THE PROMISE OF EMBRYONIC STEM CELLS

UNITED STATES SENATE SPECIAL COMMITTEE ON AGING

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TESTIMONY
OF

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Senator Smith and Members of the Committee, thank you for inviting me to this important hearing.

An age-old dream of humankind has been to replace damaged, diseased, or worn out parts of the body with new, functional parts. This fanciful dream is coming closer to reality with the recent advances in stem cell research. For the past 13 years I have been deeply involved in stem cell research utilizing sources of human stem cells from embryonic and adult tissues. In 1998, my laboratory at Johns Hopkins published one of the two research papers that year that first demonstrated it was possible to isolate cells from human tissue that could form all the over 200 different cell types in the human body. These unique stem cells are only found in the earliest stages of human development.

The concept behind cell-based therapies is simply stated - if there is a tissue deficit (through disease or injury); correct it by providing the patient with normal, functioning cells. The power of this developing technology is derived from information inherent in our genes and the availability of stem cells, particularly those known as embryonic stem cells. Stem cells, for the immediate future, will be at the center of the developing technology for cell-based therapies. The problems associated with the development of therapies that are effective and safe are immensely difficult, but the potential benefits are extraordinarily great, for those who seek to understand biology or to help the disabled.

The promise of embryonic stem cell research

The promise and hope for the field of embryonic stem cell research was highlighted when stem cells were chosen as *Science* magazine's 1999 "Breakthrough of the Year." Although the first embryonic stem cells were not isolated until 1998, the field has advanced quickly as scientists have already made important progress investigating these cells. Embryonic stem cells are particularly valuable to medical research because they have the unique potential to develop into any cell type, meaning they could produce replacement cells for any tissue and have an impact on virtually every disease. Embryonic stem cells also represent the earliest stages of development, offering a unique insight into human development and the biology of disease. In addition, embryonic stem cells are capable of dividing and renewing themselves for long periods and can be grown easily in culture, lending themselves to investigation and distribution. Researchers are now learning more about the properties of these cells, optimizing conditions for creating new lines, and have produced encouraging results in a number of experiments regarding their therapeutic potential.

In the area of diabetes research, for example, researchers have made exciting discoveries in recent years that give great hope to the millions of Americans suffering from the disease. In 2002, scientists at Stanford University used special chemicals to transform undifferentiated embryonic stem cells of mice into cell masses that resemble islets found in the mouse pancreas. When this tissue is transplanted into diabetic mice, it produces insulin in response to high glucose levels in the animals. Several studies have since suggested this can be done using human embryonic stem cells. In a 2004 study at Harvard University and the Howard Hughes Medical Institute (HHMI), researchers learned that adult stem cells in the pancreas do not contribute to new beta cell formation in mice. This finding strongly suggests that embryonic stem cells may be the only stem cells that will be useful to generate beta cells for the treatment of type 1 diabetes.

<u>Advances with embryonic stem cells in the areas of heart disease, Parkinson's disease, juvenile diabetes, and motor neuron loss (Lou Gehring's disease)</u>

Stem cell research is supported by overwhelming scientific opinion because the technology may enable us to develop new forms of therapies for some of the most debilitating diseases and crippling disabilities. Presently there are only proofs of principle behind this optimism, but these strongly suggest that if we are permitted to explore these opportunities, their benefits will be realized. Research and clinical efficacy are the only means of validating whether stem cell-mediated therapies will materialize. We are ethically and morally obligated to pursue them for the benefit of those who suffer. To me, a major ethical issue attending stem cell research is the slow pace at which the work is moving to diminish human suffering.

The scientific and medical challenges to attain our goal of providing cell-based therapies that are safe and effective are formidable. As we are learning, it will take the efforts of many scientists and clinicians in a variety of disciplines to bring this technology to clinic. The results of laboratory investigations, to date, however, are highly encouraging and consistent with this goal being attained.

