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STEM CELL SCIENCE: THE FOUNDATION FOR FUTURE CURES

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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STEM CELL SCIENCE: THE FOUNDATION FOR FUTURE CURES

THURSDAY, MAY 8, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2322 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (chairman) presiding.

Members present: Representatives Pallone, Waxman, Towns, Green, DeGette, Capps, Baldwin, Dingell (ex officio), Deal, Hall, Pitts, Ferguson, Myrick, Sullivan, Murphy, Burgess, Blackburn, and Barton (ex officio).

Staff present: Jessica McNiece, Katherine Martin, Melissa Sidman, Chad Grant, and Robert Clark.

Mr. PALLONE. I call the meeting of the subcommittee to order.

First of all, let me say good morning to everybody, and explain that today the subcommittee is meeting to hear about stem cell science and the potential it holds, and I will recognize myself for an opening statement initially.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. In terms of the potential for stem cell science to develop new treatments, therapies, and cures for a myriad of diseases, conditions, and disabilities, there is obviously a lot of potential and could impact so many people in their lives. There are few areas of scientific inquiry that hold the same level of promise to revolutionize the practice of medicine. Stem cells offer the possibility of replacing damaged or diseased cells inside the body with healthy ones. They could make it possible to strengthen failing heart muscle, regenerate severed spinal cord nerves, replace damaged brain cells, and cure many other currently incurable disorders.

Through my service on the subcommittee, I have had the opportunity to meet and hear from people from communities across the country and they have come to share their stories or the stories of their loved ones; just as an example, a young child with diabetes who requires daily medical attention, an adult who has left her job to care for a father whose mind has been ravaged by the effects of Alzheimer's disease, a husband who watched his wife's motor function deteriorate with the onset of Parkinson's disease. Their stories

vary tremendously and range from the heartbreaking to the harrowing yet they all share one common theme, and that is the message of hope, hope that someday stem cell research will unlock the door and reveal a new discovery that will cure them of their ailments.

I believe it is our obligation as legislators to enact a Federal policy that will help advance all types of stem cell research and provide the opportunity for such discoveries to take place. Unfortunately, the current Federal policy on stem cell research is falling short of that goal. The President's 2001 Executive order limits the use of Federal funds for research on the few lines of stem cells that had already been harvested. At the time he said that, stem cell research offered great promise. Almost 7 years later, it is clear to me that the President's policy has placed arbitrary constraints on stem cell research and has put patients in great peril.

Since the President issued his Executive order, we have undoubtedly lost valuable time and resources that could have been devoted to advancing stem cell research. While there have been important advancements in certain fields such as stem cells harvested from cord blood and adult stem cells, the scientific community appears to be in agreement that it is embryonic stem cell research that holds the greatest promise for the development of new cures and treatments. Unfortunately, the Administration's current policy on embryonic stem cell research has tied the hands of researchers, impeding scientific progress and inhibiting America's ability to compete with scientists around the world. Thankfully, the private sector and individual States have decided to forge ahead, paving the way without any Federal funding.

In 2005, my home State of New Jersey became the first State to provide for the public funding of embryonic stem cell research. Since then, plans for construction have begun on a new state-of-the-art facility that will house the Stem Cell Institute of New Jersey, a joint initiative undertaken by the University of Medicine and Dentistry of New Jersey and Rutgers, the State University of New Jersey, and I want to welcome Dr. Bertino, the interim director of the Stem Cell Institute of New Jersey, who will be testifying on our second panel today.

But New Jersey is not the only State taking the lead. A number of other States have either enacted their own measures that would fund various forms of stem cell research or have bills pending before their legislatures. While I am thankful for these efforts, I believe that in order to truly propel the advancement of stem cell research, we need a Federal policy that builds upon the advancements being funded in the private sector and at the State level.

Last year, the House and Senate passed such a policy with overwhelming bipartisan majorities. The Stem Cell Research Enhancement Act, sponsored by Ms. DeGette, would have allowed Federal funding for stem cell research to be conducted on embryos that would otherwise have been discarded from fertility clinics and with the consent of the embryos' donors. Unfortunately, this commonsense policy was met swiftly with the President's veto pen, the very first of his presidency. I know this is a controversial issue for many Americans, including many members who serve on this subcommittee, and I can respect that. However, I still have trouble un-

derstanding the opposition that exists to such a commonsense approach that would allow for the progression of stem cell science in what I view as a careful, ethical, and respectful fashion.

