

Testimony to Senate Committee on Appropriations
Subcommittee on Labor, Health and Human Services, Education, and Related Agencies
“Human Embryonic Stem Cells” September 16, 2010
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Chairman Harkin and distinguished members of the sub-committee, thank you for the invitation to testify today on the subject of human embryonic stem (ES) cells. I am here to assert that human ES cells offer unique advantages for understanding a number of human diseases and are essential to a vigorous portfolio of stem cell research here in the United States. I also wish to recount how recent upheavals in federal funding have disrupted our research and how ambiguous federal policy saps the motivation of junior scientists and threatens American preeminence in this vital field of biomedical research.

My name is George Daley and I am the Samuel E. Lux IV Professor of Hematology/Oncology and Director of the Stem Cell Transplantation Program at the Children’s Hospital Boston and the Dana Farber Cancer Institute. I am also Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Principal Faculty and founding member of the Executive Committee of the Harvard Stem Cell Institute, and an investigator of the Howard Hughes Medical Institute. I am past-President of the International Society for Stem Cell Research (ISSCR; 2007-2008), the major international organization of stem cell scientists with over 3000 members worldwide. I chaired the international task force that wrote ethical guidelines for human embryonic stem cell research (ISSCR Guidelines for Human Embryonic Stem Cell Research 2006 [1]) and as ISSCR President empanelled and participated in the international task force that wrote guidelines for the responsible clinical translation of stem cell therapies (ISSCR Guidelines for the Clinical Translation of Stem Cells 2008 [2]). I am here representing the American Society for Cell Biology, whose members number some 10,000 scientists.

As Director of the Stem Cell Transplantation Program at Children’s Hospital I speak as a doctor who uses adult stem cells to treat patients with life-threatening blood diseases—including leukemia, sickle cell anemia, immune-deficiency, bone marrow

failure, and others—but I also speak as a scientist working to improve those treatments through research on adult stem cells, embryonic stem (ES) cells, and induced pluripotent stem (iPS) cells. Stem cell research is important to real live patients, and I believe to my core that stem cell research offers tremendous promise for curing a range of diseases. It is a mistake to cast the different types of stem cells as competing priorities. Adult stem cells are not better than or more promising than embryonic stem cells. And iPS cells do not obviate the need for ES cells. Would it make sense to fund cancer and cardiovascular research but not diabetes research? All are essential research avenues. The most successful strategy to advance stem cell research is to let scientists decide which cells to study.

Let me first speak to the success and the limitations of adult stem cell therapies. Hematopoietic stem cells harvested from bone marrow, mobilized peripheral blood, and umbilical cord blood are the most successful adult stem cell treatments, and potentially curative for cancers of the blood and some genetic diseases. At Children's we perform some 80 stem cell transplants per year for childhood leukemia and conditions like immune deficiency. Casting our success in a positive light, we have cured many kids over the years. On transplant rounds last week, I was heartened to meet a little girl about to receive her transplant for a rare inherited immune condition, the second in her family that we will likely cure. Saving the life of a child is deeply gratifying. However, confronting our shortcomings, we must acknowledge that fewer than half of all patients treated with hematopoietic stem cell transplants are cured. Despite 50 years of research and practice in hematopoietic stem cell transplantation, blood cancers still relapse, and patients still die or become severely disabled because the transplant regimens are so toxic. Many patients who might benefit never make it to the transplant stage because they are too sick or lack a suitable donor.

Such limitations of even our most successful adult stem cell therapies for blood diseases drive me, as a medical research scientist, to seek improvements through stem cell research. I have been a student of the hematopoietic stem cell for twenty-five years, and I remain an ardent advocate for research on adult stem cells. But starting more than

fifteen years ago, I began to explore a new approach to bone marrow transplant based on making blood stem cells from embryonic stem cells. I envisioned one day generating customized stem cells perfectly matched to my patients, thus bypassing the challenge of immune matching, eliminating the problems of donor shortages, and making transplants safer because they would be performed with a patient's own cells. Moreover, for patients with genetic diseases, this new approach offered potentially safer ways to repair gene defects and to return healthy cells to the patient. Indeed, we have succeeded in treating mice with genetic immune deficiency with this strategy, and we are making headway towards the goal of developing similar treatments with human cells.