In our laboratory at Hopkins, to which I would like to extend to you an invitation to visit and learn firsthand about ES research, we are pursuing studies on cardiomyocytes, motor neurons and glia, dopaminergic neurons, and insulin-producing cells among several others. We have been concentrating on deriving all these cell types from the stem cell and our success has been dependent upon the state of our basic science knowledge with each cell type. We have been most successful with motor neurons. For the motor neurons and cardiomyocytes we have grafted cells into animals models of heart attacks and motor neuron loss and the grafted cells are functioning. We have a long way to go to improve on the efficiency of generating the cell types of interest and on demonstrating that the grafted cells will do no harm to hosts. In studies with dopaminergic cells and insulin cells, grafts have also shown some success and we are now working to increase the cell numbers and function.

We do not limit our studies to embryonically derived cells. In our experiments we compare and contrast embryonic, adult and umbilical cord sources of stem cells. This is the only way we will be able to determine which source will be best.

<u>What we've learned since August 9, 2001: Limitations of the current federal policy</u>
In the four years since the President announced his policy decision, the U.S. government's stem cell policy has fallen far short of its original goals, as less than one-third of the stem cell lines the Administration believed would be available for federally funded research are, in fact, available. In addition, a study at the University of Washington found that at least five of these available 22 lines will never be useful for the clinic, and the Chair of the NIH Stem Cell Task Force, Dr. James Battey, has stated that only 23 lines will ever be available for research.

Scientific research and progress since 2001 have revealed the limitations of the eligible lines, and shown us the extent to which these existing lines are not adequate to realize the full potential of embryonic stem cell research. The 22 lines now eligible for federally funded research are contaminated with animal cells, lack genetic diversity, are not disease-specific, and are not adequate for researchers to apply to a wide variety of diseases. Limiting researchers to work only with those lines with federal funding ignores scientific advancements and places unnecessary obstacles in the way of possible therapies and treatments.

Since 2001, we have learned that all the NIH-approved stem cell lines were isolated in contact with mouse "feeder" cells. The possibility of contamination in these lines compromises their quality, makes their therapeutic use in humans uncertain, and raises a high regulatory hurdle that discourages the biotech and pharmaceutical industries from developing treatments using those lines. Fortunately, the field has advanced to a point today where scientists have successfully replaced mouse feeders with either human cells used as feeders or with feeder-free conditions. For example, researchers at the University of California, San Diego and the University of Wisconsin, Madison recently published methods for growing human embryonic stem cells in the absence of mouse-derived "feeder" cells. Laboratories in California, the Czech Republic, Singapore, Israel, Sweden, and Finland have also isolated lines of embryonic stem cells that are not contaminated by mouse feeder cells. However, none of these lines are accessible to federally funded researchers in the United States.

The absence of disease-specific stem cell lines eligible for federal funding means that the current policy is limiting research on dozens of genetic diseases and potentially adding years to the discovery of treatments for millions of Americans. Since 2001, scientists have created "disease specific" stem cell lines that were derived from embryos identified as having a serious genetic disorder such as muscular dystrophy, fragile X syndrome, or Fanconi's anemia. None of the 22 stem cell lines approved for use by the NIH carry a gene defect for these or other genetic diseases such as cystic fibrosis and Huntington's disease. Even diseases such as heart disease and cancer that are only partly genetic would greatly benefit from federally funded research on cells carrying disease-linked genes. Stem cells can be used to both gain a better understanding of normal cell development, and to derive insights about defects in that development, which cause the disease. This type of research could speed the development of treatments and cures for millions of Americans who are in a race against time.

A survey of laboratories around the world found that at least 128 human embryonic stem cell lines have been created since the current federal policy on embryonic stem cell research was enacted in 2001. Fifty-one of these lines are now available to researchers worldwide, but none of the lines can be used by federally funded researchers in the United States because the lines were developed after the 2001 policy enactment. Many of these new lines are "disease specific," and all of the lines were created in the absence of the mouse "feeder" cells that threaten therapeutic use in humans. In addition, scientists now know that the conditions in which cells are cultured plays an important role in maintaining cell stability, which is crucial for experiments, and that the older cells that are eligible for federal funding are more susceptible to abnormalities and chromosomal changes because the longer stem cell lines are grown, the more likely they are to lose their properties. Permitting the use of federal funds on stem cell lines created after August 9, 2001 would allow scientists to reap the benefits of the many advancements made since that date, and allowing this promising field to keep pace with science.