The fact is that Americans want stem cell science to advance. An overwhelming majority of Americans support embryonic stem cell research and their representatives in Congress do so as well, and they want us as legislators to do everything we can to help unlock the potential of embryonic stem cells in the quickest fashion possible and bring new life-saving therapies to the patients who need them.

With millions of Americans dying each year from diseases that might be cured by stem cell therapies, we can't wait any longer. The time has come to enact a new Federal policy, and I know that Ms. DeGette in particular is concerned about that. She asked that we have this hearing today.

Mr. PALLONE. I now recognize our ranking member, Mr. Deal, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. NATHAN DEAL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. DEAL. Thank you, Mr. Chairman.

With individuals with degenerative life-altering diseases or life-changing events resulting in paralysis, the possibilities presented by embryonic stem cell research represent a glimmer of hope to heal a loved one or reverse the damage caused by debilitating disease. For others, this issue seems just as personal as they struggle to reconcile the possibilities presented by research and science with their own personal convictions about the sanctity of any human life. It is at this intersection where we find ourselves this morning. My hope is that we could explore the possibilities presented by all types of stem cell research and willingly confront the ethical and scientific questions raised by this issue.

To my knowledge, adult stem cell research, which does not raise the ethical questions surrounding the destruction of a human embryo, has resulted in many new and exciting discoveries. I would hope that our witnesses could further elaborate on the potential of research conducted with adult stem cells and other cells that are capable of producing all or almost all of the cell types of the developing body. We must consider whether we should be taking funding away from the areas of research which have been proven to work and the promising adult stem cell therapies which have already improved patient health. Specifically, I hope our witnesses can tell us about the existing track record of adult stem cell research as compared to embryonic stem cell research.

I think the question we should be trying to answer here is whether or not there is a middle ground which allows scientists to continue their cutting-edge research while respecting the sanctity of every human life. Hopefully our witnesses today can describe the variety of research being done with all types of stem cells today. It would be very useful to learn more about the future of embryonic stem cell research and the time frame in which researchers expect to develop these treatments, which are often cited by supporters of embryonic stem cell research.

I think this should be a good hearing on the issue and certainly one that warrants our complete attention, and I thank all of our witnesses for coming and I look forward to your testimony. I yield back.

Mr. PALLONE. I yield 5 minutes to the gentleman from California—I am sorry—3 minutes to Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman, for recognizing me and for holding this hearing today.

Stem cell research is truly exciting scientific research. Stem cells, both embryonic and adult, hold great potential. For example, we will hear today about how adult stem cells may be used to treat potentially deadly heart conditions and embryonic cells have the potential to become any cell in the body. There is great hope that these cells will help us understand more about such devastating diseases as Parkinson's and diabetes and perhaps some day lead to treatments. And in a fascinating advance announced last year, several labs have been able to reprogram adult cells to develop into multiple kinds of cells, much as embryonic stem cells can.

What I think will become clear as we hear from scientific experts today is it doesn't make any sense to pit one type of stem cell research against another. Each line of research holds distinct promise. They function differently as research models and may function differently as potential routes to therapies. It makes sense to encourage the growth of all of these types of research, not to sit here and argue about which is more promising than another and why.

Unfortunately, all too frequently, discussions of stem cell issues are based more on politics than on science. As we have seen in too many areas, from stacked advisory committees to the deletion of accurate scientific information from government Web sites, the science around stem cells has at times been distorted to justify a particular political or ethical view. We are given inaccurate accounts of the availability of embryonic stem cell lines derived from the President's moratorium and in certain cases, misleading claims about adult stem cells have been used to argue that there is no scientific need whatsoever for embryonic stem cell research. Of course, ethical, political, and other considerations affect policy decisions, but distorting science is wrong.

I think we are going to hear from a number of experts who will tell us that there is a consensus among scientists that we should support embryonic stem cell research. New methods of creating stem cells are promising. Without funding embryonic stem cell research, we are guaranteed to learn nothing from it. We will leave the field behind in the United States and we will lose the opportunity to develop a meaningful Federal framework of oversight and ethical guidelines.

I hope today's hearing creates a better understanding in Congress and America of why support for all kinds of stem cell research continues to be so important.

Mr. PALLONE. Thank you, Mr. Waxman.

