

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

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

**DECLARATION OF FRANCIS S. COLLINS**

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

1. I am the Director of the National Institutes of Health (“NIH”). I am responsible for setting policy for NIH and for planning, managing, and coordinating the programs and activities of all the NIH components. I am informed about program priorities and accomplishments through Office of the Director staff, Institute and Center staff, as well as through the extramural scientific community, patient advocacy and voluntary health groups, and Congress. Prior to assuming the role of NIH Director in August 2009, I served as the Director of the National Human Genome Research Institute from 1993-2008. I have also worked part-time as a senior investigator of an NIH intramural research laboratory where I conduct experimental research and lead a team of biomedical research scientists.

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 at NIH by intramural scientists, and 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. Extramural research accounts for approximately 84 percent of the NIH's budget. NIH also employs scientists who conduct research in government laboratories on the NIH campus and elsewhere. Research conducted directly by NIH through its scientist employees is referred to as intramural research, and accounts for approximately 10 percent of the NIH budget. Funds for intramural and extramural research are specifically budgeted each fiscal year and are not readily interchangeable. NIH supports all of its research through Institutes and Centers (ICs) that award grants and conduct intramural research, as well as the Office of the Director. See List of Institutes, Centers and Offices, at <http://www.nih.gov/icd/>. NIH supports both intramural and extramural human embryonic stem cell research.

#### **The Importance of Human Embryonic Stem Cell Research**

5. Human embryonic stem cells ("hESC") were first isolated in 1998 by Dr. James Thomson at the University of Wisconsin. 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 begins with destruction of the embryo) was initiated prior to 9 pm EDT on August 9, 2001, (ii) the stem cells had to be derived from an embryo that was created for reproductive purposes and no longer needed, (iii) informed consent must have been obtained for the donation of the embryo, and (iv) there could be no financial inducements for the donation. NIH ultimately determined that 21 hESC satisfied President Bush's criteria and therefore were eligible for use in NIH funded research. Investigators have embraced this opportunity to realize the remarkable potential of hESC to pursue critical questions about how the different cells of the human body develop, how they are affected by disease, and how hESC can contribute to the development of therapeutics through cell replacement and/or drug screening.

One of the first awards for hESC research was made to Dr. George Daley at Children's Hospital in Boston in 2002 to dissect the molecular mechanisms responsible for turning hESC into blood cells and their precursors. He is currently funded to compare the ability of hESC and induced pluripotent stem cells (described in ¶ 7) to produce blood cells. Including that initial award and his present funding, NIH has provided more than \$2.7 million dollars to his laboratory



alone, and as a result, Dr. Daley has produced a detailed procedure for the generation of blood cells from hESC. Based on his progress in directing hESCs to develop into blood cells, it is possible in the future that they could be used to address virtually all genetic and malignant blood diseases that are currently treated by gene therapy or bone marrow transplant. These include sickle cell anemia, Fanconi's and other congenital anemias, Hodgkin's lymphoma, chronic lymphocytic and myelogenous leukemias and myelomas, among others.

Since those first awards in 2002, NIH has a total aggregated investment of \$546 million in intramural and extramural hESC research. As a result of these investments, NIH funded animal studies, often referred to as preclinical studies, are underway to test whether cells or tissues derived from embryonic stem cells, human and/or mouse, are of benefit for retinal degeneration, stroke, liver failure, muscular dystrophy, myelin deficiencies, motor neuron diseases, and Huntington's disease.

Stem cell research holds great promise for the development of treatments for a wide range of serious and life-threatening diseases and conditions. Some of those opportunities for basic and applied research are described in a document from the National Academies of Science, *Understanding Stem Cells: An Overview of the Science and the Issues* (2009). Research into the unique properties of stem cells may lead to major medical breakthroughs that would offer hope to people suffering from cancer, diabetes, cardiovascular disease, spinal-cord injuries, neurodegenerative conditions, and many other disorders. Both adult stem cell and hESC research show further promise to develop our understanding of and treatments for many diseases, conditions, and injuries, such as blood disorders, heart disease, autoimmune disorders like multiple sclerosis, lysosomal disorders, as well as joint and bone disease.