Opponents of ES cell research will argue that adult stem cells are more promising, that embryonic stem cells have yet to cure anyone, and that with iPS cells in hand, ES cells are no longer needed. By similar reasoning, why try to develop new classes of antibiotics? Let's just keep trying to improve penicillin. The only time I confront the argument that adult stem cells are superior to embryonic stem cells and should replace embryonic stem cells is at hearings like this. At scientific meetings, discoveries with adult and embryonic stem cells are discussed and debated as integrated and complementary aspects of cell and developmental biology, not as contestants on American Idol. In my opinion, such arguments are not sound scientific advice, but rather ideologically-driven attempts to prohibit scientist's from using ES cells to search for new cures. No matter how much progress is made with other forms of stem cells, ES cells will remain a vital research tool, and any expulsion of ES cells from the researcher's toolkit would gravely weaken stem cell research overall.

Embryonic stem cells are valuable because they are pluripotent, that is, able to make any tissue in the human body, and can grow indefinitely in a petri dish. In contrast, adult stem cells show a restricted potential for generating cells of a given tissue, and are difficult to propagate in a petri dish and thus available in limited quantities. Not all tissues regenerate from adult stem cells, which is a major reason why we need ES cells. Indeed, in juvenile diabetes, there is little or no regeneration of the insulin-

producing beta cells that have been destroyed by immune attack. We are technically capable of transplanting whole pancreas or isolated pancreatic islets to replace beta cells, but there is a shortage of these organs for transplanting even the most severe diabetics. Consequently, embryonic stem cells are being developed by the biotechnology company Novocell as an alternate and more readily available source of beta cells for treatment of diabetes.

Only three years ago, a new form of pluripotent stem cell was introduced into stem cell research, the induced pluripotent stem cell, popularly called the iPS cell. At the end of 2007, my lab was one of three world-wide to report the successful derivation of human iPS cells [3], and in 2008, my lab was the first to produce a repository of customized iPS cells from patients with a range of diseases like Parkinsons, diabetes, and immune deficiency [4]. iPS cells share the defining features of ES cells—pluripotency and limitless growth, and one goal of stem cell research is to refine techniques for making iPS cells that are indistinguishable from ES cells. Thus, given that iPS cells exist, why is there a need for human ES cells, and what is the value of continued development of new human ES cell lines?

First, it is important to note that the iPS breakthrough was founded upon the study of ES cells, and isolation of human iPS cells depended upon specific culture conditions for human, not mouse, ES cells. Today, human ES cells remain the gold standard against which our cultures of human iPS cells are compared. Human ES cells hold many more secrets, and no one can be sure where the next breakthrough will emerge.

Second, it is not clear that even ideal iPS cell lines are identical in all respects to ES cells. My lab and that of Konrad Hochedlinger recently demonstrated that iPS cells tend to retain chemical modifications of their DNA reminiscent of their tissue of origin, so that when the iPS cells are differentiated in the petri dish, they reflect a preference to form the tissues from which they were derived [5, 6]. This so-called “epigenetic memory” dictates that iPS cells made from blood cells make better blood than iPS cells made from skin cells. We are working towards ways to erase these memories, but these data

teach us that in practice, iPS cells harbor important differences from ES cells that influence their behavior and potential utility in research and therapy.

Third, although iPS cells provide a flexible alternative to ES cells in modeling human diseases, not all diseases are readily modeled with iPS cells. One of the first diseases we attempted to model with human iPS cells was a fascinating but rare condition called Fanconi anemia that leaves kids with bone marrow failure and a predisposition to leukemia and various cancers. Despite repeated attempts, we have been unable to generate iPS cells from patients with Fanconi anemia, and last year the laboratory of Juan-Carlos Izpisua-Belmonte published that Fanconi anemia cells were resistant to iPS generation [7]. Mice that lack the same genes as human Fanconi patients do not develop the same marrow failure and leukemia of human patients. Thus, we turned instead to modeling Fanconi anemia by depleting the relevant genes from human ES cells, and then examining the effects on human blood formation in the petri dish. Using genetically modified human ES cells, we discovered that Fanconi anemia alters the earliest stages of human embryonic blood development, teaching us that the condition develops in utero, such that children are born with stem cell deficiency, a new insight for a condition thought to develop only later in childhood [8].

Another example where human ES cells offer an advantage over iPS cells is in the study of Fragile X Syndrome, the most common genetic cause of mental retardation. Fragile X is caused by a defect in the FMR1 gene, which is expressed early in human development but in affected individuals becomes aberrantly silent in adult tissues, including nerve cells. My Israeli colleague Nissim Benvenisty had generated human ES cells from discarded embryos that carried the gene defect. When these ES cells were differentiated in the petri dish, the gene shut off, just as it does during human development. In collaboration with the Benvenisty lab, we asked what would happen to the FMR1 gene in iPS cells made from skin cells of Fragile X individuals. To our surprise, the gene remained silent in iPS cells, showing that Fragile X-iPS cells differed from Fragile X-ES cells, with only the ES cells reflecting the dynamic FMR1 gene

silencing observed in human development [9]. For studying gene silencing in Fragile X, human ES cells provide a unique advantage.