Mr. Pitts.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. Thank you, Mr. Chairman. I would like to thank you for convening this hearing today to discuss the future of stem cells, and I am grateful for this rare platform to highlight the incredible developments in stem cell research that are being used to successfully treat people for several dozen different conditions. These conditions include heart disease, juvenile diabetes, Parkinson's, liver failure, lupus, sickle cell anemia, and spinal cord injuries to name a few.

Over the last decade, there has been contentious debate over the issue of taxpayer funding for stem cell research that results in the destruction of a human embryo. At the center of this debate has been the hope for treatment and cures for patients across the world who suffer from a host of different diseases. So I would like to talk about just that, the patients.

We have here on the left a picture of three patients. The first one here on the left is Amy Daniels. Amy was diagnosed with systemic scleroderma, a rare autoimmune disease that affects connective tissue in the body. Next to Amy is Barry Gowdy, who suffered from multiple sclerosis. And last is Joe Rosen, a patient with antiphospholipid syndrome, an autoimmune disorder that causes blood clots. These three patients endured vastly different experiences but share two things in common. First, all three of them had lost hope that they could ever live a normal life, and second, all three of them found hope in the form of adult stem cell treatments, which have successfully mitigated their symptoms.

Another patient is seated here with us today. In 2003, Carol Franz was diagnosed with multiple myeloma. Myeloma is a blood cancer that eats away at the bones. X-rays of Carol's bones made them look like target practice. Faced with the daunting fears of a deadly form of cancer, Carol found hope as she was told about a treatment that could help her by using her own stem cells, and now Carol sits before us having survived two bouts with cancer after receiving two stem cell transplants, and she wears a bright green tee shirt that says "Survivor: adult stem cell transplant." And this mantra is based not on ideology but on science. It is based on what works. It is based on what saved Carol's life twice. Adult stem cells are doing what we have all hoped for and wished for: they are successfully treating patients.

I look forward to hearing the testimony of yet another patient and witness on this panel, Doug Rice, who has been treated for heart disease using adult stem cells. Unfortunately, the political agenda for taxpayer-funded research that destroys human embryos and has failed to treat any patients has diverted the focus away from the success of adult stem cells. In fact, it was just 1 year ago that Dr. Richard Burt, along with Brazilian researcher Dr. Julio Voltarelli, conducted a study that used stem cells from patients' own bodies to successfully reverse type 1 juvenile diabetes in 13 out of 15 patients over a several-year period. It was regrettable that this remarkable research had to be conducted in Brazil due to a lack of interest in the United States.

Thankfully, last fall, the contentious and heated debate surrounding stem cell research was quieted by a scientific breakthrough which has shown the ability to create embryonic-like stem cells. This research will face all of the same hurdles as embryonic stem cells, including tumors and rejection. However, it holds all the potential touted by proponents of embryonic stem cell research but without any of the ethical concerns. Dr. Rudolph Jaenisch of the Whitehead Institute confirmed that, "Biologically, there is no difference" between iPS and embryonic stem cells. Dr. James Thomson, University of Wisconsin——

Mr. PALLONE. Mr. Pitts, if you could just wrap it up. You are a minute and 26 seconds over.

Mr. PITTS. I am sorry. Dr. Thomson, the pioneer of embryonic destructive stem cell research, was one of the scientists to discover this new method and he described significant advantages of iPS cells because they don't pose the same ethical challenges as destroying embryos, cloning or harvesting eggs. So the topic of this hearing is the future of stem cells.

Thank you, Mr. Chairman, for holding this important hearing.

Mr. PALLONE. Let me just mention to members that we are going to have, I believe, five votes in another 15 minutes but we will continue and try to get a couple more opening statements in before then and then we will come back.

I now recognize the chairman of the full committee, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy. I thank you for the recognition and I commend you for this hearing this morning.

Stem cell research holds great promise for a better understanding and treatment of a broad range of debilitating and deadly diseases and conditions including Parkinson's disease, cancer, Alzheimer's disease, diabetes, and multiple sclerosis, amongst others, yet a significant problem is created by politics and the promise is being somewhat imperiled or indeed seriously threatened by politics.

This committee is engaged in a practice that is very important: oversight, the gathering of information to understand what our national policies should be and what our actions should be here in the Congress in the way of legislation, what we should do in the way of expenditure of monies and national efforts to achieve great national purposes.