6. Indeed, remarkable progress has already been made in realizing the possible benefits of hESC research. Even though hESC were not even isolated until 1998, the first clinical trial of a hESC-derived therapy has received FDA approval to begin enrolling spinal cord injury patients. This trial will test the safety of using hESC-derived precursors for the cells that insulate nerves in the spinal cord to restore spinal cord function. This is a remarkable achievement and heralds what should be the beginning of a new era in cell-based therapy. Equally important, differentiated cells derived from hESC are already successfully being used to develop new therapeutic drugs for a number of diseases including amyotrophic lateral sclerosis ("Lou Gehrig's disease") and spinal muscular atrophy, to name just a few. Without dependable and consistent

support from NIH, hESC research and development of new therapies will be dealt a critical blow that will have dire ramifications for those suffering from the many diseases and disorders may be treatable with hESC-based therapies or drugs developed using hESC testing.

7. Opponents of hESC research posit that adult or non-embryonic stem cells have the same potential for therapeutic benefit as hESC. In considering the relative benefits of adult and embryonic stem cell research, it is critical to remember that adult stem cells were identified over a half century ago and have been the subject of robust research for decades. This research has produced FDA-approved treatments that reconstitute the immune system after leukemia, lymphoma, and various blood or autoimmune disorders have been treated with chemotherapy.

NIH believes that it is important to continue to support research using adult stem cells since there may be additional clinical applications for which they will be useful. However, adult stem cells also have serious limitations that fifty years of research have not been able to overcome. First, they are currently available in quantity only from blood forming tissues and cord blood and once collected, they do not divide indefinitely and therefore produce a finite number of cells. Second, despite many years of work, it has not been possible to differentiate adult stem cells into cell types that are very different from their tissue of origin. A bone marrow stem cell, for instance, cannot be differentiated into a neuron. In contrast, hESC can be expanded in cell culture to essentially limitless numbers. They are also "pluripotent": with appropriate protocols, it appears that they can be turned into any of the different cells of the human body. These expanded cell populations can be used to elucidate disease pathogenesis and screen new drugs, as well as to develop cell-based therapies. This is particularly important in the case of human brain cells, which are not readily available from other sources as brain biopsies are only justified for diagnostic purposes and brain autopsies do not yield viable nerve cells. Thus, hESC may offer significantly more scientific and clinical potential than do adult stem cells.

Very recently, scientists discovered that it is possible to instruct adult skin cells to return to a very early developmental stage. This can be accomplished using viruses carrying molecular signals that turn back the developmental clock so that they possess hESC-like properties: they continue to divide indefinitely and are pluripotent, with the potential to give rise to all the cells of the human body. These induced pluripotent stem cells ("iPSC") represent a new, third category of stem cells and were discovered as a direct result of the knowledge gained from studying hESC. They are of great interest to scientists. However, they are not well understood yet, and a



growing body of research suggests that there are significant biological differences between iPSC and hESC. In addition, there are significant safety issues because viruses and a cancer gene are used to induce pluripotency in most of the protocols used to generate iPSC. Most scientists believe that it is essential to continue research on hESC as we explore the potential of iPSC.

In FY 2009, NIH funded over 1,000 extramural projects and subprojects involving non-embryonic human stem cells (including adult stem cells and iPSC), totaling \$397 million. During FY 2010, NIH has provided an estimated \$380 million in non-embryonic human stem cell research funding.

#### **The Impact of the Court's Order on hESC Research**

8. The preliminary injunction issued in this case will have extraordinary adverse effects not only on the prospects of delivering new therapies to patients suffering from numerous diseases and disorders but also on scientific progress from the wider biomedical research community. It will result in immeasurable loss of valuable and one-of-a-kind research resources. Unique modifications and applications of hESC, underway in laboratories with federally-funded research as far back as 2002, could be lost irretrievably or could take years to recreate. Experiments that may have been months or years in development will be halted prematurely, before any promising results can be obtained. Investigators who have devoted their careers to this exciting area of research may have to close their laboratories or move to another country. Government resources already expended on hESC research to date, including over \$546 million dollars of public funds, will have been wasted and the mission and operations of NIH will be severely hampered as a result of this Court's Order.

#### **Disruption to Extramural Research**

9. As a result of the Court's Order, NIH is prohibited from awarding funds to extramural research projects involving hESC, thereby jeopardizing grants for research projects that are in varying stages of funding. These grants include research projects that have the potential to advance the use of hESC in therapies for heart disease, sickle cell disease, liver failure, muscular dystrophy, and other critical diseases and conditions. Grants typically have 3-5 year project periods but receive funding only on an annual basis, consistent with NIH appropriations. At this time, three categories of grants are affected: (1) grants already awarded that are up for their next year of continuation funds by September 30, 2010, (2) applications for grants that have successfully completed the first level of peer review and are scheduled to

receive final approval by Institute Advisory Councils, after which NIH expected to provide the first year of funding by September 30, 2010, and (3) applications for grants that are currently in the peer review process.