Finally, human ES cells remain valuable tools for research. There is still much to be learned about human ES cells, and about how stem cells derive from human embryos. Only recently have we learned that human ES cells are markedly different from mouse ES cells, and represent a distinct type of pluripotent stem cell. Only recently have we learned that deriving human ES cells in reduced oxygen conditions preserves two active X chromosomes, which is the natural embryonic state, leaving us to question whether any of the existing human ES cells have been derived in an optimal way [10]. When we still have so much to learn, how can we conclude that ES cells are no longer needed?

We are told that restrictions on federal funding do not inhibit stem cell research because private philanthropy fills the gap. Realistically, however, research careers are built upon the architecture of federal grant support. Investment by the NIH has made the US the preeminent incubator for biomedical research, has produced American dominance in Nobel prizes in medicine, and has contributed directly to our robust biotechnology industry. Medical research is one of the chief sectors projecting job growth over the next decade, and one of the few areas of technological innovation where US leadership remains largely uncontested. A loss of federal funding threatens American competitiveness in stem cell research.

Unfortunately, during the last decade prohibitions and restrictions on federal funding for human ES cell research has greatly restricted progress and dissuaded numerous scientists from entering the field. President Bush allowed funding for a very restricted set of cells—in practice only a small handful—but prohibited funding for the more than 1000 human ES cell lines generated since his policy was enacted on August 9, 2001. Many of these ES cell lines have important advantages for medical research, like carrying the precise gene defects responsible for human disease. President Obama's policy has expanded access to many more lines and has succeeded in bringing many

dozens of additional laboratories into the field, as evidenced by the new grants submitted or approved for research in the last year.

Against this backdrop of rising enthusiasm after nearly a decade of frustration for patients, their families, their physicians, and the research community, the announcement of the injunction against federal funding came as a major blow. I was justifiably confused by what the injunction meant for our research program, which depends heavily on federal grant dollars, and personally, I was deeply discouraged and worried for the future of human ES cell research.

Several cases illustrate the immediate harm to our research program and the potential harm to the careers of young scientists by the current confusion. A doctoral student in my lab has just completed nearly a year of work mastering a protocol for generating red blood cells from human ES and iPS cells, a critical step in her research on sickle cell anemia. Because of variability among the iPS lines, human ES cells are essential for her studies, and she has just started to have success with the H1 line of human ES cells. However, because she is being paid by federal dollars and the future prospects are so uncertain, she has abandoned the use of human ES cells, and is instead restricting her efforts to iPS cells that may give sub-optimal red blood cell production. Such a compromise—driven by politics and not science—is deeply troubling. Several other scientists in my lab have altered their projects out of concern for a loss in federal funding. Two scientists being funded on federal training grants abandoned plans to test human ES cells for their response to a unique cocktail of growth factors that had stimulated blood stem cell formation from mouse ES cells. Moreover, I face losing my largest NIH grant, which is aimed at defining the precise similarities and differences between ES and iPS cells. I have been scrambling to come up with private funding so that I don't have to lay anyone off. I wrote to my seven co-investigators on this project and warned them not to expect funding for the second year, which would stop cold major new research collaborations that have already proven remarkably productive. Scientific research is challenging enough without adding the uncertainty and fickle nature of federal support for one's research to the task.

With the recent upheavals, scientists have again been reminded that human ES cell research is on fragile and fickle footing. The cloud that hangs over the field saps enthusiasm for planning a long-term program of NIH grant-funded human ES cell research, which is the bedrock of most research careers. Younger researchers are discouraged from entering the field, while established researchers like myself are spending a disproportionate amount of time on regulatory compliance, legal interpretation, program management and external fundraising. With the economy in turmoil, private funding for stem cell research has become scarce. Ambiguity about federal policy itself has a negative impact that extends beyond the practical restrictions of legislation. Having devoted the last 25 years of my career to aspects of adult and embryonic stem cell biology, I am convinced that human ES cells are critical to a multi-faceted portfolio of NIH stem cell research, and in the long run will save lives. New legislation is needed to sustain the momentum of human ES cell research in the United States, and to allow scientists—not politicians and judges—to determine which research priorities to pursue.

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