S. HRG. 109–249

STEM CELLS RESEARCH, 2005

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED NINTH CONGRESS

FIRST SESSION

SPECIAL HEARING

OCTOBER 19, 2005—WASHINGTON, DC

Printed for the use of the Committee on Appropriations

Available via the World Wide Web: http://www.gpoaccess.gov/congress/index.html

U.S. GOVERNMENT PRINTING OFFICE

25–119 PDF WASHINGTON : 2006

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2250 Mail: Stop SSOP, Washington, DC 20402–0001

COMMITTEE ON APPROPRIATIONS

THAD COCHRAN, Mississippi, *Chairman*

TED STEVENS, Alaska
ARLEN SPECTER, Pennsylvania
PETE V. DOMENICI, New Mexico
CHRISTOPHER S. BOND, Missouri
MITCH MCCONNELL, Kentucky
CONRAD BURNS, Montana
RICHARD C. SHELBY, Alabama
JUDD GREGG, New Hampshire
ROBERT F. BENNETT, Utah
LARRY CRAIG, Idaho
KAY BAILEY HUTCHISON, Texas
MIKE DEWINE, Ohio
SAM BROWNBACK, Kansas
WAYNE ALLARD, Colorado

ROBERT C. BYRD, West Virginia
DANIEL K. INOUYE, Hawaii
PATRICK J. LEAHY, Vermont
TOM HARKIN, Iowa
BARBARA A. MIKULSKI, Maryland
HARRY REID, Nevada
HERB KOHL, Wisconsin
PATTY MURRAY, Washington
BYRON L. DORGAN, North Dakota
DIANNE FEINSTEIN, California
RICHARD J. DURBIN, Illinois
TIM JOHNSON, South Dakota
MARY L. LANDRIEU, Louisiana

J. KEITH KENNEDY, *Staff Director*
TERRENCE E. SAUVAIN, *Minority Staff Director*

SUBCOMMITTEE ON DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES

ARLEN SPECTER, Pennsylvania, *Chairman*

THAD COCHRAN, Mississippi
JUDD GREGG, New Hampshire
LARRY CRAIG, Idaho
KAY BAILEY HUTCHISON, Texas
TED STEVENS, Alaska
MIKE DEWINE, Ohio
RICHARD C. SHELBY, Alabama

TOM HARKIN, Iowa
DANIEL K. INOUYE, Hawaii
HARRY REID, Nevada
HERB KOHL, Wisconsin
PATTY MURRAY, Washington
MARY L. LANDRIEU, Louisiana
RICHARD J. DURBIN, Illinois
ROBERT C. BYRD, West Virginia (Ex officio)

Professional Staff
BETTILOU TAYLOR
JIM SOURWINE
MARK LAISCH
SUDIP SHRIKANT PARIKH
CANDICE ROGERS
LISA BERNHARDT
RACHEL JONES
ELLEN MURRAY *(Minority)*
ERIK FATEMI *(Minority)*
ADRIENNE HALLETT *(Minority)*

CONTENTS

STEM CELLS RESEARCH, 2005

WEDNESDAY, OCTOBER 19, 2005

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:31 a.m., in room SD–138, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter, Cochran, Harkin, and Landrieu.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning.

Today our focus is on stem cells. Our hearing coincides with the announcement by the South Korean Nuclear Transplantation Consortium that they are starting an operation today on a world stem cell foundation which will be based in the Seoul National University in South Korea with satellite offices in San Francisco and England. I applaud what they are doing, but I regret that the United States is falling farther behind in world leadership on scientific research generally and specifically on stem cell research.

Now, this is the 17th hearing which this subcommittee has held on this important subject since we first learned about stem cells in November 1998. It is well known that the stem cells have the possibility for curing or alleviating the problems of so many maladies.

The House of Representatives has passed legislation which would remove the restriction by the Federal Government on funding stem cell research, and Senator Harkin and I have introduced identical legislation in the Senate, S. 471. The House bill received support from some 50 Republicans crossing party lines, and it is my view that with sufficient focus and sufficient attention, there could be amassed enough votes to override a presidential veto. I say that regretfully and reluctantly, but this is a matter of utmost importance and has a direct impact to some 110 million Americans.

President Nixon declared war on cancer in 1970 and had the United States devoted the resources to that war which we devote to other wars, I think the war on cancer could have been won. I say that with special concern because I have had my own problems with Hodgkin's lymphoma cancer this year, and cancer continues to claim deaths in the hundreds of thousands.

This happens to be an especially busy day. Most days are busy on Capitol Hill, but we are in the midst of proceedings on the nomination of Ms. Miers for the Supreme Court, and I am going to have

to excuse myself at about 10:00, but I will have an opportunity before that occurs to hear all of the witnesses.

Now I would like to yield to my distinguished ranking member, Senator Harkin.

Senator HARKIN. Thank you very much, Mr. Chairman. Senator Landrieu I know has to leave right away. If I could just yield a couple minutes for her of my time, I would appreciate it.

Senator SPECTER. Well, I was about to yield a couple minutes to Senator Cochran, but since you spoke first, Senator Landrieu.

STATEMENT OF SENATOR MARY L. LANDRIEU

Senator LANDRIEU. Thank you, Mr. Chairman. I thank Senator Harkin just for one moment because I have got to leave for another meeting. It is a very busy day, as the chairman said.

Let me thank the chairman and Senator Harkin for their pursuit of a solution to this dilemma and to this great challenge. I have a slightly different view that I will submit for the record in written testimony.

For this morning, I will just say that as we pursue cures for the many diseases that challenge us and while I understand that embryonic stem cells hold promise for curing diseases, as the chairman and many others have pointed out, I think that we have to be very mindful of what many of our ethical leaders have said and the Catholic bishops in particular that it is important in the pursuit of progress to not undermine human dignity. And there is a line that can be drawn between progress and human dignity, and creating embryonic stem cells for the purpose of creating human beings for the purposes of destroying them for science crosses that line in my opinion.

PREPARED STATEMENT

I will submit more to the record, but I understand that this will be a continued debate, and I thank the Senator for allowing me to express my views.

Senator SPECTER. Thank you, Senator Landrieu.

[The statement follows:]

PREPARED STATEMENT OF SENATOR MARY L. LANDRIEU

Thank you, Mr. Chairman. I have had the privilege of serving as a member of this subcommittee for four years now. I think it is important to note that one of the very first hearings I attended was on this very issue. A lot has changed since then—both in the ethical debate and in the science. But what have not changed are the moral parameters that must guide us in these decisions. As Richard Doerflinger of the Catholic Conference of Bishops put it—"We must be careful not to undermine human dignity in the pursuit of human progress."

Since that hearing four years ago, in August of 2001, the President issued an executive order, allowing for federal funding for stem cell research on the then existing stem cell lines. In November of that same year, he appointed a council to monitor stem cell research, to recommend appropriate guidelines and regulations, and to consider all of the medical and ethical ramifications of biomedical innovation. To date, this council has issued six hundred plus page reports on the bioethics issues involved in stem cell research. Meanwhile, the scientific community has moved forward in its advancements in knowledge and discovery. And everyday we, as members of Congress are faced with the questions of how far we should go in the name of science.

There is no doubt that embryonic stem cell research holds the promise of curing diseases such as Parkinson's, diabetes, Alzheimer's and cancer. Even President Bush stressed the importance of federally funded research in approving the original

stem cell lines in 2001—he explicitly stated that federal dollars help attract the best and brightest scientists and help ensure that new discoveries are widely shared at the largest number of research facilities. Federal funding not only allows us to encourage and financially support this research, it allows us to use the power of the purse to be sure it is done in the most safe and ethical way possible. Mr. Chairman, I want to state clearly for the record, I support federal funding for embryonic stem cell research provided that the embryos used in these studies are those that are in excess from the fertility process and are knowingly donated for this purpose.

I have met with many constituents suffering from life altering and fatal diseases and they have told me the impact that this research may have on their lives. One such constituent who I will never forget is a nine year old girl, Sarah, who suffers from juvenile diabetes. Sarah told me of her daily routine of shots and blood tests. Her parents told me of some of the effects of diabetes such as vision loss, kidney failure, blindness, nerve damage, amputations, heart attack, and stroke. They begged me, on her behalf, not to block this important research that could mean a normal childhood for Sarah. Sarah is not alone in this hope, 35 children a day are diagnosed with Type One Diabetes.

There are currently 400,000 frozen embryos at IVF clinics around the country—88.2 percent of which are used for implantation in the mother's womb—2.8 percent are given up for adoption—the wonderful "snowflake babies" we all hear so much about. This translates to a total of 11,000 embryos that are not going to be implanted and are voluntarily donated. It is important to note, if these embryos were not donated then they would be destroyed—not for science—but thrown away with the rest of the medical waste for the day. We cannot allow these valuable embryos to be discarded when even according to the President's Council on Bioethics, "stem cells and their derivatives may prove a valuable source of transplantable cells and tissues for repair and regeneration. If these healing powers could be harnessed, the medical benefits for humankind would be immense, perhaps ushering in an era of truly regenerative medicine."