10. With respect to research projects already under way, the Court's Order prevents NIH from providing \$54 million in funds to 24 hESC research projects that were expecting to receive continuation funds by September 30, 2010. These 24 projects have already received a combined \$64 million in funding from NIH over the previous years of their project periods. Taxpayer money already invested in these research projects will be irretrievably lost due to this Order. In addition, these institutions depend on NIH for continued financial support. Prior to this Court's Order, these projects would have been eligible to receive their next year of continued support, contingent upon the completion of an annual progress report. The grants include projects that study basic aspects of stem cell biology, advance stem cell technology, and work towards applying hESC to therapies for a variety of diseases and disorders. Examples of these projects include the following and all use lines that were eligible before the NIH Guidelines for Human Stem Cell Research ("Guidelines") were issued on July 7, 2009 (described in ¶ 5 above):

- Dr. Church and his research team from Children's Hospital in Boston, Massachusetts, and Harvard Medical School are conducting a comprehensive comparison of hESC and induced pluripotent stem cells ("iPSC"). It is absolutely essential that we learn whether or not there are significant functional differences between hESC and iPSC. A growing body of evidence suggests that the two classes of pluripotent cells are not identical and therefore iPSC cannot be universally substituted for hESC. This research is expected to provide invaluable information on the use of hESC as compared to iPSC for many applications, including development of life-saving therapeutic strategies.
- Dr. Fox at the University of Pittsburgh is exploring hESC as a potential replacement source of liver cells for transplantation. At present the only treatment for liver failure is liver transplantation. There are not enough donor livers available and the surgery is technically difficult and risky. One way to overcome these problems would be to use liver cells derived from hESC. Dr. Fox is making excellent progress and has shown that he can generate 100,000 to 200,000 pure liver cells and transplant them successfully into an animal model of liver failure. The next steps would be to develop methods to significantly increase the number of liver cells produced in preparation for exploring non-human primate models.



- Dr. Spence at the Children's Hospital Medical Center in Cincinnati, Ohio is working on methods to direct hESC more efficiently into therapeutically important tissues including the lung, liver, pancreas, and intestine. He has identified two chemical signals that determine whether the hESC will become liver or pancreas. This grant is a two-year fellowship to support his training before he looks for a position as an independent scientist. Absent a stay of this Court's Order, the funding for the second year would be suspended, likely terminating his training and quite possibly jeopardizing his future career.
- Dr. Parsons from the University of California Riverside is studying how to manipulate hESC differentiation into brain cells, both neurons and supporting cells. Death of nerve cells has devastating consequences since they do not regenerate and there is no source for replacement. As noted earlier, it is extremely difficult to obtain brain cells from children and adults for studies of possible therapeutic agents. The development of recipes for directing hESC reliably to form nerve cells would have extraordinary implications for cell replacement in neurodegenerative diseases like Parkinson's disease and amyotrophic lateral sclerosis ("Lou Gehrig's Disease"). Such derived nerve cells can also be extraordinarily useful for identifying new drugs that may protect the brain and prevent conditions like Alzheimer's disease. Dr. Parsons, who is early in his career as an independent scientist, is making remarkable strides toward this goal. If his funding lapses as a result of this Court's prohibition on funding hESC research, progress will cease and he may not be able to continue as an investigator.

11. The preliminary injunction affects not only NIH's ability to fund projects that have been initiated after Executive Order 13505 issued on March 9, 2009, and the Guidelines that the Plaintiffs challenge, but also its ability to fund projects that were already in progress during the previous Administration. Of the 24 hESC grants discussed above, almost all of them were in progress prior to July 7, 2009, when the Guidelines were issued. The preliminary injunction would therefore not return NIH and the research community to the position that they were in before the Guidelines issued, but would impede research that has been ongoing since 2002. Long-existing projects up for renewal in the period between now and final judgment will be shut down by lack of NIH funding and the scientific community and taxpaying public now stand to lose much of the benefits of many years of research in which NIH has thus far invested.

