DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

# The Promise of Human Embryonic Stem Cell Research

Witness appearing before the

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Good morning, Chairman Harkin and distinguished Members of the Subcommittee. It is an honor to appear before you today to discuss human embryonic stem cell research. First, I'd like to thank this Subcommittee for its steadfast support of the National Institutes of Health's (NIH) mission: discovering fundamental knowledge about living systems and then applying that knowledge to fight illness, reduce disability, and extend healthy life. NIH is grateful for the confidence that Congress – and this Subcommittee in particular – has shown in our ability to achieve this mission, as evidenced by our current $31 billion budget, and the $10.4 billion provided to NIH through the American Recovery and Reinvestment Act. Your support makes our mission possible, and we are very grateful.

Nowhere has this support been more evident than in this Subcommittee's leadership in advancing human embryonic stem cell research. From your first hearing in December 1998, this Subcommittee has provided a forum for discussing the great promise this research holds. With your steadfast support, NIH has invested more than $500 million in human embryonic stem cell research; one of the most promising research avenues of recent times.

The preliminary injunction issued on August 23 by U.S. District Court Judge Royce Lamberth in the Sherley v. Sebelius case, now stayed pending further order from the Court of Appeals, has created uncertainty in the field of human embryonic stem cell research. Many researchers across the country have considered modifying their research plans to turn away from an area of research that, while promising, is now fraught with uncertainty. Some of our nation's best researchers, who have written grant applications proposing innovative new ideas, are now asking, "Should I even bother to submit my

proposal to NIH?" Likewise, young scientists excited about careers in stem cell research are concerned about going into this field, given the legal uncertainty.

But the real reason for distress about the current legal uncertainty is that patients may have to put hope on hold. While we continue through the legal process, I hope that we can keep the patients and their families in our thoughts. They are at the heart of the NIH mission, and they are the ones who stand to benefit the most, or lose the most, by the stem cell policies we are discussing today.

I am not a lawyer, and I speak to you today as a doctor and a scientist. In that capacity, I want to outline for you the promise of human embryonic stem cell research — research that could be hobbled permanently unless stable federal funding can be assured over the long term.

I want to begin with a brief overview of the remarkable properties of human embryonic stem cells and then describe how research using these cells will:

- provide key insights into the molecular pathways in development and disease;
- allow for the development of tissue replacement or regenerative medicine; and
- enable more targeted and efficient screening of new drug candidates.

Human Embryonic Stem Cells

Human embryonic stem cells possess several unique characteristics. First, these cells are pluripotent, which means that they have the potential to become nearly every one of the different types of cells in the human body. Second, these cells are self-renewing, which means that they are able to multiply in essentially limitless numbers in the lab over many years and to be shared with many researchers around the world.

To be sure, scientists are also interested in other types of stem cells. Adult stem cells are found in various organs and tissues throughout the body. These cells, also sometimes referred to as multipotent or somatic stem cells, can develop into a limited number of specific cell types, depending upon the organ or tissue from which they are derived. However, adult stem cells are less than ideal for many types of research and therapy because they do not divide indefinitely in culture, and they produce only a limited number of cells and cell types.

In considering the relative benefits of adult and embryonic stem cell research, keep in mind that research on the most abundantly available source of adult stem cells, hematopoetic stem cells in bone marrow, began more than a half-century ago. In fact, Drs. E. Donnall Thomas and Joseph Murray were awarded the Nobel Prize in Medicine in 1990, "for their discoveries concerning organ and cell transplantation in the treatment of human disease." Indeed, this research has produced clinically-validated and widely-used treatments that reconstitute the immune system after leukemia, lymphoma, and various blood or autoimmune disorders have been treated with chemotherapy.

NIH is strongly committed to research using adult stem cells because there may be other clinical applications for which they prove useful. NIH has invested many hundreds of millions of dollars over the years in adult stem cell research. Indeed, annually we are spending almost three times as much on adult stem cell research as on human embryonic stem cell research.

A new and third category of stem cells are induced pluripotent stem (iPS) cells, which were created as a direct result of the knowledge gained from studying human

embryonic stem cells. This type of stem cell was first produced in 2007, when scientists discovered that it is possible to instruct adult skin cells to return to a very early developmental stage. They accomplished this by using viruses to insert molecular instructions into the DNA of skin cells – instructions that acted to turn back the cells' developmental clock. These new cells possess many properties of human embryonic stem cells: they continue to divide indefinitely and are pluripotent, with the potential to give rise to all the cells of the human body.

