance of the Guidelines. These 75 stem cells lines may then be used to supply hundreds of different researchers.

15. To derive stem cells from an embryo, a scientist typically removes the inner cell mass of a blastocyst and places it in culture with the appropriate nutrient medium and substrate. If the deriver is satisfied with the appearance of the disaggregated cells after weeks of culture and multiple passages, he/she can attempt to expand them to establish a cell line. No NIH

funding may be used for the elaborate research process in which stem cells are derived, nor for any of the many derivation experiments involving embryos, including experiments designed to test how best to culture the embryonic cells and experiments relating to the timing of derivation. The research process used to derive stem cells is entirely distinct from any research that may subsequently be conducted using the stem cell line.

16. As noted, the scientific merit of hESC research was not an issue to be decided within the scope of the Guidelines. However, because Plaintiffs in this action have made a series of misleading statements regarding these merits, it is worth noting that there is a broad scientific consensus that all avenues of stem cell research, including hESC research, are valuable tools in the pursuit of treatments for a variety of debilitating diseases and injuries. *See, e.g.*, Stem Cell Basics, FAQs and Regenerative Medicine at <http://stemcells.nih.gov/info> and Highlights of Stem Cell Research at <http://stemcells.nih.gov/research>. Indeed, the fact that all three types of research have met with success in NIH's rigorous peer review process defeats the assertion that any is scientifically unworthy as a categorical matter. NIH has funded and continues to fund the best scientific research proposals, whether that research builds upon well-established technology and knowledge or is exploring novel approaches to understanding human biology or testing new therapeutics.

17. While adult stem research has produced greater tangible results for clinical applications to date, this is unsurprising. The biomedical research community has been exploring the biology and uses of the adult stem cell populations that exist in bone marrow and blood for five decades. In contrast, the first publication describing the establishment of hESC lines was not until 1998, and there continued to be serious constraints on the funding of hESC research for years thereafter. The fact that hESC research has not, in its short history, produced the same results that five decades of research in adult stem research has, speaks not to the relative merit of the two types of research, but to the pressing need to allow hESC research to develop to its full potential. The scientific community recognizes the limitations on uses of multipotent adult stem cells: they are currently not available in sufficient quantity (except for hematopoietic stem cells) to be useful in many research and clinical applications, they cannot be grown and expanded without limit in culture, and they are not pluripotent – a given adult stem cell cannot differentiate into all of the cell types of the body.

18. In a declaration submitted in connection with Defendants' Motion to Stay the Preliminary Injunction, Dr. Teresa Deisher rejected the merit of hESC research. Her view is contrary to the general scientific consensus. In her declaration, Dr. Deisher downplays or ignores the many advancements in hESC research in the short period of time in which it has been conducted, arguing that hESC research will not lead to therapeutic applications. Deisher Decl. ¶ 9. In fact, significant progress has already been made toward this end. As just one example, in 2004 – only six years after hESCs were first isolated – an investigator successfully differentiated hESCs into human dopamine neurons, the type of brain cell that is lost by those who suffer from Parkinson's disease.<sup>1</sup> Four years later, another group of researchers had not only modified the protocol to produce large numbers of human dopamine neurons but had transplanted them into an animal model of Parkinson's disease and elicited clear behavioral recovery.<sup>2</sup> With the animal model and the availability of large number of the appropriate human cells – dopamine neurons which cannot at this time be obtained from bone marrow<sup>3</sup> – scientists are continuing to move forward in the area of cell replacement therapy for Parkinson's disease in humans.<sup>4</sup>

19. Therapeutic medicine is also not the only promising area of hESC research. Since hESCs are pluripotent and can develop into all the cell types of the human body, scientists have elucidated the molecular signals that trigger their conversion into heart cells, liver cells, many kinds of neurons, blood cells, skeletal muscle cells, retinal cells and neural crest among others.<sup>5</sup>

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<sup>1</sup> See *Derivation of midbrain dopamine neurons from human embryonic stem cells*. Perrier AL, Tabar V, Barberi T, Rubio ME, Bruses J, Topf N, Harrison NL, Studer L. Proc Natl Acad Sci U S A. 2004 Aug 24;101(34):12543-8. Epub 2004 Aug 13.

<sup>2</sup> See *Highly efficient and large-scale generation of functional dopamine neurons from human embryonic stem cells*. Cho MS, Lee YE, Kim JY, Chung S, Cho YH, Kim DS, Kang SM, Lee H, Kim MH, Kim JH, Leem JW, Oh SK, Choi YM, Hwang DY, Chang JW, Kim DW. Proc Natl Acad Sci U S A. 2008 Mar 4;105(9):3392-7. Epub 2008 Feb 27.

<sup>3</sup> Although Dr. Deisher contends that bone marrow can be differentiated into neurons, see Deisher Decl. ¶ 15, she relies on an outdated NIH report from 2001, ignoring a subsequent 2006 report which suggests that such differentiation is so exceedingly rare as to be unavailable for therapeutic applications. See <http://stemcells.nih.gov/info/2006report/2006Chapter2.htm>

<sup>4</sup> See *Towards stem cell replacement therapies for Parkinson's disease*. Arenas E. Biochem Biophys Res Commun. 2010 May 21;396(1):152-6.