<u>Why the current policy should be expanded</u>

As we discuss the potential for embryonic stem cell research, it is important to remember the nature of science and the time it takes to investigate different paths, form and test hypothesis, pass rigorous clinical trials to advance to the desired result of therapeutic use in humans. Although embryonic stem cell research remains on the cutting edge of biological science today, the field is still in its infancy. It is in these early stages of research that federal funding is so essential. Since its founding, the United States government has taken the lead in funding the breakthrough medical research that has improved the health of the nation and saved lives. Today, the NIH is the engine of scientific research in this nation, investing more than $28 billion annually into medical research. The absence of strong federal support in this area has clearly hindered the field of embryonic stem cell research by discouraging researchers from entering the field and removing the collaborative and oversight mechanisms that are so vital to the advancement of medical research.

Expansion of the current federal policy on embryonic stem cell research is more than just a matter of deriving new stem cell lines. We will be assured that we are working with the best lines available from the standpoints of utility (no feeder layers, in defined media), safety (no contact with the products of other animals) and performance (we will be able to determine which lines out of many will produce the cell types that we need). We will be able to utilize cell lines with a wide range of genetic backgrounds, being able to investigate the role if these backgrounds in a variety of studies, from toxicology to tumor formation. These new lines will also help in avoiding immune responses to grafted cells by eventually being able to match HLA types (genes involved in graft rejection) with patients – if clinical trials are started. All of these factors are important and significant improvements over existing lines that are eligible for federal federal funding.

Due to the uncertain political landscape of the field, few young investigators have been willing to begin careers in this area—despite NIH's efforts to attract investigators to the field. Young researchers are unwilling to begin their careers in a field that, no matter how promising, lacks guidance and support at the federal level. Perhaps the most vivid example of researchers' reluctance to join this promising field is seen at the level of funding and applications for stem cell research. Despite an Administration goal to fund $100 million annually in stem cell investigation, less than $25 million was allocated in Fiscal Year 2003. Researchers are clearly wary of entering a field that holds so much promise, yet remains mired in uncertain funding, regulatory, and political conditions.

In the absence of a strong, coherent federal policy, the field of stem cell research will progress slowly and inefficiently. The nation's top scientists, researchers, and 80 Nobel Laureates have urged the NIH to lead our nation in oversight of this research. State initiatives and legislation on stem cell research are not a substitute for strong, federal control. The recently released guidelines on embryonic stem cell research by the National Academy of Sciences (NAS) signal a strong step forward in the field, and should viewed as a model for oversight by the federal government.

CLOSING POINTS :

- progress is being made but there are formidable obstacles to provide effective and safe cell-based therapies. It will take time and it will take investment.
- an expanded federal policy would untie hands of researchers and hasten pace of progress
- we know more about embryonic stem cells than we did in 2001 and this knowledge has made it clear the current federal policy will not enable us to achieve the goals stated by President Bush in a reasonable time frame.

We have an incredibly diverse society, with many different cultures, beliefs, morals, religions and laws. In our pluralistic society, there must be ample room for differences concerning the moral and ethical interpretations of the earliest stages of human development, especially where acknowledging these alternative legitimate views can mean the difference between life and death for many of our citizens. If we can realize the potential of these incredible stem cells we will be witness to, and in benefit of, one of the greatest contributions that science has made to the improvement of our quality of life. The promises of embryonic stem cell research are too great, and the alternatives are too few. Research in this area must go forward under appropriate oversight and with funding that will enable US investigators to fulfill these promises rapidly. Therapies delayed are therapies denied.