

Why Federal Stem Cell Policy Must Be Expanded

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Executive Summary

JDRF approaches this issue with a single agenda: to find a cure for type 1 diabetes. Juvenile, or type 1, diabetes afflicts almost two million Americans, many of them children, and strikes tens of thousands more every year at an accelerating rate.

Embryonic stem cell research offers one of the most promising avenues to accomplish JDRF's ultimate goal of a cure. JDRF had hoped that the August 2001 Federal stem cell policy would be the beginning of intense scientific effort to reach this goal. But the objective truth echoed by every leading researcher in the field is that the policy, while well intentioned, will not permit research to advance at the pace it can and must; in fact, the policy is actually *slowing* the scientific progress in Federally funded research that the President himself championed.

As much as anything, the call for an expansion of Federal stem cell policy reflects what scientists have learned since the August 2001 announcement. Our understanding of the science has progressed since then, and knowledge of the NIH-approved stem cell lines has grown much deeper. It is time to adjust the Federal policy so that it accurately represents the latest understanding of the science. The simple, inescapable fact – acknowledged by the Federal government itself – is that access to additional stem cell lines will accelerate the potential breakthroughs required to cure not only diabetes, but a range of diseases afflicting millions of Americans.

The problems with the existing policy are numerous and pervasive. They include:

- 1) Of the original 78 stem cell derivations that were declared eligible for US Federal funding under the August 2001 policy, only 21 are actually available for distribution and study;
- 2) Because the NIH-approved stem cell lines were developed using science that has since seen significant improvements and progress, they may prove to be far more limited in their biomedical research utility than lines created more recently;
- 3) The NIH lines lack the genetic diversity scientists need to do research that could create therapeutic treatments for millions of Americans;
- 4) Because human embryonic stem cells are heterogeneous, with some showing a greater propensity to become certain types of cells, a limited number of stem cell lines can decrease the breadth of research opportunities for scientists;
- 5) The absence of disease-specific stem cell lines eligible for Federal funding means that the current policy is limiting stem cell research from beginning on dozens of genetic diseases such as Duchenne muscular dystrophy and Huntington's Disease, potentially adding years to the discovery of treatments for millions of Americans;
- 6) All the NIH-approved lines were isolated in contact with mouse 'feeder' cells. As a result, the FDA must consider any therapies developed using these stem cells as xenotransplants, creating a huge hurdle that discourages the biotech and pharmaceutical industries from developing treatments utilizing those lines; and
- 7) Policy limits on stem cell research discourage scientists from entering the field.

Following is a more detailed discussion of each issue.

PROBLEM ONE:

Of the original 78 stem cell derivations that were declared eligible for U.S. federal funding under the August 2001 policy, only 21 are actually available for distribution and study.

Soon after the Bush policy statement, the NIH established the Human Embryonic Stem Cell Registry, listing the human embryonic stem cell lines that met the President's criteria for research to be eligible for Federal funding. The list now includes 78 stem cell derivations. While there is debate among researchers as to whether even 78 lines is an adequate number to create the necessary environment to initiate widespread scientific investigation in the field, the more critical point is that few of those 78 stem cell derivations are, or ever will be, usable for scientists. From a practical standpoint, many of the derivations were in the early phases of development in August of 2001, and have still not been characterized and then expanded so they can be readily available to the research community.

A year after the policy statement was issued, scientists estimated that of more than 70 purported human embryonic stem cell derivations that met the Administration criteria for Federally funded research, only 16 were then available for distribution. Today, the current NIH Human Embryonic Stem Cell Registry lists just 21 cell lines as being available, including two that have limited availability. The President's vision for developing a Federally funded U.S. stem cell research community was predicated on the immediate and widespread availability of more than 70 stem cell lines; unfortunately, some two years later, less than a third of the lines the Administration thought would be available for research are, in fact, available.

PROBLEM TWO:

Because the NIH-approved stem cell lines were developed using science that has since seen significant improvements and progress, they may prove to be far more limited in their biomedical research utility than lines created more recently.

In the development of non-Federally funded stem cell lines over the past three years, there has been continuous improvement in our understanding of the importance of culture conditions.

The emerging picture indicates that the culture conditions used to grow human embryonic stem cell lines plays an important role in maintaining cell stability. Research has shown that as stem cell lines are grown in long-term culture, some of them may begin to accumulate chromosomal damage. Implicit in this finding is the suggestion that some older (i.e., late passage) cells can be more susceptible to chromosomal abnormalities than earlier passage cultures.