While induced pluripotent stem cells are of great interest to scientists, and have the added potential clinical benefit of avoiding transplant rejection since they can be derived directly from the patient, they are not well understood yet. A growing body of research, including a publication just two months ago from Dr. George Daley, who is here today, and his collaborators suggests that there are subtle but potentially important differences between iPS cells and human embryonic stem cells. On close examination with powerful molecular fingerprinting, it seems that iPS cells retain some memory of the tissue from which they were derived. Whether this will matter for clinical applications is not clear, but virtually all investigators working in the field agree that additional comparisons between iPS cells and human embryonic stem cells are critically important. Human embryonic stem cells remain the gold standard for pluripotency: to prohibit work on human embryonic stem cells will thus do severe collateral damage to the new and exciting research on iPS cells.

Molecular Pathways in Biological Development and Human Disease

While many researchers are focused on coaxing human embryonic stem cells to develop into a particular cell type, such as insulin-secreting cells or liver cells, understanding the basic biology of stem cells themselves will be extremely valuable to understanding human development. We have learned much about the genes required for pluripotency, but there is much more to understand. For example, what genes are expressed in human embryonic stem cells? How is that program altered as these cells move down pathways to become blood cells, muscle cells, or brain cells? How are these steps regulated? What happens if one of the genes doesn't function properly? Our best window into human development is using human embryonic stem cells.

In addition to understanding normal human development more completely, human embryonic stem cells are providing key tools to help us study the origins of many devastating diseases that afflict babies and young children. Such research may even help to uncover targets for drug development. We now have a number of human embryonic stem cell lines that are known to carry mutations that cause specific diseases. For example, scientists are studying cell lines with a mutation in the *FMR1* gene that causes Fragile X, a developmental disability. The *FMR1* gene normally makes a protein that the brain needs to develop properly. However, the Fragile X mutation in the *FMR1* gene causes the body to make only a little or none of the protein. Research using human embryonic stem cells with this mutation showed that although the *FMR1* gene is expressed normally in Fragile X, it is turned off after the cells begin to differentiate. How this happens is something we can study using human embryonic stem cell lines. Dr.

Daley also studies a number of human embryonic stem cell lines with various genetic mutations, and I am sure he can tell you more about his research.

One ongoing NIH grant focuses on Rett syndrome, a debilitating, developmental brain disorder generally afflicting young females and caused by mutations in a gene called *MECP2*. This research uses human embryonic stem cells to generate human brain cells with a deficiency in the *MECP2* gene, and then studies the effects of this deficiency on the development and functions of these brain cells. Such research could improve our understanding of Rett syndrome, and facilitate the development of therapies for it.

Another research team has recently generated human embryonic stem cell lines containing mutations in the *HTT* gene that causes Huntington's disease, a late-onset neurodegenerative disease. Huntington's disease has been studied for a long time, but the normal function and pathogenesis of the protein coded for by the *HTT* gene is not fully understood.

Tissue Replacement or Regenerative Medicine

One of the more exciting and high-profile potential applications of human embryonic stem cell research is the possibility that such cells can be programmed to replace or regenerate tissues damaged by disease or injury. For example, we might one day be able to regenerate damaged heart muscle tissue in heart attack patients, develop insulin-producing pancreatic beta cells to replace those lost or damaged in people with Type 1 diabetes, or restore spinal cord neural connections in patients paralyzed by catastrophic spinal cord injury.

Part of the devastation that heart attack victims suffer is that, because of restricted blood flow and oxygen deprivation, their heart muscle cells die, leaving the heart much weaker and less able to pump blood throughout the body. Today we are studying the tantalizing possibility that human embryonic stem cells, or perhaps adult stem cells or iPS cells, might be programmed to replace damaged or destroyed heart muscle cells, known as myocardial cells. The prevalence of heart disease, along with the scarcity of hearts and heart tissues available for transplantation and the associated clinical and autoimmune problems of transplantation, make this line of research imperative.

Type 1 diabetes is a disease in which a specific type of cell, insulin-producing pancreatic beta cells, is damaged or destroyed by the patient's own immune system. A major challenge is to understand the autoimmune response that kills these cells in children who then develop Type 1 diabetes, but human embryonic stem cells offer the hope that we might one day produce replacement cells that avoid the autoimmune challenges associated with today's rudimentary transplantation therapies. To do that, we need to know more about how stem cells are genetically programmed, how they differentiate, and how they renew themselves; but as our understanding and ability to work with these cells expands, we are laying the foundation for an entirely new — and much more effective — way to address the devastation of Type 1 diabetes.

One of the most exciting — and most advanced — possible therapeutic applications of human embryonic stem cells is for patients who have been paralyzed by catastrophic spinal cord damage. Researchers at the University of California-Irvine and at the biotech company Geron Corp., as well as at other universities and companies

around the country, are pursuing the possibility that human embryonic stem cells can be directed to generate spinal cord cells for transplantation.