Please do no let my views expressed today confuse your understanding of my support of legislation banning human cloning. Embryonic stem cell research using excess embryos from IVF treatments and creating cloned embryos for scientific purposes should not be confused. I believe that creating a human embryo for the sole purpose of its destruction through experimentation is wrong, unethical and should be illegal. Since I mentioned the hearing on stem cell research conducted by this committee four years ago at the beginning of my remarks, I think it is important to note that many members of this subcommittee also expressed concerns about the creation of human embryos for research.

The human body is not a product to be mass-produced and stripped for parts, most especially in the earliest stages of its development—women's eggs and wombs should never be commodities sold to the highest bidders. But this is a very real risk of so called "therapeutic cloning." Experts estimate that over 800 million eggs would be needed to support one-sixteenth of the possible human cloning experiments. We are already getting reports that clinical researchers in Seoul, Korea, in England, and in San Francisco will be working with the South Korean veterinarian and stem-cell biologist whose laboratory leads the world in the use of the somatic-cell nuclear transfer technique, to recruit women to donate eggs and patients to donate somatic cells.

What's more, regardless of what proponents of this research will tell you, there is only one kind of cloning. The only difference between what has come to be called "reproductive cloning" and "therapeutic cloning" is what is done with the clones once they are created. Legislation that purports to ban the birth of a cloned human being does not ban its creation, only its implantation into a human uterus. Once we support and encourage the creation of millions of cloned human beings, do we really believe we would have the power to successfully monitor and ban their implantation? The only effective way to ban human cloning is to stop the process before it starts.

Finally, Mr. Chairman, it is because I believe that there is immense potential in embryonic and adult stem cell research that I oppose federal support for human cloning. I believe that banning, even if only temporarily, this one procedure helps to focus science and funding for research to equally promising but less problematic areas such as embryonic and adult stem cell research.

I look forward to hearing from the witnesses today and thank you, Chairman Specter for holding this important hearing.

Senator SPECTER. Senator Harkin.

STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Thank you, Mr. Chairman. Again, let me just compliment you on your great leadership on a lot of things, but especially on this issue since 1998, as you mentioned, and for calling this hearing.

We have had a pretty busy year with hurricanes on the Gulf Coast, of course, and as the chairman knows better than anyone else, the Senate having to have hearings on two Supreme Court nominees, which the chairman chairs that committee. And yet, the need to continue our push for stem cell research is as critical as ever.

I was privileged this summer to meet with some of the South Koreans, and you mentioned the article that was in the paper this morning, Mr. Chairman, that they are moving ahead on this, the whole area of somatic cell nuclear transfer, and the kind of promise that holds.

I am just hopeful that we can move ahead on this. People are suffering and dying. They need hope. We know this holds great promise. We all know that medical research is not just done by one person, not done by two. The best research is when a lot of people are involved in it and it is spread around. That is what we need to do. We need to get more involved in this type of research.

Yet, we have manacles put on our researchers today and we need to remove those. That is what the bill that Senator Specter and I have supported, the one that passed the House, does. That is why we hope today we can move ahead with a look at somatic cell nuclear transfer and what that means for the future of stem cell research.

So, again, Mr. Chairman, I thank you for holding this hearing and, again, I thank you for your great leadership on this issue.

Senator SPECTER. Senator Cochran, would you care to make an opening statement?

STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. Mr. Chairman, thank you very much. I congratulate you on your continued strong leadership in helping to explore the possibilities that medical research holds for curing and preventing illness and disease. You have done more than anybody I can remember since I have been in the Senate to not only focus attention on these opportunities that we have to legislate and support research and to authorize programs to achieve these goals. So I congratulate you and thank you again for this hearing.

I am really here to introduce Anthony Herrera who is a friend of mine since 1961, who is a member of this panel. So I will await your advice as to when that would be appropriate.

Senator SPECTER. Well, thank you very much, Senator Cochran. We appreciate your continuing support for this subcommittee and your membership on the subcommittee, notwithstanding your very onerous duties as chairman of the full Appropriations Committee.

STATEMENT OF ANTHONY HERRERA, AUTHOR AND CANCER SURVIVOR

Senator SPECTER. We now move to our panel of witnesses and our lead witness is Mr. Anthony Herrera. I yield to you again, Mr. Chairman, for the formal introduction.

Senator COCHRAN. Thank you very much. It is a great pleasure for me to introduce to the committee Anthony Herrera, whom I have known since 1961. We met when I was entering my first year of law school and he was beginning his first year of undergraduate school at the University of Mississippi, and I happened to be in the same residence hall and became the dormitory manager, as we called it, back in those days. He was young, but energetic, full of an interest in all of the things that were going on at that campus.

He became an excellent student and then went on to a successful career in the performing arts as an actor, writer, director. He has been on As the World Turns off and on for a long, long time. James Stenbeck is his stage name on that show. And James Stenbeck has been a survivor too of sorts. He would disappear. People would think he was a goner and then he would reappear sometime later full of life and enthusiasm. That is the story of Anthony Herrera as well.

He has battled cancer and has survived. He has written a book about it, The Cancer War, which I recommend. I know the chairman has read it. I have read it. It is very instructive into the challenges that confront someone who is a victim of lymphoma or other forms of cancer. He had a rare kind of lymphoma. And transplants of bone marrow, stem cells, all of these things have been involved in his life. He has lived through it all and can help us understand the challenges that victims face and the possible successes there are in our effort to deal more successfully with some of these forms of cancer.

So it is a great pleasure for me to welcome him and thank him for being here to help us understand the challenges.

Senator SPECTER. Thank you very much, Mr. Chairman.

Mr. Herrera, we do very much appreciate your being here today, especially since you came from Buenos Aires to participate in this hearing. I compliment you on the book which you have written, and I pay particular note to your references to stem cells as they relate to your situation.

We now begin the customary 5-minute rounds for the witnesses and we start with Mr. Anthony Herrera.

Mr. HERRERA. Thank you.

In January 1997 at New York Hospital, I was diagnosed with mantle cell lymphoma and was told this disease will kill you. There is nothing we can do. You are going to die.

Then without anesthesia, this oncologist drilled through my skin, through my periosteum and into the bone, and extracted marrow. The pain was incredible.

That night I debated whether to put my .38 Smith & Wesson to my temple and pull the trigger or saddle up. I pondered each option. Then I pictured myself on a horse riding into a dark canyon. I found a poem by Tennessee Williams from the Night of the Iguana. I read it every day.

I then went to Sloan Kettering where I was told we are going to work hard and hope for the best. They had a new protocol for mantle cell developed with a hospital in Paris. I was the fifth patient in the United States to undergo this regimen, massive amounts of chemotherapy and total body irradiation to kill lymphoma cells and take my immune system to zero.

On August 1, 1997, I received an autologous stem cell transplant, autologous meaning the stem cells were taken from my body. My mouth was full of sores. My skin was gray. I had no hair, no fingernails, no toenails, but I was found to be in remission. I lived under the belief that if the disease came back that I would die.

In November 1998, I relapsed but during these 18 months, a new approach to the stem cell transplant for mantle cell had been developed at M.D. Anderson Cancer Center in Houston, Texas where I was admitted March 30, 1999.

In April, I underwent an allogeneic stem cell transplant using a non-myeloablative regimen, allogeneic meaning the cells came from a donor, non-myeloablative meaning they did not burn my immune system to zero with chemo, hence less toxicity.

Six weeks later, the lymphoma was still active. We tried a donor lymphocyte infusion, adding more of my brother's cells. I then suffered from CMV. I bled internally and lost 30 pounds in 3 weeks, followed by a mild stroke and a seizure, but I was in remission.

One year later, August 15, 2000, the CT-scan showed that I had relapsed. The disease was back. I was told without treatment you will die in less than 12 months and that another donor lymphocyte infusion could kill you. There was a small amount of disease, so I had time to think.

Six weeks later, I saddled up and requested a CT-scan. At this juncture, medical history was made. This scan showed less disease than 6 weeks before, which meant that my new immune system had started fighting the lymphoma without chemotherapy, without drugs, without radiation. My new immune system was taking out the cancer, my new immune system and my bone marrow created by donor stem cells.

Throughout this journey, I listened to Willie Nelson, Louis Armstrong, and Agustin Lara of Mexico. I recited Tennessee Williams every day. I quoted from John Ford's The Searchers. When asked if he wanted to quit, John Wayne retorted, that will be the day.

I found dedicated and inspired doctors and nurses, such as Sergio Giralt and Joyce Newman, doctors and nurses with guts and vision.

In 1950, William Faulkner won the Nobel Peace Prize for literature. He concluded his acceptance speech with the following. "I believe that man will not merely endure: he will prevail. He is immortal, not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice.

"The writer's duty is to write about these things. It is his privilege to help man endure by lifting his heart, by reminding him of the courage and honor and hope and pride and compassion and pity and sacrifice which have been the glory of his past. The poet's voice need not merely be the record of man, it can be one of the props, the pillars to help him endure and prevail."

I hope that you Senators and this Congress find it is your privilege and your duty to fight with your intelligence and pride and compassion to continue to build the pillars of man, the arts for the spirit, education for the mind, and medical research for the body.