Unfortunately, some of the stem cell lines available under the Federal policy have no early-passage cells available; researchers can only receive late-passage cells. A number of reports have emerged describing chromosomal abnormalities that have appeared in some NIH-approved stem cell lines after prolonged culture. These reports indicate that among the NIH-approved lines, fewer than the 21 lines may be useful for research or therapies.

PROBLEM THREE:

The NIH lines lack the genetic diversity scientists need to do research that could create therapeutic treatments for millions of Americans.

The ability to transplant cells or tissues created from hES lines into individuals in order to restore function (insulin-secreting cells for diabetes, dopamine-producing nerve cells for Parkinson's disease, etc.) will depend on overcoming immune system rejection of the transplanted material. Potential recipients of life-saving therapies will come from diverse genetic backgrounds, and it will be more difficult to develop therapeutics from an extremely limited starting population. The limited number of available stem cell lines could have a significant impact in limiting the number of people who might benefit from a transplant using stem cells or tissues derived from stem cells. While perfect HLA matches between cells and patients are economically unfeasible, the 21 NIH lines that are currently approved will not represent the genetic diversity required to develop potential therapies for a large number of Americans.

Research in pursuit of a particular goal, such as differentiation of embryonic stem cells into insulin-producing cells, would be accelerated and hold a greater likelihood of success if researchers have the opportunity to study variations in the greatest number of lines, rather than an arbitrary limit that is not based on biologic functional potential. Researchers need to study many lines in order to derive general conclusions, or to develop therapeutics. Expanding the current policy will allow researchers to make important comparisons among stem cell lines.

PROBLEM FOUR:

Because human embryonic stem cells are heterogenous, with some showing a greater propensity to become certain types of cells, a limited number of stem cell lines can decrease the breadth of research opportunities for scientists.

The number of available lines is particularly important because scientists have learned that some stem cell lines are more effective than others in differentiating to become specific tissues; i.e., some lines may be more effective treating neurological disorders, while others might be more effective treating heart disease or diabetes. This was theorized, but not known in 2001.

Human embryonic stem cells are heterogeneous and diverse, reflecting the fact that each has unique genetic characteristics and differing biological potentials. Clear differences among human embryonic stem cell lines are confirmed by multiple studies that report the characteristics of different cell lines. These functional differences mean that there are also differences in potential to differentiate into various cell types. Some cell lines are more likely to develop into nerve cells, for example, while others are more likely to develop into other tissues.

Scientists working over the past three years with the limited number of available NIH-approved lines have had difficulty in robustly and reproducibly differentiating the lines to become specific tissues.

PROBLEM FIVE:

The absence of disease-specific stem cell lines eligible for federal funding means that the policy is limiting stem cell research on dozens of genetic diseases such as Duchenne muscular dystrophy and Huntington's disease, potentially adding years to the discovery of treatments for millions of Americans.

Stem cell lines can provide a model system for research to gain a better understanding of the mechanisms underlying a disease, and to develop strategies or drugs designed to treat those illnesses. But because the current Federal policy limits the number of stem cell lines available to researchers using Federal funding, scientists have been limited in their ability to use stem cells to do research on literally dozens of genetic diseases – some rare but others widespread – that impact millions of Americans. An enhanced policy would create broader, more comprehensive, and more beneficial research into dozens of these diseases.

Of the large number of couples who undergo IVF treatment, some have a family history of various genetic disorders. These couples can use techniques such as pre-implantation genetic diagnosis to identify embryos that are unaffected by those genetic diseases before pregnancy is established. Embryos that are identified in the IVF process as having serious genetic disorders (such as neurofibromatosis, myotonic dystrophy, Fragile X Syndrome, and Fanconi's anemia) are typically not used for fertilization treatment. But such embryos, with genetic diseases, have been the source for non-Federally funded stem cell lines that have these disease characteristics. Such a stem cell line provides a model system for researchers to gain a better understanding of the mechanisms underlying the disease, and help them to develop strategies or drugs to treat the illness – but cannot be used by scientists accepting NIH funding.

This application is a reality for the disorders listed above – but there are literally dozens of similar genetic diseases that cannot be studied and treated in a similar manner.

PROBLEM SIX:

All the NIH-approved lines were isolated in contact with mouse 'feeder' cells. As a result, the FDA must consider any therapies developed using these stem cells as xenotransplants, creating a huge hurdle that discourages the biotech and pharmaceutical industries from developing treatments utilizing those lines.