This summer, Geron began Phase I safety trials of its technique for converting stem cells into a type of neuronal cell, known as oligodendrocytes, intended for injection into the patient's spinal cord at the site where it has been severed by injury. The hope, which has been repeatedly demonstrated in animal tests, is that the newly-injected oligodendrocytes might repair the damaged insulation around the severed nerve cells of the spinal cord, and thereby enable those cells to once again send signals to the patient's limbs and organs. We are not sure that this approach will work, and even if it does, it will take years of additional research and testing before we can develop a standardized therapy using these techniques. Still, the potential that this research holds is truly amazing.

For all of these efforts, there are many scientific challenges that must be addressed. We need to figure out how to get human embryonic stem cells to differentiate down specific pathways in a well-controlled process. We also need to make sure that the resulting cells behave in predictable ways. Because human embryonic stem cells are immortal and can proliferate endlessly — much like cancer cells — we need to be sure that they or their differentiated "daughter" cells do not produce tumors or otherwise harm patients. The field of regenerative medicine is young. It is unreasonable for us to think we will have cures within a set time period. It is also wrong to overpromise on the speed and scope of such research to patients and their families. But we must persevere and move this research forward in a strong and consistent manner. That is why the delay and uncertainty associated with the current legal situation is so disheartening for both

researchers and patients. As I said at the time the injunction was issued, this unexpected development is like pouring sand into the engine of discovery.

Targeted, Efficient Screening of New Drug Candidates

Recently, human embryonic stem cells have received increasing attention as a tool for drug screening. High throughput drug screening is done in a miniaturized format that allows researchers to test the effect of more than 100,000 chemicals on a gene, protein, cell, or organism of interest. It is a highly automated process that can test in one day what would otherwise take a researcher months or years. Because human embryonic stem cells can differentiate into specific human cell types in large quantities, they provide the foundation for high throughput screening of candidate drug compounds for a given disease. This means that we now have the capacity to identify efficiently drugs that work in a targeted cell type.

This is not a promise, it is reality. Human embryonic stem cells are currently being used to identify drug candidates that can slow or stop the progression of amyotrophic lateral sclerosis (ALS). Also called Lou Gehrig's disease, ALS is an ultimately fatal disease characterized by the progressive loss of motor neurons, which provide the connection between the brain and the muscles of our body. The possibility that human embryonic stem cell research might one day enable us to identify a therapy for the disease that afflicts astrophysicist Stephen Hawking and claimed the life of Senator Jacob Javits, gives you some sense of the hope this new application might provide.

There are very few drugs available for ALS, and none that prolong the patient's life for more than a few months. Dr. Lee Rubin, a researcher at Harvard's Stem Cell Institute, and his colleagues have developed an elegant set of studies to screen for drugs that prevent motor neuron death. The scientists differentiated mouse embryonic stem cells into large numbers of motor neurons and exposed them to thousands of compounds to find the ones that improve the survival of these vital cells. Dr. Rubin and his team identified a handful of promising compounds that they then tested in motor neurons derived from human embryonic stem cells. The most promising of these can now be moved further along the pipeline from drug discovery to clinical trials.

Drugs fail for many reasons: lack of efficacy in humans is responsible for 30% of drug failures, and unpredicted toxicity is responsible for more than 20% of failures. The traditional methods of using animal or abnormal human cell lines for safety and efficacy testing provide a poor model of how a human will respond to a particular drug. Human embryonic stem cells can generate the appropriate cell type and even disease cell lines for efficacy testing early on, as in the case of the ALS study. They are also being used to understand the toxicity of promising compounds in the early stages of drug development. For example, liver toxicity is a common cause of drug failure. Human embryonic stem cells can be differentiated into human liver cells, or hepatocytes, which are then exposed to novel drugs to identify any obvious liver toxicity and provide early insight on how a drug will be metabolized by the liver. In this manner, human embryonic stem cells provide drug developers and researchers a model of how actual human livers will respond to a drug. Our hope is this will reduce the number of drugs that fail in human clinical trials because of low efficacy or unacceptable toxicity.

The NIH Stem Cell Guidelines

President George W. Bush first funded research on human embryonic stem cells – but that decision only allowed the use of cell lines that had been derived before August 9, 2001. Ultimately, that only amounted to 21 cell lines, and as science moved forward it was clear that this somewhat arbitrary time stamp was significantly inhibiting the field. On March 9, 2009, President Barack Obama issued Executive Order 13505, *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*. The Executive Order states that the Secretary of Health and Human Services, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research. This Executive Order prompted a rapid expansion of scientific effort and progress.