PREPARED STATEMENT

Ladies and gentlemen, let me leave you with this thought. The stem cell is the future of medicine and I am alive because of the progress in stem cell research. Thank you.

[The statement follows:]

PREPARED STATEMENT OF ANTHONY HERRERA

I was diagnosed with Mantle Cell Lymphoma in January of 1997 and was told at New York University Hospital, "This disease will kill you. There is nothing we can do. You are going to die."

That night I debated whether to put my .38 Smith & Wesson to my temple and pull the trigger or "saddle up." I pondered each option. Then I saw myself on HORSE heading into a dark canyon.

I found a poem by Tennessee Williams from the Night of the Iguana. I read it every day.

I then went to Memorial Sloan-Kettering and was treated with a regimen of chop and ICE chemotherapy and total body irradiation.

On August 1, 1997 I received an autologous stem cell transplant and was found to be in remission.

In November 1998, I relapsed and received four cycles of chemotherapy. On March 30, 1999 I was admitted to the University of Texas, M.D. Anderson Cancer Center in Houston Texas, under the care of Dr. Issa Khouri, M.D.

I underwent an allogeneic stem cell transplantation using a non-myeloablative regimen. My brother John, was my donor. I required a boost of donor lymphocyte infusion after transplantation.

I then suffered from CMV, a mild stroke and a seizure.

I was found to be in remission August 15, 1999.

This treatment was based on a concept developed at M.D. Anderson Cancer Center, that many neoplastic diseases can be treated by immune modulation only without the need for toxic high dose chemotherapy.

Up until recently high dose chemotherapy was considered essential for marrow or stem cell transplantation.

This new treatment offers new hope and new horizons for patients suffering from this otherwise fatal disease.

I relapsed August 15, 2000. I was told without treatment "You will die in less than twelve months." And that "another donor lymphocyte infusion—could kill you."

He then worked with Dr. Ira Braunschweig, formerly of MD Anderson Cancer Center, now medical director of Director of Bone Marrow Transplantation—The Albert Einstein College of Medicine. The plan at that time was to use Rituxan to control the lymphoma and then return to MD Anderson for a donor lymphocyte infusion.

A CAT-scan from September 27, 2000 showed less disease without any treatment of any kind. This meant that his new immune system had started battling the disease.

This was a medical history in the treatment of Mantle Cell Lymphoma in that the new immune system had started killing lymphoma cells and there by reducing the amount of disease without treatment of any kind.

Dr. Braunschweig and I debated and then decided to proceed with four rounds of high dose Rituxan during the month of October, with the hope that the Rituxan would assist his new immune system in the battle.

CAT scans and Gallium scans that followed from November through 30 January 2001 showed a steady decrease in the amount of lymphoma and lymphoma related activity.

Dr. Braunschweig and I have discussed several times whether there was a chance the rituxan aided his new immune system in the battle to control the Mantle Cell Lymphoma.

We will never know.

What is concluded by Dr. Braunschweig, Dr. Andre Goy, Dr. James Gajewski and Dr. Sergio Giralt is that the donor infusion of my brother's cells and the engrafting of this new immune system in his body that has kept me in remission for five years.

This unexpected development of Graft vs. Lymphoma approach is positive news for fighting cancer and other life threatening diseases.

Throughout this journey I listen to Willie Nelson, Louis Armstrong and Agustin Lara of Mexico. I quoted Tennessee Williams every day. I quoted from John Ford's THE SEARCHERS . . . When was asked if he wanted to quit. John Wayne retorted, "That'll be the day."

I am alive because of great Doctors and nurses with guts and vision. 1950 William Faulkner won the Nobel Prize for Literature . . . he concluded his speech with the following.

I believe that man will not merely endure: he will prevail. He is immortal, not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice and endurance.

The poet's, the writer's, duty is to write about these things. It is his privilege to help man endure by lifting his heart, by reminding him of the courage and honor and hope and pride and compassion and pity and sacrifice which have been the glory of his past. The poet's voice need not merely be the record of man, it can be one of the props, the pillars to help him endure and prevail . . .

The stem cell is the future of medicine . . .

I hope you senators and this congress find that it is your privilege and duty to fight with your intelligence and pride and compassion to continue to build the pillars of man—the arts for the spirit—education for the mind and medical research for the body. Stem cell research. All stem cell research.

Thank you.

Senator SPECTER. Thank you very much, Mr. Herrera, for that very poignant and emphatic testimony and for the authentication as to what stem cells can do, for what they have done for you.

Our next witness is Dr. Judith Gasson, Director of Jonsson Comprehensive Cancer Center at UCLA. Dr. Gasson has a doctorate in physiology from the University of Colorado and post-doctoral work at Saulk Institute. Thank you very much for joining us today, Dr. Gasson, and the floor is yours.

STATEMENT OF JUDITH GASSON, Ph.D., DIRECTOR, JONSSON COMPREHENSIVE CANCER CENTER

Dr. GASSON. Thank you very much, Mr. Chairman. It is a great pleasure to continue the conversation that you and I began several years ago when you were visiting UCLA Medical School. At that time, we had a very serious discussion about how important it was that we continue to do this very important stem cell work, and I am happy to be here today.

Cancer is now the leading cause of death in Americans under the age of 85. This year alone, 550,000 Americans will die from their disease. These numbers fail to account for the additional pain and suffering felt by their families and friends.

Many scientists believe that stem cell research has the power to revolutionize cancer therapy in much the same way that targeted therapies have impacted cancer treatment over the past decade. There is now considerable evidence that many types of cancer, including breast cancer, prostate, brain, and certain leukemias, arise through mutations that occur in our adult stem cells. These so-called cancer stem cells retain the ability to self-renew, which is a signature feature of stem cells. However, they lose the ability to respond to the proper cues and to differentiate.

Our current therapies are targeted to the bulk of the tumor and not to the cancer stem cell. How can we develop therapies that destroy the malignant stem cells, thereby eliminating both the tumor

and its chance to recur at a later time? Like all therapeutic advances, targeting cancer stem cells must be based on outstanding basic science. For this reason, embryonic stem cells must be studied to educate us on the fundamental processes and pathways that drive the growth of cancer stem cells.

To be sure, studies are ongoing on adult stem cells, but these studies are incomplete and unable to answer all of the critical questions. Adult stem cells are rare in our bodies and cannot be induced to grow in the laboratory without also differentiating.

We believe that characterizing the pathways that embryonic stem cells use to self-renew, using high-throughput screening technology, will allow us to develop small molecule inhibitors to those stem cell-specific pathways. If these chemical inhibitors of self-renewal of embryonic stem cells are isolated and characterized in the laboratory, they may actually provide the first benefit of stem cell research in patients.

Paradoxically, as you just heard from Mr. Herrera, bone marrow stem cells are not only perhaps the source of some cancers, but they also have been used to treat certain cancers for the past 4 decades. Many patients are unable to benefit from this potentially lifesaving treatment because they either do not have a matched bone marrow donor or their own bone marrow has been compromised by treatment or invasion of cancer cells. The technique of somatic cell nuclear transfer would enable us to insert the DNA from a cancer patient's skin cells into an egg and reprogram that DNA to become a pluripotent stem cell again. In this way, the patient's blood and immune systems could be reconstituted and genetically identical to the patient.

It has been estimated that there are currently 400,000 frozen embryos generated in in vitro fertilization clinics that will not be used. The vast majority of these frozen cells will be destroyed.

The thousands of physicians and scientists, represented by the American Association of Cancer Research and the American Society of Clinical Oncology, issued public statements this year strongly endorsing the expansion of funding for embryonic stem cell research to improve the prevention, detection, and treatment of cancer. We estimate that this represents 30,000 physicians and scientists who believe that this important work will have an impact on the dreaded disease of cancer.

PREPARED STATEMENT

To be sure, my commitment to this area of research is professional, but it is also personal. Three years ago next week I lost my own father to lymphoma.

Thank you very much, Mr. Chairman.

[The statement follows:]

PREPARED STATEMENT OF JUDITH GASSON

Cancer is now the leading cause of death in Americans under the age of 75. This year alone 550,000 Americans will die from their disease. These numbers fail to account for the additional pain and suffering felt by their family and friends.

Many scientists believe that stem cell research has the power to revolutionize cancer therapy in much the same way that "targeted" therapies have impacted cancer treatment over the past decade. There is now considerable evidence that many types of cancer including breast, prostate, brain and leukemias arise through mutations

acquired in our adult stem cells. These so-called "cancer stem cells" retain the ability to self-renew, which is the signature feature of stem cells. However they lose the ability to respond to normal differentiation signals.

Our current therapies are targeted to the bulk of the tumor, but not to the cancer stem cells. How can we develop therapies that destroy the cancer stem cells, thereby eliminating the tumor and its chances to recur? Like all therapeutic advances targeting cancer stem cells must be based upon outstanding basic science. For this reason embryonic stem cells must be studied to educate us on the fundamental processes and pathways that drive the growth of cancer stem cells. To be sure studies are ongoing with adult stem cells, but these studies are incomplete and unable to answer all of the critical questions. Adult stem cells are rare and cannot be induced to grow in the laboratory without also differentiating. We believe that characterizing the pathways that embryonic stem cells use to self-renew, using high-throughput screens, will lead to the development of small molecule inhibitors. It is these chemical inhibitors of self-renewal of embryonic stem cells that may provide the first benefits of stem cell research in patients.