12. Even a temporary suspension of funds would jeopardize ongoing research projects. When a laboratory experiment is prematurely interrupted, it cannot be easily restarted. Such experiments involve biological materials such as cell lines growing in lab incubators that must be managed daily to encourage growth and prevent contamination. Valuable laboratory animals serving as models of spinal cord injury, Parkinson's disease, or diabetes that were being used to test new therapies under grants using hESC may be lost, many of them forced into euthanasia. Once critical research tools and reagents – including unique materials that have taken years to develop – have been lost due to the termination of research for lack of funding, it may take months or years to recreate them, if recreation is even possible. In addition, laboratory personnel whose jobs depend on grant funds may be let go and the best investigators, including promising young investigators, may abandon this line of research or move to other countries that support hESC studies. In fact, during the period when only 21 hESC lines were available for investigators to use with NIH funds, one prominent United States stem cell scientist moved to England to pursue hESC research.

13. Prior to this Court's Order, NIH had already provided funding to 199 grants for research on hESC in FY 2010 in the amount of \$131 million. We do not interpret the intent of this Court's Order to require NIH to deobligate the funds already awarded to these projects. NIH payments on grant awards are managed through an electronic payment system. Each of the institutional grantees has its own account. These accounts hold funds for all the grants the institution has received from both NIH and other HHS operating divisions; thus, the funds in the grantees' accounts are from multiple grant awards addressing a variety of research topics. After the grant award, authorized grantee representatives access their accounts and draw down funds as needed at their discretion through the electronic payment system, with no involvement of agency officials.

14. Discontinuing support for all hESC grants in future Fiscal Years will have drastic economic and scientific consequences. Economically, it is estimated that each NIH grant directly supports six jobs at the local institution. See McGarvey, WE, Morris, P, Li, X, Li, J, Probus, M, Cissel, M, Haak, LL (2008) How Many Scientists Do the NIH Support? Improving Estimates of the Workforce. NIH Analysis Report 20081219, 1-23, <http://report.nih.gov/FileLink.aspx?rid=530>. Thus, discontinuing financial support for the 223 research projects (mentioned above as 199 grants given FY 2010 funds and 24 continuing grants



awaiting FY 2010 funds prior to this Order) would result in the loss of over 1,300 full or part-time jobs, as well as the potential loss of top U.S. scientific talent as lead scientists may be forced to move to other countries to pursue their cutting-edge hESC research. In addition, since these projects are being discontinued mid-stream, all the funds that have been put in accounts or already drawn down until this point (\$270 million over the two to five year life of these grants, including what has been provided FY 2010) will have been wasted as investigators and labs can neither finish their current projects nor pursue what has been learned. The momentum that has finally been established in the hESC research field will be lost. Young scientists may turn away from this field due to the instability of stopping, then starting and now stopping again. More senior investigators may look to other countries such as Singapore, China, and the United Kingdom to pursue their work. The greatest loss, however, will be for the millions of Americans suffering from illnesses currently under study with hESC, including liver diseases, cardiovascular diseases, eye diseases, and neurodegenerative diseases like Alzheimer's and for those who might in the future have received transplants of cells and tissues created from hESC because donated organs are not available.

15. This Order also will prevent about 20 new hESC applications from being awarded for \$24 million dollars. These 20 applications have not been previously supported by NIH, were approved in a rigorous peer review process as scientifically meritorious, and were expected to be approved by the Institute Advisory Councils in September 2010 to receive funding prior to this Order. As science is always changing, supporting new, cutting-edge science is critical to spur innovation and prevent stagnation of scientific progress.

16. In addition, this Order will prevent 211 grant applications, which have been submitted and are at varying stages of the peer review process, from completing the peer review process. It is not known how many of these applications would have been deemed sufficiently meritorious in peer review to be funded.

#### **Disruption to Intramural Research**

17. Implementation of this Order will have particularly harsh effects on the NIH intramural program. Currently there are 8 intramural hESC research projects staffed by approximately 45 scientists and other personnel, with a total combined budget of about \$9.5 million (FY 2009 data). The scope of these projects is broad, covering research areas such as cancer, neurological diseases, cardiovascular disease, human development, and eye diseases.

NIH has already initiated research project termination activities in response to this Court's Order. In addition to the specific research projects, the intramural program also has a Human Stem Cell Unit which supports intramural hESC researchers. The members of the Unit characterize the properties of hESC lines, train intramural investigators to use hESC in experiments, and collaborate with them on specific projects. This unit has an annual operating budget of \$800,000 and employs four people. NIH is also in the process of recruiting a new Director for the Center for Regenerative Medicine, one of my highest scientific priorities for the intramural program. The goals of this Center are to move pluripotent stem cells into clinical trials. The inability to use hESC for such comparison studies will likely affect this recruitment severely; recruiting a top notch scientist to take on this role under such circumstances is highly unlikely, and so the scope and value of the research planned for this regenerative medicine center will be lost.

