Joint Committee of the U.S. Senate Committee on Health, Education, Labor and Pensions and the U.S. Senate Labor, Health and Human Services Appropriations Subcommittee

"Can Congress Help Fulfill the Promise of Stem Cell Research?"

Friday, January 19, 2007, Dirksen Senate Office Building

Professor John E. Wagner, MD
Director, Pediatric Hematology/Oncology and Blood and Marrow Transplantation
Director, Center of Molecular and Cellular Therapeutics
University of Minnesota

Executive Summary:
Over the past decade, two major events promise to revolutionize the practice of medicine-unraveling the genetic code and the isolation of the stem cell. Today, there is only one proven use of adult stem cells and that is in the context of blood and marrow transplantation to treat diseases such as leukemia, lymphoma, sickle cell disease and various other blood and immune disorders.

Accomplishments using stem cells from adult and neonatal tissues include our demonstration of their capacity to differentiate into cells of multiple tissues, 2) their safety and efficacy in laboratory models of disease, and 3) procedures for manufacturing stem cells for human testing.

There are many new adult stem cell projects moving to clinical trials. It is unrealistic to expect that there will be home runs; and, it may take several generations of studies to make a new therapy work. The Stem Cell Therapeutic and Research Act of 2005 authorized substantial funds to be used to increase the nation's inventory of cord blood by 150,000 units. The NCI and NHLBI are supporting multi institutional trials in children and adults to validate these results pioneered at the University of Minnesota. This is an example of what your support has accomplished and what it takes to move stem cell therapeutics from concept to clinical testing to standard of care.

We are now ready to test the multipotent adult stem cell, the cells discovered by Dr. Verfaillie and colleagues. But, importantly we have also identified obstacles, reasons why these may fail to repair injured tissues. While it is touted as one more advantage of adult stem cells over ES cells, it is now clear that the most primitive adult stem cells, even those directly from the patient, are susceptible to immune attack. This serves as a clear example of why it is not enough to show that a cell can differentiate into a tissue, the right models need to be used to predict clinical outcome.

Gap funding for Phase I clinical trials is an obstacle to our success. Currently, the federal grants are too small to complete the trials and we must compile several funding sources to move forward.

There are things we can do now that will speed the process of moving new laboratory discoveries to clinical trials. First, you need to understand the translational pipeline, its components, how it is funded, and the potential obstacles. Second, it is necessary to understand why there are disincentives for clinicians and basic scientists to engage in this translational research—as this will help identify solutions. Third, and perhaps most important, you must be able to differentiate speculation from fact, as it pertains to stem cells, as there is a considerable misinformation and misunderstanding out there on what adult stem cells can and cannot do.

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Senator Kennedy, Senator Harkin, Senator Enzi, and Senator Spector, thank you for the opportunity to speak today. My name is John Wagner. I am the Director of Hematology/Oncology and Blood and Marrow Transplantation Program and Scientific Director of Clinical Research for the Stem Cell Institute at the University of Minnesota.

Over the past decade, two major events promise to revolutionize the practice of medicine-unraveling the genetic code and the isolation of the stem cell. The rate that new genes are discovered and their function understood have been extraordinary. Take for example, BRCA2-the breast cancer gene. In my own clinic in the treatment of children with rare life threatening disorders, we have learned that this genetic defect is not only associated with breast and ovarian cancer in adults but also leukemia, brain tumors and kidney tumors in very young children. In fact, detection of this genetic defect in young children has allowed me to predict with high certainty what cancers will develop and when. This is powerful information because it has allowed me the opportunity to preemptively intervene and alter the future predicted by these genes. One intervention has been the use of stem cells.

Today, there is only one proven use of adult stem cells and that is in the context of blood and marrow transplantation to treat diseases such as leukemia, lymphoma, sickle cell disease and various other blood and immune disorders. This has been known for 40 years. For these diseases, we infuse stem cells to repair marrow that has either been destroyed by the disease itself or by treatments, such as high doses of chemotherapy and radiation. These blood producing stem cells come from adult marrow or cord blood (the blood left in the placenta after a baby is born).

A year and a half ago I presented before Senators Harkin and Spector to defend the vital importance of embryonic stem cell research. While I unequivocally support embryonic stem cell research, it must also be clear that adult stem cells have an important place in medicine as well. While adult stem cells do not replace the need for ES cells, they will likely complement it.

The principal accomplishments over the past five years using stem cells from adult and neonatal tissues (such as cord blood, amniotic fluid and the cord itself) include our demonstration of their capacity to differentiate into cells of multiple tissues (eg. mesenchymal cells into neurons; cord blood stem cells into cells of the lung), 2) their

safety and efficacy in laboratory models of disease, and 3) procedures for manufacturing stem cells for human testing. In fact, the first clinical trials have already been initiated in acute heart disease (heart attacks) and chronic heart failure, acute brain injury and lung injury. In addition, clinical trials with organ-specific stem cells are already being studied in diabetes in addition to those in bone marrow transplantation.