Paradoxically bone marrow stem cells have been used to treat certain cancers for the past four decades. Many patients are unable to benefit from this potentially lifesaving treatment because they don't have a matched bone marrow donor and their own bone marrow has been comprised by treatment or invaded by cancer cells. The technique of somatic cell nuclear transfer would enable us to insert DNA from a cancer patient's skin cell into an egg and re-program it from a skin cell to a pluripotent stem cell. In this way, the patient's blood and immune systems could be reconstituted and genetically identical to the patient.

It's been estimated that there are currently 400,000 frozen embryos generated from in vitro fertilization that will not be used. The vast majority of these will be destroyed. The thousands of physicians and scientists represented by the American Association of Cancer Research and the American Society of Clinical Oncology issued public statements this year strongly endorsing the expansion of funding for embryonic stem cell research to improve the prevention, detection and treatment of cancer.

Senator SPECTER. Thank you very much, Dr. Gasson.

Our next witness is Dr. Rudolf Jaenisch, Professor of Biology at Massachusetts Institute of Technology and a member of the Whitehead Institute for Biomedical Research. He received his doctorate in medicine from the University of Munich. Thank you for joining us today, Dr. Jaenisch, and we look forward to your testimony.

STATEMENT OF RUDOLF JAENISCH, M.D., PROFESSOR OF BIOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Dr. JAENISCH. Thank you, Mr. Chairman.

So I am a founding member of the Whitehead Institute and a professor of biology at MIT. My main research interest is epigenetic regulation, embryonic stem cells, and to understand the mechanisms of nuclear transfer and the reprogramming of the genome following nuclear transfer. We have studied this in mice, and the conclusion from all work was that reproductive cloning in humans is unsafe and should be banned.

Our work was also of relevance for the therapeutic application of somatic cell nuclear transfer. We have done this in a mouse model again of severe combined immune deficiency, SCID. This condition exists in humans. And we have used this technique to restore the immune system in these mice. And I believe that this proof of principle experiment is directly relevant for treatment of human blood diseases, such as leukemia as we heard.

The recent success by the Korean group indicates that nuclear transfer in humans is much more efficient than we assumed before, and they believe the treatment of bone marrow diseases will likely be the first human disease that will be treated by SCNT.

Embryonic stem cells clearly—and we heard this—are of great potential value to treat diseases, and I am confident that if we are allowed to derive new stem cells from in vitro fertilized embryos, that would enormously help us to understand the system. But I want to talk about nuclear transfer today.

The proof of principle experiments are clear. In principle, this technology will work in humans to treat diseases such as blood diseases, Parkinson's, and diabetes. We have to learn technology, but this I think is only technology.

So what are the concerns of those who oppose nuclear cloning in humans for the purpose of generating customized embryonic stem cells for therapy or for research?

I believe the key concern is that the derivation of an embryonic stem cell from a cloned construct would necessarily involve the destruction of the blastocyst and thus destruction of potential normal human life. The crucial question is: does the cloned blastocyst really represent potential normal human life? And that is what I want to concentrate on.

From all experience with cloned animals, I would argue that the cloned blastocyst has little, if any, potential to ever develop into a normal baby. Most will die in development and the few that survive to birth will develop severe defects with age because of the reprogramming faults following nuclear transplantation.

For these reasons, it has been suggested, because a cloned blastocyst is so different from the normal blastocyst which is derived from a fertilized egg, that it should not be designated as an embryo. And I agree with this notion. However, we have to admit that the cloned blastocyst has a chance, although an exceedingly small chance, to develop into cloned animals such as Dolly. But Dolly died because she suffered from major ailments, as most clones do. But it is this statistically small chance of a clone to develop to birth and beyond what troubles most who oppose the technology.

The altered nuclear transfer approach has been proposed by Dr. Hurlbut as a potential solution. This approach would cause the product of nuclear transfer to be inherently unable to ever develop into a fetus or a baby because of its inability to establish the very first step of embryonic organization and the inability to establish that fetal/maternal connection. The procedure, as proposed by Hurlbut, involves the genetic manipulation of the donor cell, not of the embryo, with the goal to generate a construct which can still generate embryonic stem cells but cannot implant and generate a fetus. So the goal is, therefore, to generate what he calls a biological construct or biological artifact that lacks the essential attributes of an embryo and has no potential whatsoever to develop into a fetus but still could proliferate and give rise to ES cells.

ANT, altered nuclear transfer, was last year proposed as a thought experiment. We have now performed the proof of principle experiment in the mouse, published this week in Nature, that validates this proposal. So let me explain.

In our experiment, we introduced an RNAi construct into the skin cells prior to nuclear transfer. The RNAi was directed against Cdx2. This is a gene which is crucial for the establishment of the very first lineage in embryonic development which is established at the 16-cell stage. The genetically altered skin cells do not express

Cdx2, but once the nucleus is transferred to the egg, the cloned product cannot establish this key lineage. It will develop still to an abnormal blastocyst which collapses because the trophectoderm lineage, which will give rise to the placenta, cannot form.

The embryonic stem cells derived from this construct are indistinguishable in their potential from a normal embryonic stem cell. So the key question for the debate here is: does it generate embryos and how abnormal are they?

So I would argue that the ANT, altered nuclear transfer, embryo is already abnormal at the 4- to 8-cell stage molecularly because the gene is then expressed. It is not expressed then. But it becomes morphologically only abnormal within 2 cell divisions.

Senator SPECTER. Dr. Jaenisch, could you summarize your testimony at this point? Your full statement will be made a part of the record.

Dr. JAENISCH. So I will then summarize that the question is can we designate these ANT embryos as normal, these ANT blastocysts as normal embryos. And I would think they are a mass of differentiating cells, but they definitely lack the intricate organization of the embryo and its potential.

PREPARED STATEMENT

I want to emphasize that ANT is a modification, not an alternative, to nuclear transplantation. It requires additional manipulation of the donor cells that may complicate the logistics of an already complex procedure, and this has concerned many scientists. However, our procedure has shown that the procedure is so simple and straightforward that it may be acceptable as a requirement if it would resolve the ethical objections against somatic cell nuclear transfer and allow this research to go ahead.

[The statement follows:]

PREPARED STATEMENT OF DR. RUDOLF JAENISCH

Mr. Chairman and members of the Subcommittee, my name is Rudolf Jaenisch. I am a founding Member of the Whitehead Institute and Professor of Biology at MIT. Before coming to the Whitehead Institute I was the head of the Department of Tumor Virology at the Heinrich-Pette Institute of the University of Hamburg in Germany. I am privileged to have helped establish the field of transgenic science. Transgenic science deals with the transfer of genes to create mouse models of human disease. My present research focuses on epigenetic gene regulation, on embryonic stem cells, and on nuclear cloning. Our focus is understanding the mechanisms that bring about reprogramming of a somatic nucleus to an embryonic one after its transfer into the egg. I work with mice and our results have demonstrated that nuclear cloning is inefficient, that most clones die at an early embryonic stage and that the few that survive to birth and beyond harbor serious defects and are not normal. The conclusion from this work is that reproductive cloning of humans is an unsafe technology that should be banned.

Our work has shown that somatic cell nuclear transfer (SCNT) can generate "customized" embryonic stem cells that can be used for the treatment of genetic diseases. We have performed a "proof of principle" experiment in mice that carry a specific mutation which causes a defective immune system. Human patients with a corresponding mutation (designated as Severe Combined Immune Deficiency or SCID) are unable to fight infections and have a grim prognosis. In our proof of principle experiment the nuclei of SCID mouse skin cells were transplanted into enucleated eggs to generate cloned blastocysts (NT-blastocysts) that were then placed into tissue culture to derive "customized" cloned embryonic stem cells (NT-ES cells). The genetic mutation was corrected by gene targeting, the "repaired" NT-ES cells were then induced to differentiate into blood stem cells and, when transplanted back into the mutant mouse, restored immune function. I believe that this proof of principle

experiment is directly relevant for the treatment of human blood diseases such as thalassemia, sickle cell anemia or leukemia. The recent success by the Korean group (Hwang et al.) indicates that nuclear transfer in humans is more efficient than was assumed before and I believe that treatment of bone marrow diseases will likely be one of the first human diseases that will be treated with SCNT.

Embryonic stem cells have an enormous potential for therapy of debilitating diseases such as cancer, diabetes, Parkinson's or other degenerative diseases. To realize this therapeutic potential much research is needed to learn how to differentiate the embryonic cells into cells used for transplantation. I am confident that the possibility to derive new ES cell lines from IVF embryos as debated in Congress would enormously help this research.