The President asked NIH to review existing human stem cell research guidelines and issue new guidelines, consistent with the President's Executive Order, within 120 days. NIH immediately began a comprehensive review that resulted in draft guidelines that were published in the Federal Register for public comment on April 23, 2009. After careful analysis of more than 49,000 comments from scientific, patient advocacy, medical, and religious organizations, as well as private citizens and members of Congress, NIH published final guidelines, effective July 7, 2009. The guidelines provide a framework for funding scientifically worthy research using responsibly derived human embryonic stem cells. The guidelines restrict federal funding to cell lines derived from embryos that: were created for reproductive purposes and were no longer needed for that purpose; were donated for research by individuals who sought reproductive treatment;

and for which the donors gave voluntary written consent. Since the President issued his Executive Order and NIH implemented its guidelines, 75 human embryonic stem cell lines have been approved for use in NIH-funded research. All were reviewed rigorously and found to meet the high ethical standards laid out in the NIH guidelines. The review process is so rigorous that 48 stem cell lines have not been approved for use in federally funded research. Prior to the court's order, in FY 2010, NIH funded 199 grants for research on human embryonic stem cells totaling $137 million. These grants support a broad range of research including studies to improve stem cell technologies, studies to compare different types of stem cells, and studies to develop cell types for use in treating debilitating diseases and disorders such as diabetes, liver failure, and neurodegenerative diseases.

If the government is not successful in defending the guidelines in this litigation, and NIH will have to withdraw future NIH support for all grants involving human embryonic stem cell research, drastic scientific consequences will occur. Since funding for these projects would be discontinued mid-stream, all the funds that have been put in accounts or already drawn down — $270 million over the two- to five-year life of these grants, including what has been provided FY 2010 – would have been wasted. The research momentum that this Subcommittee worked so hard to achieve would be lost.

Young scientists may opt out of this field due to the chaos 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 with conditions currently under study with human embryonic stem cells. Such people include those suffering from heart

disease, diabetes, liver disease, and vision problems, along with those afflicted by spinal cord injuries and neurodegenerative conditions like ALS and Alzheimer's disease. The many messages I have received from patients since the issuance of the preliminary injunction reflect these deep concerns. Here is part of just one such message:

> "I am a mother of two adult sons with Type I diabetes (since age 7), and a person with young onset Parkinson's disease. I have watched as my oldest son moved from taking the old beef/pork insulin to taking genetically engineered insulin, and have held my breath with hope that my sons would benefit from the early stem cell research.
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> I watched as American scientists and science fell farther behind on the global scene during the past decade. In 2009 I had such hope that once again our medical schools and universities would begin to attract the best and brightest young minds to work in this exciting and promising area of research.
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> This week's news was devastating to me. I had no idea how strongly I would be affected by it. Your message of support for the research once again gives me hope. Hope that there will be change. Hope that we will see effective treatments in our lifetimes for these devastating diseases."

Thank you, Mr. Chairman, for your strong support of stem cell research. I would be happy to answer any questions.

**Francis S. Collins, M.D., Ph.D.**

Francis S. Collins, M.D., Ph.D., was officially sworn in on Monday, August 17, 2009 as the 16th director of the National Institutes of Health (NIH). Dr. Collins was nominated by President Barack Obama on July 8, and was unanimously confirmed by the U.S. Senate on August 7.

Dr. Collins, a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the Human Genome Project, served as director of the National Human Genome Research Institute (NHGRI) at the NIH from 1993-2008. With Dr. Collins at the helm, the Human Genome Project consistently met projected milestones ahead of schedule and under budget. This remarkable international project culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book.

In addition to his achievements as the NHGRI director, Dr. Collins' own research laboratory has discovered a number of important genes, including those responsible for cystic fibrosis, neurofibromatosis, Huntington's disease, a familial endocrine cancer syndrome, and most recently, genes for type 2 diabetes and the gene that causes Hutchinson-Gilford progeria syndrome.

Dr. Collins has a longstanding interest in the interface between science and faith, and has written about this in The Language of God: A Scientist Presents Evidence for Belief (Free Press, 2006), which spent many weeks on The New York Times bestseller list. He is the author of a new book on personalized medicine, The Language of Life: DNA and the Revolution in Personalized Medicine (HarperCollins, 2010).

Dr. Collins received a B.S. in chemistry from the University of Virginia, a Ph.D. in physical chemistry from Yale University, and an M.D. with honors from the University of North Carolina at Chapel Hill. Prior to coming to the NIH in 1993, he spent nine years on the faculty of the University of Michigan, where he was a Howard Hughes Medical Institute investigator. He is an elected member of the Institute of Medicine and the National Academy of Sciences. He is the recipient of the Presidential Medal of Freedom (2007) and the National Medal of Science (2009). On April 22, 2010, Dr. Collins was a co-recipient of the Albany Medical Center Prize in Medicine and Biomedical Research.