All the NIH-approved stem cell lines were isolated in contact with mouse 'feeder' cells, which were required to prevent the uncontrolled differentiation of the embryonic stem cells. Because of the possibility of contamination, treatments could not, under ordinary circumstances, be developed for humans using those stem cell lines. The FDA would consider any therapies developed using these cells to be xenotransplants, requiring clearance of a very high regulatory hurdle before they could be used in humans. For many researchers in academia and industry alike this prospect represents an extraordinary (and expensive) challenge. In comparison, many of the 100 stem cell lines developed since 2001 either do not use feeder cells, or use material that would not present potential xenotransplant issues if eventually transplanted into humans.

Since 2001, scientists have successfully replaced mouse feeders — either with human cells used as feeders, or with feeder-free conditions. Given these advances, forcing researchers to work only with NIH-eligible stem cell lines places arbitrary and unnecessary obstacles to success in the way of possible therapies and treatments.

PROBLEM SEVEN:

Policy limits on stem cell research discourage scientists from entering the field.

While each of the other seven supply and quality issues is, in and of itself, a significant reason why the current embryonic stem cell policy needs to be expanded, taken together they create a scientific environment that makes significant discoveries or advances in embryonic stem cell research difficult. The result is a self-fulfilling prophecy: the lack of progress shown to date is a direct reflection of the limited amount of work done with embryonic stem cells, yet more scientists are wary of entering the field because of the lack of progress.

Fewer investigators have focused their efforts on embryonic stem cell research than anyone – including the Administration – would have expected in 2001, given the promise of stem cells to benefit an estimated 100 million Americans. Due to the uncertain landscape of the stem cell research field, few junior investigators have been willing to begin careers in this area – despite NIH’s efforts to attract investigators to the field. Nowhere is the research community’s lack of involvement more noteworthy than in scientists taking advantage of NIH’s available funding for stem cell research: despite an Administration goal to fund \$100 million annually in stem cell investigation, less than \$25 million was allocated last year.

An expansion of the current policy would begin to create an environment that would attract scientists to a field seen as scientifically promising, politically supported, and academically rewarding for researchers. That robust environment would, in turn, help hasten the pace at which important scientific discovery may proceed.

Such an environment would have an exponential impact on scientific investigation in general, given the potential for embryonic stem cells to address a wide range of diseases. Because of their unique capabilities, embryonic stem cells appeal to researchers as both a possible treatment for diseases and injuries, and as a way to study and better understand the development and pathology of various diseases, like cancer. They can give scientists a map of the pathology of genetic problems, but can also be used to gain a better understanding of normal cell development, and to gain insights into defects in that development that may eventually lead to serious medical conditions that impact huge percentages of the U.S. population.

APPENDIX A:

Is adult stem cell research a feasible alternative?

A policy limiting embryonic stem cell research cannot be justified by redirecting resources to other scientific avenues such as adult stem cells, which unfortunately have not yet shown the same potential for treating a wide range of diseases.

Researchers have been studying mature or adult stem cells for more than 35 years. Clinical therapeutic application has succeeded to the greatest extent with hematopoietic stem cells (HSC) as replacement for bone marrow components, usually for patients with cancer who are receiving radiation or chemotherapy. Such stem cell transplants have proven to be very useful in this setting, but have shown no use in most other areas, including type 1 diabetes.

Recent research notes that HSC appear to be able to develop into non-hematopoietic cell types, i.e., they can become nerve, or liver, or heart. At the same time, nerve stem cells or muscle stem cells have been reported to be able to give rise to blood cells. This data has given rise to the hypothesis that adult stem cells have the ability to “transdifferentiate.” If so, the argument goes, then we might use adult stem cells for developing therapies without having to derive embryonic stem cells.

However, new studies have provided alternative explanations that show that hematopoietic cells do not actually transdifferentiate into nerve, liver, or cardiac muscle cells. So while adult stem cells might have limited clinical value for a narrow range of diseases, embryonic stem cells remain the only populations of cells with genuine potential for pluripotency. In fact, there is no scientific evidence that there are adult stem cells for certain tissues, such as pancreatic beta cells.

To that end, a recent report by Harvard University researchers noted that in mice, new beta cells in the pancreas are formed through the replication of existing beta cells, rather than through the differentiation of adult stem cells. This finding has important implications, especially if confirmed in humans. In type 1 diabetes, the autoimmune response destroys the beta cells. This means that in order to cure type 1 diabetes, scientists will have to rely on an external source of beta cells. Embryonic stem cells may prove to be the main source for generating beta cells.

Because embryonic stem cells have qualities that give them the potential to treat a range of diseases and injuries that other areas of scientific investigation, including research involving adult stem cells, simply do not, a policy limiting the number of stem cell lines limits the opportunity for scientific discovery of cures that could impact millions of Americans.