I will focus on nuclear transfer (NT). In addition to its potential for customized therapy, nuclear transfer derived ES cells would be an extraordinary important tool to study complex diseases such as ALS or Alzheimers in the test tube since "customized" ES cells derived from a patient would carry all the genetic alterations that caused the disease in the patient. The exciting prospect is that differentiation of the ES cells in the culture dish may provide clues to what goes wrong with the cells and how to establish therapies. This is not a future promise but this could be done today using the technology established by the Korean group that was the first to successfully derive human stem cells from cloned blastocysts.

What are the concerns of those who oppose nuclear cloning in humans for the purpose of generating "customized" embryonic stem cells for research or for therapy? I believe the key concern is that the derivation of an embryonic stem cell would necessarily involve the destruction of the blastocyst and thus the destruction of potential human life. The crucial question is: does the cloned blastocyst really represent potential normal human life?

From all experience with cloned animals I would argue that the cloned blastocyst has little if any potential to develop into a normal baby as most would die in development and the few that survive will be abnormal and will develop severe defects with age. This is because reprogramming of the somatic cell's genome after nuclear transplantation is a faulty process causing the great majority of clones to have hundreds of genes incorrectly expressed. For these reasons it has been suggested that, because the cloned blastocyst is so different from the normal blastocyst derived from a fertilized egg, it should not be designated as an "embryo"—and I agree with this notion. However, the cloned blastocyst has some chance, an exceedingly small chance, to ever develop into a cloned animal such as Dolly. And Dolly died early because she suffered from major ailments due to faulty reprogramming as most if not all cloned animals do. It is this statistically small chance of a clone to develop to birth and beyond that troubles, I believe, those who are opposed to the NT technology.

The Altered Nuclear Transfer (ANT) approach has been proposed by Dr. Hurlbut from Stanford as a potential solution for the ethical dilemma. This approach would cause the product of nuclear transfer to be inherently unable to ever develop into a fetus or a baby, because of its inability to establish the very first step of embryonic organization and its inability to establish a fetal-maternal connection. With other words, the ANT procedure would reduce the statistically low chance of an NT blastocyst to develop to birth to zero. The procedure, as proposed by Hurlbut, involves the genetic manipulation of the donor skin cell with the goal to inactivate a gene that is required for embryo development if the nucleus of the manipulated cell would be transplanted into an enucleated egg as in SCNT. The manipulation would, however, have no ill effect on the derivation of embryonic stem cells from the product of SCNT. Thus, the alteration causes the somatic nucleus to function in such a way that no embryo is generated but embryonic stem cells can be produced. The goal of ANT is to generate a nuclear transfer product that lacks the essential attributes of an embryo and has no potential whatsoever to develop into a fetus but still could proliferate and give rise to embryonic stem cells. ANT was suggested last year as a thought experiment. We have now performed a proof of principle experiment in the mouse (published this week in Nature) that validates the proposal.

In our experiment an RNAi construct that inactivates the Cdx2 gene was introduced into skin cells. Cdx2 has a crucial function in the establishment of the first embryonic lineage, the trophectoderm that is established at the 16-cell stage and forms the placenta of the embryo. Skin cells normally do not express the Cdx2 gene. But when used as donors for nuclear transplantation, the ANT product is unable to activate the gene and therefore unable to establish the trophectoderm lineage. However, the product of nuclear transfer did proliferate and formed an abnormal NT-blastocyst. The normal blastocyst consists of the inner cell mass (which will form the embryo proper) and a cavity which is surrounded by trophectoderm cells (which will form part of the placenta). In contrast to the normal embryo, the ANT blasto-

cyst collapses because the trophectoderm cells are lacking. Importantly, when placed into tissue culture, the ANT blastocyst generates embryonic stem cells that have the full potential for differentiation and therapy and thus are indistinguishable from embryonic stem cells that are derived from a fertilized embryo.

Does the ANT procedure generate "embryos", even if only abnormal ones? Our experiments clearly show that the Cdx2 deficient blastocyst has no potential to implant and to ever develop into a fetus because it lacks the trophectoderm lineage that gives rise to the placenta. Cdx2 is activated at the 8-cell stage and activation of this key gene is prevented in the ANT product. Thus, the product of ANT-SCNT is already molecularly different from the normal embryo at the 8-cell stage and becomes morphologically abnormal within the next two cell divisions. The placenta is an integral part of the embryo and not some component that could be separated from the embryo. It is like the engine of a car: one cannot separate the engine from the car and still call it a car. Because the ANT product lacks essential properties of the fertilized embryo, it is not justified to call it an "embryo".

It is important to emphasize that ANT is not an alternative to nuclear transplantation but a modification of an experimentally highly demanding process. It requires additional manipulations of the donor cells that will complicate the logistics of an already complex procedure, and this has raised concerns among many scientists. Also, it has not been determined whether Cdx2 has a similar function on human placentation as in mouse. Because the effect of gene inhibition on human placentation cannot be directly tested, surrogate assays such as in vitro differentiation of human ES cells are required to assess the effect of CDX2 deficiency on human placental development. The experiments in mice have shown a proof of concept of the ANT procedure. It would be unfortunate, however, if the implementation of this approach would delay the research on human SCNT.

Senator SPECTER. Thank you very much, Dr. Jaenisch.

Our next witness is Dr. Steven Teitelbaum, Professor of Pathology at Washington University School of Medicine, an M.D. from Washington University, residency at New York University. Thank you very much for coming in today, Dr. Teitelbaum, and we are interested in hearing your testimony.

STATEMENT OF STEVEN TEITELBAUM, M.D., WILMA AND ROSWELL MESSING, PROFESSOR OF PATHOLOGY AND IMMUNOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Dr. TEITELBAUM. Mr. Chairman, I thank the committee for the honor of speaking to you today.

Mr. Chairman, I have been a physician scientist for more than 30 years. I have authored in excess of 300 scientific papers, and I am here to tell you that in my estimation we are facing a unique opportunity in the form of embryonic stem cell research to potentially alleviate the misery of our fellow Americans with a number of presently incurable diseases. But to get there, we must do the science.

Opponents of embryonic stem cell research often articulate their position as a contest between adult and embryonic stem cells. Mr. Chairman, this is not a contest between various types of stem cells. It is a contest between us as a society and disease. We should be moving forward on all fronts, adult, embryonic, and umbilical cord stem cells to win the battle. The tool is not important. What counts is curing our neighbors.

That said, because of their flexibility, embryonic stem cells hold more promise to ameliorate presently incurable diseases than any other approach. I stress the word "promise" because we are not there yet, and it is my belief that it will be some time before we are positioned to safely use these cells for therapy. But if scientists are prevented from exploring the biology of human embryonic stem cells, we will never get there.

Mr. Chairman, as you know, human embryonic stem cells can presently be obtained from two sources; namely, the spare products of in vitro fertilization, which ultimately would be destroyed, and by somatic cell nuclear transfer, also known as SCNT or therapeutic cloning. Although both approaches hold enormous therapeutic potential, I am particularly taken with the promise of SCNT because it may alleviate the major complication of tissue and cell transplantation, namely rejection and its attendant life-threatening consequences.

Mr. Chairman, I am a bone biologist and physician, and as such, I see many patients who have received organ and cell transplants. These patients typically develop severe osteoporosis and often have many fractures because of the harsh medications they must take to prevent rejection of their transplant. It is my hope that embryonic stem cells, generated by SCNT, which contain the transplant recipient's own DNA will reduce the necessity for these devastating anti-rejection drugs.

But, Mr. Chairman, my hopes for SCNT are more personal and harken back more than 20 years when I was a young assistant professor. At that time, I became interested in a genetic disease of the skeleton known as osteopetrosis, or marble bone disease, and I want to tell you a story about a child who profoundly impacted my life.

Osteopetrosis is a disease in which kids make too much bone. Consequently, their skulls become very thick and compress their brains and nerves, such as those leading to the eye. Bone also overgrows the bone marrow, preventing formation of blood cells. Until the story I am about to tell you, all kids with the malignant form of osteopetrosis developed fatal neurological complications, including blindness, and infections due to bone marrow suppression. These children invariably died in the first decade, most before the age of 5.

In the early 1980's, our team thought we had identified the abnormal cell causing osteopetrosis and concluded it resided in the bone marrow. We reasoned, therefore, that if we gave an osteopetrotic infant a bone marrow transplant which contains adult stem cells, we might cure the disease. We realized the enormous risk of rejection, so we waited until we had a perfect immunological match between the donor and recipient, in this instance the 3-month-old little girl you see in the top picture. So we gave this baby a bone marrow transplant and achieved the first cure of this disease. The middle panel shows her at 3 years of age, and the bottom picture, which is recent, was taken upon her graduation from college. Senators, being part of a team which was first to cure a fatal disease, particularly that of children, is a doctor's dream. It does not get any better.

You may be asking yourselves why this guy, who is here as an advocate of embryonic stem cell research, is telling us about his victory with adult stem cells. Senators, I am recounting the story to underscore the importance of moving forward on all fronts because, regrettably, there is a down side to my tale. You will remember that this was a perfect immunologic match, and therefore there was little chance of rejection. Unfortunately, such matches are extremely rare and therefore, we presently cure less than 10 percent

of kids with osteopetrosis. The use of SCNT, in which embryonic stem cells contain the patient's own DNA, if successful, would markedly increase the cure rate of this disease.