<sup>5</sup> See Laflamme et al. *Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts*. Nature Biotechnology 25(2007); Duan Y et al., *Differentiation and Characterization of Metabolically Functioning Hepatocytes from Human Embryonic Stem Cells*. Stem Cells 28:674-686 (2010); Li, Xue-Jun et al. *Specification of motoneurons from human embryonic stem cells*. Nature Biotechnology 23 (2005); Blood 113(24):6094-101; Laboratory of D.S. Kaufman. 2009 Jun 11; Barberi, T et al. *Derivation of engraftable skeletal myoblasts from human embryonic stem cells*. Nature Medicine 13:642-648 (2007); Lambda DA et al. *Transplantation of Human Embryonic Stem Cell-Derived Photoreceptors Restores Some Visual Function in Crx-Deficient Mice*. Cell Stem Cell 4 (2009); Lee G et al. *Isolation and directed differentiation of neural crest stem cells derived from human embryonic stem cells*. Nature Biotechnology 25:1468-75 (2007).

These findings provide insights into how normal development proceeds and may be disrupted, resulting in birth defects and developmental disabilities. hESCs also serve as an invaluable tool for understanding the toxicity of drugs that are in the early stages of development and identifying new drugs for possible use in treating diseases. For example, liver toxicity is a common cause of drug failure. hESCs can be differentiated into human liver cells in large numbers and then exposed to novel drugs in order to identify any obvious liver toxicity and provide early insight on how the drug will be metabolized by the liver. This use of hESCs is not a promised future use, but a current reality, as is the use of hESCs as a tool for identifying drug candidates for the fatal neurological disease amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

20. Dr. Deisher also suggests that hESCs are not "normal" and therefore "may form tumors when injected into a patient's body." Deisher Decl. ¶ 9. While it is true that injecting undifferentiated hESCs (*i.e.*, hESCs that have not been developed into a particular cell type) into mice causes benign tumors, or teratomas, no credible scientist would propose injecting undifferentiated hESC into a human patient. Undifferentiated hESCs are injected into mice only as a means to test for pluripotency. Dr. Deisher also notes the existence of "major" challenges encountered during particular hESC research projects, as though such challenges are reason to abandon hESC research wholesale. Deisher Decl. ¶ 10. There will always be obstacles and uncertainties in any nascent avenue of scientific inquiry. If researchers categorically abandoned an entire avenue of scientific study at the first sign of difficulty or obstacle, we would not have many of the standard methods of treatment we have today, including bone marrow transplants: the first transplants resulted in failure and some in the scientific community questioned whether the method could ever become successful.

21. Dr. Deisher also understates the uncertainties of iPSC research, which she posits as a superior alternative to hESC research. Although iPSC research is exciting and promising, there is much that is not known about iPSCs. The existence of this new avenue of research is not a reason to abandon other promising avenues, including hESC research. Indeed, the researcher who discovered iPSCs, who was selectively quoted in Dr. Deisher's declaration, *see* Deisher Decl. ¶ 17, has expressed the view that advances in iPSC research do not obviate the need for

continued hESC research.<sup>6</sup> The degree to which hESCs and iPSCs are similar is scientifically unsettled. More research is necessary – including research using hESCs – to determine what differences exist and what effect those differences might have on therapeutic applications. It is also worth noting that at present, hESCs appear to be better than non-embryonic stem cells at generating certain types of cells and providing disease models.<sup>7</sup> They also may be better at generating functional adult cells than non-embryonic stem cells. One important example is the so-called natural killer (NK) cells used in cancer therapies. In an NIH-funded study at the University of Minnesota, researchers found that hESC-derived NK cells were more effective than stem cells derived from umbilical cords in destroying both leukemia and solid tumors, such as breast and prostate cancer. hESC-derived NK cells not only destroyed human cancers in mice, but also protected mice from recurrence and metastasis.<sup>8</sup>

22. **Ultimately, however, the debate about which avenue of stem cell research carries the most promise is a distraction.** In the search for knowledge about the origins and treatment of diseases, it is unsurprising that the scientific community would seek to use all tools at its disposal. We cannot know in advance and with absolute certainty what avenues of research may ultimately lead to a cure for Parkinson’s disease, spinal injury, or a host of other debilitating conditions. That is why it is important to pursue all avenues of research deemed most scientifically meritorious through NIH’s rigorous peer review process.

I declare under penalty of perjury that the foregoing is true and correct. Executed at Bethesda, Maryland this 27th of September, 2010.



STORY LANDIS, PH.D.  
Director  
National Institute of Neurological Diseases and Stroke  
National Institutes of Health

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<sup>6</sup> See *New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells*, Cell Stem Cell, Volume 1, Issue 4, 367-368, 11 October 2007, [http://www.cell.com/cell-stem-cell/fulltext/S1934-5909\(07\)00176-2](http://www.cell.com/cell-stem-cell/fulltext/S1934-5909(07)00176-2).

<sup>7</sup> See Hu B *et al.* *Neural differentiation of human induced pluripotent cells follows developmental principles but with variable potency*. Proceedings of the National Academy of Sciences 107:4335-40. (2010); Urbach A *et al.* *Differential modeling of fragile X syndrome by human embryonic stem cells and induced pluripotent stem cells*. Cell Stem Cell 6:407-411 (2010).

<sup>8</sup> See Blood 113(24):6094-101; Laboratory of D.S. Kaufman. 2009 Jun 11.