#### **Disruption to Agency Administration and Mission**

18. Implementation of this Order has severely disrupted NIH from completely fulfilling its mission. For example, peer review, a cyclical rolling process involving approximately 15,000 reviewers reviewing approximately 80,000 applications on an annual basis, has been halted for hESC applications. If disruption to the cycle continues for a significant length of time and then the process is reinstated, it could take up to 6-8 months for the hESC applications that are currently in the system and being deferred to undergo consideration by peer review, causing significant delay to additional hESC research projects.

19. In addition, the process for determining eligibility of hESC lines for NIH funding and inclusion on the NIH Human Embryonic Stem Cell Registry will be halted, causing major disruption to the NIH and the biomedical community. Owners of cell lines who wish to receive a designation of eligibility for their lines from NIH must submit detailed documentation of the consent process and other factors related to compliance with the Guidelines. Review of this detailed documentation is performed by outside expert reviewers. NIH has already had to cancel a meeting of the reviewers overseeing these applications that had been scheduled for August 24, 2010, and the future of that group is in jeopardy.

20. Finally, the proposed change to the NIH Guidelines (per February 23, 2010 Federal Register notice) has been suspended. This change, as proposed, would have expanded the definition of "human embryonic stem cells" to include those derived from embryos that did not reach the blastocyst stage and allowed for additional lines to be considered by NIH.



21. Although difficult to quantify exactly, the financial loss to NIH and to the taxpaying public which has funded the research to date, including the hundreds of millions already spent on funding interrupted extramural research projects, the millions lost on intramural research, and the administrative costs of shutting down and restarting the NIH regulatory regime for hESC research, would be enormous. Though not all of the indirect consequences can be easily quantified, NIH has directly invested over \$546 million of taxpayers' money in intramural and extramural hESC research since 2002.

#### **Effect On Plaintiffs Sherley and Deisher**

22. The plaintiffs argued that NIH support for hESC research harmed their ability to obtain funding for their own work on adult stem cells. But applications for research using adult stem cells, iPSC, and hESC are not in direct competition with each other for funds. As cited above, NIH estimates it will support \$380 million in human non-embryonic stem cell research in FY 2010. That total is significantly more than the \$131 million provided for all hESC research to-date in FY 2010. But it is highly unlikely that Plaintiffs would benefit from any additional available funds that would have gone to existing or approved hESC projects. Only a very small part, if any, of the money made available to the NIH's \$26 billion extramural research program is likely to go to stem cell research because stem cell research proposals must compete with *all* other extramural research applications according to the ordinary NIH grant review process, which takes into account the research priorities of each NIH institute as well as the scientific merit of each proposal.

23. Plaintiff Dr. James Sherley has been a successful principal investigator ("PI") on prior research grants from NIH. In 2006, the Massachusetts Institute of Technology, with Dr. Sherley as PI, received the first year of a five year grant totaling \$2.5 million in direct costs under the NIH Director's Pioneer Award (NDPA) Program that is expected to continue through 2011. In 2007, the NDPA was transferred to Dr. Sherley's current employer, the Boston Biomedical Research Institute. A grant supplement was also made on July 20, 2009, under the American Recovery and Reinvestment Act ("ARRA") of 2009. In 2010, despite the lifting of certain prior restrictions on hESC research funding and the allowance of a broader range of hESC research consistent with the Guidelines, Boston Biomedical Research Institute with Dr. Sherley as a PI received a \$425,500 Shared Equipment Grant under the NIH ARRA program. Ongoing hESC research and applications for funding for new hESC projects have thus not posed

a barrier for Dr. Sherley. Prior to the promulgation of the Guidelines, between 2007 and 2009, Dr. Sherley has submitted five additional applications to NIH that were not awarded based on the results of peer review. The limited merits of the applications that Dr. Sherley submitted were the reasons for the declination of his applications, not competition from hESC applications. In addition Dr. Sherley's success rate equals or betters the NIH wide average of 20% since he received three grants out of eight applications.

24. While plaintiff Dr. Theresa Deisher received training support from NIH in the early 1990s, she has to my knowledge neither applied for nor received any NIH research grants either individually or as a PI for her organizations.

I declare under penalty of perjury that the foregoing is true and correct. Executed at Tecumseh, Michigan, this 31<sup>st</sup> of August, 2010.



FRANCIS S. COLLINS, M.D., PH.D.

Director

National Institutes of Health