PREPARED STATEMENT

Mr. Chairman, because of my familiarity with osteopetrosis, I am frequently contacted by parents with afflicted children. I have to tell them that the chances of curing your child is no more than 10 percent. I want to tell them it is greater than 90 percent. SCNT, if we pursue it, may get us there.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. STEVEN TEITELBAUM

Thank you Mr. Chairman. My name is Steven Teitelbaum. I'm the Wilma and Roswell Messing Professor of Pathology and Immunology at Washington University School of Medicine and I thank the committee for the honor of speaking to you today.

Mr. Chairman, I've been a physician-scientist for more than 30 years. I've authored in excess of 300 scientific papers and I'm here to tell you that, in my estimation, we are facing a unique opportunity in the form of embryonic stem cell research, to potentially alleviate the misery of our fellow Americans with a number of presently incurable diseases. But to get there, we must do the science.

Opponents of human embryonic stem cell research often articulate their position as a contest between adult an embryonic stem cells. Mr. Chairman, this is not a contest between various types of stem cells. It is a contest between us as a society and disease. We should be moving forward on all fronts, adult, embryonic and umbilical cord stem cells, to win the battle. The tool is not important. What counts is curing our neighbors.

That said, because of their flexibility, embryonic stem cells hold more promise to ameliorate presently incurable diseases than any other approach. I stress the word "promise" because we are not there yet and it is my belief that it will be some time before we are positioned to safely use these cells for therapy. But if scientists are prevented from exploring the biology of human embryonic stem cells, we will never get there.

Mr. Chairman, as you know, human embryonic stem cells can presently be obtained from two sources, namely the spare products of in vitro fertilization, which ultimately would be destroyed, and by somatic cell nuclear transfer, also known as SCNT or therapeutic cloning. Although both approaches hold enormous therapeutic potential, I'm particularly taken with the promise of SCNT because it may alleviate the major complication of tissue and cell transplantation, namely rejection and its attendant life threatening consequences.

Mr. Chairman, I'm a bone biologist and physician and as such I see many patients who have received organ and cell transplants. These patients typically develop severe osteoporosis and often have many fractures because of the harsh medications they must take to prevent rejection of their transplant. It is my hope that embryonic stem cells, generated by SCNT, which contain the transplant recipient's own DNA, will reduce the necessity for these devastating anti-rejection drugs.

But Mr. Chairman, my hopes for SCNT are more personal and hearken back more than 20 years when I was a young assistant professor. At that time I became interested in a genetic disease of the skeleton known as osteopetrosis or marble bone disease and I want to tell you a story about an afflicted child who profoundly impacted my life. Osteopetrosis is a disease in which kids make too much bone. Consequently, their skulls become very thick and compress their brains and nerves, such as those leading to the eye. Bone also overgrows the bone marrow preventing formation of blood cells. Until the story I'm about to tell you, all kids with the malignant form of osteopetrosis developed fatal neurological complications, including blindness, and infections due to bone marrow suppression. These children invariably died in the first decade, most before the age of five.

In the early 80s, our team thought we had identified the abnormal cell causing osteopetrosis and concluded it resided in the bone marrow. We reasoned, therefore, that if we gave an osteopetrotic infant a bone marrow transplant, which contains adult stem cells, we might cure the disease. We realized the enormous risk of rejection so we waited until we had a perfect immunological match between the donor

and recipient, in this case a 3 month old little girl you see in the top picture. So we gave this baby a bone marrow transplant and achieved the first cure of this disease. The middle panel shows her at 3 years of age and the bottom picture, which is recent, was taken upon her graduation from college. Senators, being part of a team which is first to cure a fatal disease, particularly of children, is a doctor's dream. It doesn't get any better.

You may be asking yourselves why this guy, who is here as an advocate of embryonic stem cell research, is telling us about his victory with adult stem cells. Senators, I'm recounting the story to underscore the importance of moving forward on all fronts because regrettably there is a downside to my tale. You'll remember that this was a perfect immunological match and therefore there was little chance of rejection. Unfortunately, such matches are extremely rare and therefore we presently cure less than 10 percent of kids with osteopetrosis. The use of SCNT, in which embryonic stem cells contain the patient's own DNA, if successful, would markedly increase the cure rate of this disease. Mr. Chairman, because of my familiarity with osteopetrosis I'm frequently contacted by parents with afflicted children. I have to tell them the chances of curing your child is no more than 10 percent. I want to tell them it's greater than 90 percent. SCNT, if we pursue it, may get us there.

Senator SPECTER. Thank you very much, Dr. Teitelbaum.

Our final witness is Dr. John Wagner, Professor of Pediatrics and Scientific Director of the Stem Cell Institute at the University of Minnesota. An M.D. at Jefferson Medical College in Philadelphia and internship and residency at Duke University School of Medicine. Thank you for coming to Washington today, Dr. Wagner, and we look forward to your testimony.

STATEMENT OF JOHN WAGNER, M.D., SCIENTIFIC DIRECTOR OF CLINICAL RESEARCH, BLOOD AND MARROW TRANSPLANT PROGRAM AND STEM CELL INSTITUTE

Dr. WAGNER. Mr. Chairman and committee members, I am coming here as a clinician, as a stem cell researcher. It is not a question of whether or not this knowledge is going to be translated into something clinically useful. The real question is, when is that going to happen?

The work should not be restricted to private industry. Stem cell research should be taking place in academic institutions, supported by Federal dollars with guaranteed oversight, peer review, and transparency.

Right now, as we have heard already in testimony this morning, there is only one proven use of stem cells and that is in the context of blood and marrow transplantation to treat diseases like leukemia, lymphoma, sickle cell disease, and a variety of other blood and immune disorders. In these instances, we need to infuse stem cells to repair the marrow that has been destroyed either by the disease itself or by the therapy we use to treat that disease, such as with chemotherapy and irradiation. These blood-producing stem cells are found in marrow and they are found in cord blood, which is the blood that is left in the placenta after a baby is born.

Tremendous achievements have already been made in these areas, particularly in the area of cord blood most recently, and in fact, the Institute of Medicine last April made recommendations that we significantly augment the Nation's inventory of cord blood to help take care of our patients around the country.

While my own work is focused on the development of stem cell therapies from cord blood or adult tissues and, perhaps surprisingly, not embryonic stem cells, I am here today really to defend ES cell work. It must be unequivocally clear that our work in cord blood and adult stem cells does not eliminate the need for work in

ES cells. Yes, it is true that stem cells and cord blood and adult tissues can differentiate into perhaps the lining cells of the gut or the liver or neural tissue, but they do not exhibit all the capacities of ES cells. For example, we have yet to see stem cells from cord blood or adult tissues differentiate into heart muscle that spontaneously beats in the petri dish. That has been shown repetitively by people working on ES cells.

The University of Minnesota is well known for its work in adult stem cells in umbilical cord blood, and with Catherine Verfaille, we have pioneered that work in cord blood and multipotent adult stem cells and we see great promise in those areas. But we recognize, although there is tremendous potential, there are also limitations.

It is critical that you also know that every discovery that has occurred with ES cells has really benefitted us working on adult stem cells and cord blood.

But speaking as a clinician who creates these new stem cell therapies for treating children and adults with a variety of "incurable" diseases, it not only gives us significant hope, but it also comes with risk. This winter we hope to be able to try our first stem cell transplants in the treatment of patients damaged by chemotherapy and irradiation, not just for bone marrow recovery, but also the other tissues that are involved in the treatment and damaged by it. We have to go through the ethics committees, we have to go through human subjects committee, and the FDA. But we are going to move this therapy forward, obvious, with all the proper oversight.

But it is incomprehensible that we do otherwise, that we restrict ourselves to one type of stem cell. Like others in this room, I feel compelled to move this forward on behalf of the thousands of patients that write to me every week asking to allow them to be the first stem cell recipient. In fact, this is just one e-mail that I received yesterday from a woman who is 39 years old saying, I had a stroke several years ago. What can you do for me? Let me be the first. Why can I not be a healthy wife to my husband, a mother to my young child?

Is this all hype? Where are the first trials with ES cells? Certainly the lack of funding and restricted access to suitable stem cell lines has been a major barrier in our research efforts. We need to address those barriers where possible. For example, can we separate reproductive cloning from nuclear transfer? If you desire rapid translation of ES cells into real clinical therapies, let us not restrict it. We need to be able to use nuclear transfer because it is likely to be instrumental in moving that therapy forward as quickly as possible.

Again, this is not some scientist's dream. It has been done with human cells, at least in South Korea. 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, and you can ask Mr. Herrera and you can ask Ms. Carolyn Kohn, who is in the audience, who had a child die of aplastic anemia.

Cord blood certainly has its proven benefits in the treatment of a variety of diseases. It has great potential perhaps in the future for tissue repair that yet has clearly to be identified. Federal dol-

lars should be devoted to the work of all these stem cell sources, including ES cells. ES cell work must continue in parallel.

PREPARED STATEMENT

As a clinician that treats these patients who are defined as incurable, I feel obligated to be here on their behalf. I am sure that many of them are anxiously waiting to hear what happens today. For them, the stakes must be simply unimaginable.

