## Exploring the Promise of Embryonic Stem Cell Research

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Mr. Chairman, Senator Smith, and Members of the Special Committee, I appreciate the opportunity to appear before you to testify about the recent progress in human embryonic stem cell research, particularly in the area relating to neurodegenerative diseases, and the future direction of stem cell research from the perspective of the scientific community.

Human embryonic stem (ES) cells were first established in 1998 by my colleague James Thomson at the Madison campus. His report attracted immediate attention in the scientific community and the entire world, because the human ES cells could become an almost limitless source for the many specific cell types in an adult body. I was studying the therapeutic potential of stem cells that were isolated from human brain tissues, one type of the so-called adult stem cells. These brain stem cells can produce nerve cells and supporting glial cells. However, the brain-derived stem cells have limited, if any, potential to produce such specialized neural cells as midbrain dopamine nerve cells that are degenerated in Parkinson's patients, spinal cord motor neurons that are lost in Lou Gehrig disease, and the myelin-producing oligodendrocytes that are attacked in multiple sclerosis patients. This remains true today after over a decade's effort in the scientific community. Hence, scientists like myself were seeking a better cell that could provide a continual and standard source of human cells for both scientific exploration and potential therapeutic application, and human ES cells were the answer.

I had the privilege to have my hands on the human ES cells at the end of 1999 through collaboration with Dr. Thomson. I was fascinated to see the plain-looking ES cells become beating heart muscles or beautiful process-bearing nerve cells in a Petri dish in a matter of weeks. Like many other investigators in this country, my laboratory, located at the NIH-sponsored Waisman Mental Retardation Center, was not able to use the human ES cells for research until the middle of 2002. In the past three years, progress and problems have begun to emerge in the field of human ES cell research.

Because of the limited number of available human ES cell lines, one question scientists asked was how stable and for how long the current ES cell lines could be maintained with current technology. Studies coordinated by a few laboratories around the world had examined some of the existing cell lines and found that human ES cells are relatively stable. However, genetic changes happen in cells cultured for a long-term and under some special culture conditions. This suggests that more cell lines will be needed.

Human stem cell lines established thus far grow on animal cells. A recent study confirms the presence of some animal contaminants in the current cell lines. Hence, new cell lines that are free of animal products will likely be needed in order to use stem cells in clinics. Through the efforts of Dr. Thomson and others, progresses have been made in this direction. Several groups have explored the possibility of using human cells, including the cells derived from human ES cells, to support the growth and derivation of human ES cells. Most recently, the WiCell Institute has developed a method to grow ES cells without the need of animal feeder cells. This technology significantly simplifies the growth of human ES cells, which will enable more investigators to get access to the stem cells. With further tuning of this technique, new human ES cells may be generated free of animal contaminants, which will clear the first roadblock to clinical application.

When the human ES cells take the path to more specialized cells such as the earliest brain cells (also known as neuro-epithelial cells), they form brain-like structures in a Petri dish at the right time when our brain begins to form during our development. This indicates that human ES cells offer an unprecedented and otherwise unavailable tool to unveil the secret of human development.

Similarly, human ES cells with genetic defects would allow us to investigate how each gene defect results in developmental disorders. Some of these human ES cells, such as those with adrenoleukodystrophy, Fragile X Syndrome, muscular dystrophy, Fanconi anemia, Huntington's disease, neurofiromatosis, and others, have been established through pre-implantation genetic diagnosis (PGD), a test used to avoid transferring diseased embryos into the uterus of a woman undergoing in vitro fertilization. This type of genetically abnormal human ES cells will be a precious asset to the scientific community to find ways to correct genetic defects.

The first and critical step in making human ES cells useful in patients is to teach the naïve stem cells to become a functionally specialized cell, e.g., dopamine neurons or pancreatic insulin-producing islet cells. In the past 2-3 years, reports have emerged that human ES cells can produce functional blood cells, cardiac muscle cells, brain cells, etc. Dopamine-secreting nerve cells and motor nerve cells can now be very efficiently produced from human ES cells. Comparing to the decade's failed effort in producing dopamine neurons from adult stem cells, the present development is very encouraging, reassuring us that the human ES cells are indeed much more plastic than other types of stem cells. Efficient production for many other specialized cell types and purification of human ES cell derivatives will likely be a major effort in the next few years.

Studies in diseased animal models have begun to show that these specialized cells produced from human ES cells may be useful in treating certain diseases. Transplantation of human ES cell derivatives into the spinal cord of rats suffering from motor neuron disease promotes the restoration of movement. Similarly, the myelin-producing oligodendrocytes, generated from human ES cells, restore the movement of spinal cord injured rats following transplantation

into the injured area. Cardiac muscle cells, produced from human ES cells, appear to repair infarcted swine heart tissue following transplantation into the infarct area. Dopamine nerve cells generated from nonhuman primate ES cells contribute to functional recovery of Parkinsonian monkeys. These developments in such a short period of time, though preliminary, are unprecedented in the history of stem cell research. It is testimony to the enormous potential of human ES cells in the future treatment of many degenerative diseases.

Immune rejection will be an issue if ES cells are to be used in patients. Scientists are exploring ways to overcome the potential rejection problem. One way is to create ES cells that have the DNA from the patient through somatic cell nuclear transfer (SCNT). A recent report from the Korean team suggests that SCNT is a potentially feasible approach. The patient-specific human ES cell lines are precious starting materials for scientists to determine if ES cells produced through SCNT have therapeutic value.

There are many questions to be answered and many more roadblocks to be removed before the human ES cell technology is applied to patients. Studies testing the function of human ES -derived specialized cells will likely be long-term. Pre-clinical investigations involving the use of nonhuman primates also require significant investment. These long-term studies involving translation of human ES cell technology to application will be significantly enhanced with the support at the federal level.

When I was asked last weekend to testify before you on stem cell research, I began to ask myself why I should work on the controversial embryonic stem cells. I suddenly realized that I already spent 20 years of my life growing nerve cells with the recent 10 years on brain stem cells. It is with the embryonic stem cells that many scientists and I are able to produce certain specialized cells such as dopamine neurons and motor nerve cells that we could not achieve for decades just a few years ago. These ES cell-derived special nerve cells may be useful in treating some devastating diseases such as Parkinson's disease, Lou Gehrig disease, Multiple sclerosis, and spinal cord injury, although significantly more research needs to be supported in that direction. Besides the transplant therapy, the stem cells can help us unravel the mystery of human development, offer a standardized tool for screening toxins or therapeutic agents, a tool for discovering the function of new genes, and a vehicle for delivering therapeutic gene products to targets, all of which can indirectly benefit our health and society. The progress in human embryonic stem cell research made in just the past few years, as outlined above, is itself the testimony of the enormous potential of human ES cells. It will be wise and responsible to support the research aiming at saving lives and improving the health of all Americans.