With National Institute of Health (NIH) research dollars and other governmental and non governmental support as well as philanthropic support, there are many new projects moving to clinical trials. At our own laboratory, we are collaborating with investigators at Johns Hopkins, helping to develop clinical manufacturing methods for testing cardiac stem cells; we are collaborating with investigators at Tulane, developing stem cell populations for treatment of genetic disease and bone repair; and, we are working with industry, such as Athersys, manufacturing multipotent adult stem cells for treatment of radiation and chemotherapy injury. Significant progress has been made.

It is unrealistic to expect that there will be home runs; and, it may take several generations of studies to make a new therapy work. As an example, cord blood used to treat leukemia and lymphoma took years before it reached its current success. In 1990, I performed the first cord blood transplant in the world for a child with leukemia. While this child unfortunately died of his underlying disease, scientifically it was a success – thereby giving us a reason to push forward. Eight clinical trials later, we made modifications that have led to extraordinary survival rates in adults with leukemia. Now, patients from all over the world are now receiving this therapy. In addition, the 'double cord blood' platform, has solved the problem of access—permitting us to find donors for more than 80 percent of patients, particularly important for patients of ethnic and racial minority descent.

The Stem Cell Therapeutic and Research Act of 2005 authorized substantial funds to be used to increase the nation's inventory of cord blood by 150,000 units. The NCI and NHLBI are supporting multi institutional trials in children and adults to validate these results pioneered at the University of Minnesota. This serves as just one example of what your support has accomplished and what it takes to move stem cell therapeutics from concept to clinical testing to standard of care.

After five years of intense study, we are now ready to test the multipotent adult stem cell, the cells discovered by Dr. Verfaillie and colleagues. We are about to submit our first application to the US Food and Drug Administration. Over the past 2 years, we have compiled safety and efficacy data in laboratory models and developed the procedures for reliably producing these cells for individual patients. The first trials will take place in the setting of radiation and chemotherapy injury and the goal is to demonstrate safety and hopefully signs of tissue repair. Will it cure patients—may be not. Do we give up—no. As in the early trials with cord blood, we have to carefully design the right studies that will insure that we learn why the cells work or why they don't work should that occur. We already know in laboratory models that multipotent adult stem cells will home preferentially to areas of tissue injury.

But, importantly we have also identified obstacles, reasons why these may fail to repair injured tissues. While it is touted as one more advantage of adult stem cells over ES cells, it is now clear that the most primitive adult stem cells, even those directly from the patient, are susceptible to immune attack. This serves as a clear example of why it is not enough to show that a cell can differentiate into a tissue, the right models need to be used to predict clinical outcome. For this reason, our first trial with the multipotent adult stem cell will be in immune suppressed patients with tissue injury, giving every chance for these stem cells to engraft into damaged tissues and effect tissue repair.

It is not enough to give hope based on the results from a Petri dish. We must have better models to move the science forward. It is exactly this stage of research that is sorely lacking in funding – this in between stage. Gap funding for Phase I clinical trials is an obstacle to our success. Currently, the federal grants are too small to complete the trials and we must compile several funding sources to move forward.

It is not a question of whether this new knowledge will 'translate' into a useful clinical treatment but rather – when? I receive hundreds of emails and letters monthly asking for direction, help and above all - hope. As a physician who sees patients for whom there is no known treatment, I explore the unknown. I have to keep trying. For the most part, I have made some good decisions and patients have benefits. While it will never be fast enough, there are things we can do now that will speed the process of moving new laboratory discoveries to clinical trials. First, you need to understand the translational pipeline, its components, how it is funded, and the potential obstacles. Second, it is necessary to understand why there are disincentives for clinicians and basic scientists to engage in this translational research—as this will help identify solutions. Third, and perhaps most important, you must be able to differentiate speculation from fact, as it pertains to stem cells, as there is a considerable misinformation and misunderstanding out there on what adult stem cells can and cannot do.

It must be clear that no study with adult or cord blood stem cells outside the context of bone marrow transplantation has proven efficacy. While there are claims to suggest otherwise, the results are either contradictory or too preliminary. While I wish that I could tell you otherwise, speculation seems to get confused with fact. While promising, adult stem cells do not exhibit all the capacities of ES cells. For example, we have yet to see stem cells from cord blood or adult tissues (outside the heart) differentiate into heart muscle cells that spontaneous beat, as has been shown repeatedly with ES cells.

Can Congress Help Fulfill the Promise of Stem Cell Research?—absolutely. We are here today to help you understand what we know, what we think we know and how you might help translate this hope of stem cells into reality. In addition, it is important to know exactly how much is currently being spent on stem cell research. This involves separating how much is spent on adult/cord blood versus ES stem cells and separating adult/cord blood stem cells into hematopoietic (bone marrow transplant) and non-hematopoietic. In my opinion, this is not clear to the public

Every single one of us will be faced with a disease amenable to stem cell therapy. It may be our child, our spouse, our friend or even ourselves. Adult and cord blood stem cells have proven benefits in the treatment of blood cancers and other disorders and perhaps even in tissue repair that has yet to be clearly proven. It is essential that federal funding be devoted to stem cell biology and therapeutics. All the required components to make this work already exist-we just need to bring them together. There are patients in this room today and parents of children who have passed away looking for a chance to see this hope move into a reality. The results are extraordinary; we have to make it happen now on their behalf. For them, the stakes are unimaginable.