[The statement follows:]

PREPARED STATEMENT OF DR. JOHN E. WAGNER

Stem cell therapy will revolutionize the practice of medicine. For the first time there will be treatments for spinal cord injury, diabetes, cancer, stroke, and heart disease with potentially long term benefits. The proof of principle already exists.

It is not a question of whether this new knowledge will translate' into clinical therapies but rather how long. Will clinical trials in diabetes or stroke be soon or decades away? Will this work be driven by private industry without any oversight or in academic environments using federal support; conducted in university settings which guarantee requisite oversight, publication, peer review and transparency?

So what do we know about stem cells today?

There is only one proven established use of stem cells and that is in the setting of bone marrow transplantation. For decades it has been known that marrow stem cells can be transplanted from one individual to another in order to replace the blood and marrow of patients with leukemia/lymphoma/multiple myeloma/other diseases after their own marrow has been destroyed by disease or treatment with high doses of chemotherapy and radiation. These stem cells come from adult marrow or umbilical cord blood.

My own work is focused on umbilical cord blood and development of novel phase I clinical trials. In this discussion, we cannot forget that cord blood is already an established treatment with tremendous potential. Recently, the Institute of Medicine summarized its findings on the benefits of cord blood and the urgent need to expand the useable inventory. Cord blood is rapidly becoming the standard of care in children. We have recently reported outcomes in adults with results that are unprecedented. However, it must be clear that cord blood stem cells are not the stem cells found in embryonic stem cell lines. The stem cells in adult tissues and umbilical cord blood have different properties and may or may not have unlimited differentiation capacity. While it is hoped that one day we will be able to take adult tissue or cord blood stem cells and trick it to become "ES-like", this is not yet possible. Despite what the opponents to ES cell work would suggest, it is simply not true.

The University of Minnesota is well known in the field of stem cell research. We have the longest standing Stem Cell Institute in the country. My work in umbilical cord blood stem cell research and Catherine Verfaillie's work on the multipotent adult stem cell clearly demonstrate our hope to maximize the potential of cord blood and adult tissue stem cells but we recognize that there are limitations. Of course we are excited about the future potential of these stem cells but never have we suggested that they obviate the need for ES cell research. For example, never have the stem cells from cord blood or adult tissues ever produced heart muscle cells that spontaneously beat or formed islets that secrete insulin, as has been shown repeatedly with ES.

It is critical for the public to know that if we are ever to make cord blood and adult tissue stem cells function like ES cells, we need to study ES cells. Every discovery with ES cells has furthered our work with stem cells from umbilical cord blood or adult tissues.

Now speaking as a clinician who actually performs new therapies with stems cells in humans, we are indeed planning to perform the first clinical trial with multipotent adult stem cells this winter in an attempt to repair tissues damaged by radiation and chemotherapy. My goal is to move stem cell therapy forward in numerous areas as the clinical director of the Stem Cell Institute. Once we meet the requirements of the Human Subjects Committee, FDA, Ethics committees, we plan to move stem cell therapies forward regardless of whether they are ES, cord blood or adult tissue-derived. It is incomprehensible to do otherwise. Like others, I receive thousands of letters, emails, phone calls per month asking me to allow them to be the first to receive stem cell treatments—these people have cancer, spinal cord injury,

diabetes, strokes, Parkinson's disease, and other genetic diseases. (Show sample emails from this week).

You ask, what is the future of ES cells to cure a disease—the answer is simply "breathtaking". Clearly there are risks as ES cells if left undifferentiated have a propensity to cause tumors. But still, many are working to make these cells therapeutically valuable. In addition to the development of novel strategies for treating Parkinson's, diabetes, stroke and spinal cord injury, some like Daniel Kaufman at the University of Minnesota are focused on manufacturing red blood cells in massive scale thus reducing our dependence upon volunteer donors or developing nature killer cells as anticancer agents-both derived from ES cells. So why has there not been a single trial thus far with ES cell—funding, access to suitable cells lines, and research on the immune response to these stem cells. Nuclear transfer will be crucial to this success—"tailor made" stem cells lines for individuals will be required to counter likely immune responses. Again, this is not futuristic, the South Korean scientists have clearly demonstrated that this is not just desirable but possible.

To restrict work with ES cells or bar SCNT would cripple our capacity to move all stem cell therapies forward ES cells are the gold standard and research with them will maximize the potential of cord blood and adult stem cells and pursuit of multiple approaches will permit the most rapid translation of stem cells possible into efficacious clinical therapies. Every single one of us will be faced with a child, friend, loved one, or even ourselves with a disease amenable to stem cell therapy in the not too distance future. Umbilical cord blood has proven benefits in the treatment of leukemia, lymphoma, blood disorders, immune deficiencies and metabolic diseases today. Banking of cord blood is in the nation's interest and federal dollars should continue to be spent to determine the breadth of what it can offer well beyond the confines of blood and marrow diseases. At the same time in parallel, we must also push ES and adult stem cells to the limits of what they can offer. And for ES cells, banning SCNT could prevent its future success as SCNT is likely to be the key that will make ES cell therapies more widely available more rapidly. I am here as an advocate for the thousands of people who have asked me to push this forward.

Senator SPECTER. Thank you very much, Dr. Wagner.

Mr. Herrera, you have testified about your situation being a medical breakthrough in medical history. Was the aspect of using stem cells on your lymphoma the unique breakthrough that you referred to?

Mr. HERRERA. Without question. The difference between the first transplant and the second transplant was at the first transplant, they took stem cells out of my body. I injected myself with a drug called Neupogen every day. This causes the bone marrow to overproduce. Little baby stem cells are floating around in the blood. They stick a pipe in here, run it through a machine, and they take out the little baby stem cells.

The problem with that transplant for mantle cell lymphoma, which they were not aware of at the time, was this is my immune system.

So the theory of the allogeneic stem cell transplant—I go back to my Mississippi roots—we are having civil disorder in Wiggins, Mississippi, so we call out the Stone County National Guard. I am told not to let anybody cross this line. Winfield Alexander wants to cross the line. I cannot stick Winfield in the gut with a bayonet because he was my Boy Scout leader in the rattlesnake patrol. But if you bring in the National Guard from Montana, they speak the same language, they can read the signs, and they are not going to have a problem sticking Winfield with a bayonet. So the foreign immune system is going to be tougher on the lymphoma, on the blood cancer, because it does not know it that well. That is kind of a basic comment, but that is how I had to understand it.

Senator SPECTER. Thank you, Mr. Herrera.

I very much regret that I am going to have excuse myself at this point. I turn the gavel over to Senator Cochran.

What I would appreciate your doing, each of you, is to write a memo or a letter to the subcommittee as to what you could do if Federal funding were available for your stem cell research. Dr. Gasson is from UCLA where I visited several years ago. Without the particulars at hand, I know UCLA is the beneficiary of very substantial NIH grants.

This subcommittee, Senator Harkin, Senator Cochran, and then the full committee has taken the lead in increasing Federal funding from $12 billion to $28 billion. And we are now on the cutting edge.

Dr. Wagner, you talked about use of Federal funds.

I regret that there are not more Senators available, but this is the third time it will be said. This is a very, very busy place, but your testimony is transcribed. Staff are here and Senators will review it. If you would supplement what you have testified to, Dr. Teitelbaum, Dr. Jaenisch, Dr. Wagner, Dr. Gasson, with what the Federal funding could do. We are going to have a vote on this one day soon, without going into all the technicalities. And the evidence that you will present will be very helpful when we fight it out on the Senate floor. Things are quiet here today, but we are going to have a pretty heavy debate on this subject and your participation and your evidence will be very, very helpful in achieving a very, very important goal for medical science.

Senator Cochran, let me thank you for taking the gavel. It belongs to you anyway.

Senator COCHRAN [presiding]. Thank you for your patience with our change of command and responsibility.

I appreciate so much each of your efforts to be here today, to take time to prepare a presentation for our committee so that we can better understand the challenges and the responsibilities that we have for identifying ways that we can continue to support medical research, to take those actions that will help find cures for diseases, prevent diseases. So this is all very serious business, and I appreciate very much the fact that you have taken time and devoted your efforts and energies to this hearing today.

Senator Specter, as I said in my opening comments, has been a champion for medical research, and the figures that he cites, the increase in the funding that we have been able to provide or to recommend—we do not get to decide. We recommend to the full committee. The full committee approves and recommends to the Senate, and we have to work out differences between the Senate and the House. But it has been a successful campaign to more than double the amount of money that is available for researchers and those providing treatment in our battle to find cures and to prevent disease, particularly cancer.

Let me ask a few questions. I understand, Dr. Teitelbaum, you are at the Washington University School of Medicine and have completed a residency at New York University. Let me ask you. What would you say is the overwhelming opinion of scientists regarding the need to expand the current stem cell policy? Is there any disagreement within the community?

Dr. TEITELBAUM. I think not, Senator. I think that the overwhelming opinion of scientists is to move forward on all fronts, that

there is potential in adult stem cell research, embryonic stem cell research, and umbilical cord blood stem cell research. We cannot determine which technique will yield what results until we do the science.

Senator COCHRAN. Dr. Gasson, I heard your comments, before I had to step out of the hearing room, in your opening statements. What forms of cancer do you think will be the most responsive to drugs developed using stem cells?

Dr. GASSON. We believe that those types of cancer that have been shown experimentally to be derived from a mutated adult stem cell would be the very best targets for those small molecules. Fortunately or unfortunately for us, they include some of the most common forms of cancer, such as breast cancer, prostate, colon, some of the leukemias, and as you are probably quite well aware, brain tumors which are truly devastating.

We think that the concept of the cancer stem cell explains a lot about the natural history of the disease. The patient develops cancer and is treated with surgery, radiation, perhaps chemotherapy, and the bulk of the tumor, the large mass of the tumor goes away. But for some patients over the next 2, 3, 4, or 5 years, the tumor comes back and the tumor that recurs is typically even more aggressive. And we think this is because the treatments that we have now do not kill the tumor stem cell, and so slowly it begins to divide and it recreates the tumor cells in the patient. And now those cells are even more resistant to the treatments that we have. So until and unless we are able to either destroy the cancer stem cell, or at least keep it under control, we will be continuing to face the possibility of recurrence in these very common and very deadly cancers.

Senator COCHRAN. Dr. Jaenisch, there was some indication in a Washington Post article that the altered nuclear transplantation technique that your lab has achieved may be a way around the objections of some who oppose embryonic stem cell research. Would you have pursued this line of research if not for the restrictions in place on stem cell research?

Dr. JAENISCH. I think our research had two goals. One is a scientific one. We wanted to see whether these cells can do what we thought they could do. But I think the major goal was to find a potential compromise which could compromise between the concerns of those who object to the nuclear transfer procedure and those who think that is really important to do.

So I think the altered nuclear transfer procedure is a modification of the nuclear transfer procedure. It is an additional step which complicates an already complex procedure. But from our experience with mice at least, it is such a straightforward and simple modification that it may be acceptable as a compromise if that would allow then this research to go on and to provide the funding for this type of research.

Senator COCHRAN. Is the kind of research you are doing susceptible to funding by the National Institutes of Health?

Dr. JAENISCH. All my research is funded by the National Institutes of Health, but I work with mice, so it is not controversial. But we would like to move into human cells. We would like to work with the new human stem cells. We would like to understand how

the human cells compare with the mouse cells, and we are very limited. We do not have funding for that.

Senator COCHRAN. Well, do you think that Federal funding should be diverted from other forms of stem cell research to support alternative methods to derive stem cells?

Dr. JAENISCH. Well, I am not sure if it should be diverted. As was said by all the speakers here, we really need to pursue all these avenues. So alternative methods—several have been proposed.

I think the final goal of the field in my opinion is to understand what reprogramming means. How does the egg reprogram a somatic nucleus and eventually do it without the egg. In order to get there, we need the egg. We need human eggs to learn how the human egg does reprogramming. So I think it is counterproductive for this goal at this point that research is not allowed to use human eggs.

Senator COCHRAN. Anthony, I am so pleased that you were able to be here today to put in perspective from a patient's point of view how important research in the development of new treatments, finding new ways of dealing with these medical problems will be, and the role that we can play. I know if you had a vote, you would probably vote to quadruple, double, exponentially increase funding.

But where in the area of research from your experience do we need to supplement and try to provide more incentives through Federal research appropriations to achieve the goals of curing cancers like yours?

Mr. HERRERA. What these ladies and gentlemen up here have said is that there should be massive amounts, billions of dollars, and no restrictions on any of this research because I have met with the doctor at M.D. Anderson—Andreyev I believe is his name—and we were talking about the embryonic versus the adult. He said we need lots of room to experiment.

The drug that helped save my life, which has probably saved hundreds of thousands of lives, Neupogen, was developed by Janice Gabrilove and two other doctors. She was in charge of my first bone marrow transplant. I said, how did you develop this drug? She said we did not have a straight line. We were in there in that region working, and all of a sudden there was a path we could follow.

So there needs to be no restriction. There needs to be massive amounts of money. South Korea, Singapore 2 years ago were ahead of us. China just put billions of dollars into research. So there should be no restrictions and massive amounts of money put behind this in my opinion.

Senator COCHRAN. From your experience, could you tell us in your own words what the difference is from a patient's point of view in a bone marrow transplant therapy and a stem cell transplant therapy?

Mr. HERRERA. Actually—someone please correct me if I am wrong—they are the same thing except the way you get the cell. The reason it is called a bone marrow transplant is before this drug Neupogen and before the apheresis machine, they had to drill into the bone marrow to suck out marrow and then get the stem cell out of that. Am I correct on that? So it evolved into simply being

called the stem cell transplant. Some hospitals still drill into the bone and suck out the marrow to get the stem cell, but they are ultimately the same thing.

Senator COCHRAN. It does not sound like much fun.

Mr. HERRERA. There was not a lot of fun through the whole process, Senator.

Senator COCHRAN. I can remember reading your description of the pain that you suffered in that first effort to get some of your bone marrow. No anesthetic.

Mr. HERRERA. That was not good medicine.

Senator COCHRAN. I hope that is not a widespread practice now.

Mr. HERRERA. I have learned that it is not.

Senator COCHRAN. Good.

Dr. Wagner, we appreciate your being here as well. Since your primary interest appears to be cord blood stem cell research, as I understand it, why are you so supportive of embryonic stem cell and nuclear transplantation research?

Dr. WAGNER. My interest is, obviously, in cord blood as one avenue. As the clinical director of the Stem Cell Institute, I am really interested in all aspects of stem cell therapies, whether it comes from embryonic stem cells, adult tissues, or umbilical cord blood. So we are exploring all avenues.

However, my own personal research area in the laboratory is with umbilical cord blood and trying to figure out what really the breadth of applicability will be. So we are investigating not only in the context of classical bone marrow transplantation, which has proven to be of great use, but also looking at what its differentiation potential is, can it differentiate into various tissues.

But remember that what we said over and over again is that ES cells are the gold standard by which everything is compared. And everything that we have learned with embryonic stem cells, in terms of the mechanisms of what makes them able to become liver or lung or brain, or whatever it is, has given us clues or techniques that allow us to see if we can get adult tissues or cord blood tissues to do the same thing. So without having that research move forward with embryonic stem cells, we have no hope to make adult tissues or cord blood stem cells become you would all like it to become as the stem cell source.

Senator COCHRAN. Does it surprise you that the NCI funds less than $5 million worth of embryonic stem cell research? And why do you think the level of stem cell research is so low in the context of a $5 billion budget?

Dr. WAGNER. You are asking my opinion now.

Senator COCHRAN. Yes.

Dr. WAGNER. Well, clearly, I think the reason why the budget is so low is, in part, related to the ethical issues associated with embryonic stem cell work. However, there is considerable funding for adult tissue stem cells, as well as umbilical cord blood. However, what we need to be doing is working on embryonic stem cells. Unfortunately, the budget is low and it has actually been extraordinarily restrictive in what we are able to do.

Right now as the clinician that hopes to move some of these cell therapies forward, we have no hope of using the existing stem cell lines that are currently approved because of the fact that many of

them were developed on murine feeder layers or they have cytogenetic abnormalities having been passaged in a culture. And as someone who manufactures cells for clinical use, they would never fulfill our criteria. So certainly we need to markedly expand the amount of resources or else we will never be able to move it forward.

Senator COCHRAN. Dr. Gasson, you also lead an NCI-designated comprehensive cancer center and support research on embryonic stem cells. Do you have an opinion about the disparity in terms of the $5 million for stem cell research compared with a $5 billion budget?

Dr. GASSON. I have two additional thoughts to add to Dr. Wagner's comments.

First of all, this notion that cancer arises from a cancer stem cell is fairly new. If you are trying to study the cancer stem cell, that is an adult stem cell, and so that particular type of work has just recently been done and probably would not be counted under the rubric of embryonic stem cell research.

But the main reason is the reason that Dr. Jaenisch articulated, which is most of the people that are trying to work in this field are working with mouse ES cells and mouse models because of the restrictions on the use of human ES cells. And Dr. Jaenisch is a perfect example. These people are extraordinarily talented. They have devoted their careers to understanding these things. If we could channel them from the mouse to working on human ES cells, we could accelerate the pace of progress enormously. So it is a follow-up on Dr. Wagner's answer, which is that the restrictions are pushing people to work in the mouse system.

CONCLUSION OF HEARING

Senator COCHRAN. Let me thank all of you for your generous contribution of time and effort to this hearing. We appreciate it very much, and I am sure we will benefit from your observations and your wisdom as we proceed through the appropriations process for writing a bill that actually is going to come to the floor next week possibly. This will be the last appropriations bill considered by the Senate this year. So we want to be sure we have our facts and arguments available to describe the reasons why we think funding of additional medical research is so important to the future of our country and mankind. Thank you for the contribution you have made to that effort.

The hearing is recessed.

[Whereupon, at 10:31 a.m., Wednesday, October 19, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

○