Scientists, it should be observed, work with two kinds of stem cells: adult stem cells and embryonic stem cells. Current science indicates that adult and embryonic stem cells differ in significant ways and therefore we need to examine both. Yet despite well-documented benefits of embryonic stem cell research and pleas from the scientific community, the Administration has regrettably adopted research restrictions that inhibit the ability of scientists to fully explore the potential of embryonic stem cells. In this Congress, the House and Senate have sent the President not once but twice bi-

partisan legislation that would limit and lift these restrictions, and both times the President has vetoed this legislation.

Researchers in my own State of Michigan have been doubly hamstrung by Federal constraints and by State limitations. The University of Michigan has an impressive Life Sciences Institute, focusing on stem cell research and a prominent University Center for Stem Cell Biology. In 2003, under the capable leadership of Dr. Max Wicha, who directs the Comprehensive Cancer Center at the University of Michigan, scientists there discovered breast cancer stem cells, and last year found stem cells in pancreatic cancer. These are especially noteworthy and impressive accomplishments and give us knowledge and warnings that are important to us in our concerns about these matters. Given the limited funding available to the university with State and Federal dollars unavailable for research, the university scrambles to support this groundbreaking research with private funds.

I do not profess to know which stem cell lines are most valuable or which ones offer the most promise or which can give the greatest hope to those living with debilitating conditions and diseases. I defer to the experts on such questions such as Dr. Zerhouni, the director of NIH, who is here today, and Doctor, by the way, welcome to you. Your comments in 2007, I will quote: "It is in the best interests of our scientists, our science, and our country that we find ways and that the Nation find a way to go full speed across adult and embryonic stem cells equally." From my standpoint, it is clear today that the American science will be better served and the Nation better served if we let our scientists have access to more cell lines.

I defer to the Institute of Medicine, IOM, which stated in 2002, and I quote, "Studies of both embryonic and adult human stem cells will be required to most efficiently advance the scientific and therapeutic potential of regenerative medicine."

Research on both adult and embryonic human stem cells should be pursued. None of us can guarantee to those suffering from Parkinson's disease, spinal cord injuries or multiple sclerosis or any other condition that embryonic stem cell research will bring success but we can assure and we can guarantee that if we don't and if we let politics, not science, guide our efforts, we are consigning ourselves to failure and to suffering.

I thank the chairman, Mr. Pallone, for holding today's hearing, and I commend our colleague, Ms. DeGette, for her dedication and commitment on this issue. Finally again, I thank our friend, the NIH director, Dr. Zerhouni, for rearranging his schedule to be here with us today. I look forward to the testimony of our expert witnesses on the current state of stem cell research and science, and I thank you, Mr. Chairman; I thank my colleagues and I thank our witnesses.

Mr. PALLONE. Thank you, Chairman Dingell.

I would like to take one more opening statement but let me just mention, we have five votes, 15 and then four fives, 10 minutes of debate on a motion to recommit, a 15-minute vote on that and then another five, so we are probably talking close to an hour once we go into recess. But I would like to have Mr. Murphy recognized for an opening statement and then after that we will go vote.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Thank you, Mr. Chairman, and let me begin by welcoming one of our witnesses here today, Dr. Patel, who is Director of Cardiovascular Cell Therapies at the University of Pittsburgh Medical Center. I look forward to hearing his testimony.

While we are talking about science and research, I think it is important to understand that ethics cannot be diminished by relabeling it as political and dismissing the value of ethical review through polling or politics. The life of a human embryo is not insignificant and not immaterial to scientific research, and one cannot perform scientific medical research without including medical ethics. A couple years ago, at the time that Congress was voting on embryonic stem cell research, a study came out out of South Korea, Seoul International University, I believe, and many were so eager to find the results they wanted to see that they failed to see that the results were not what was really found.

We need to continue stem cell research but to also review its scientific merit and outcome and to always, always review each finding under the lamp of careful scientific and ethical scrutiny.

The Federal Government does not prohibit any private individual or business from carrying out embryonic stem cell research but we have chosen to hold off taxpayers' dollars for this, and it is not just a matter of deciding on a poll. We have to acknowledge that years from now, perhaps this very subcommittee will be debating and holding hearings on what we may now consider as the unthinkable: cloning replicas of ourselves to be used as organ gardens waiting to be harvested. Indeed, that may come in the future. But let us understand when it comes to stem cell research, dozens and dozens of great scientific breakthroughs have come from using adult stem cells, placenta, umbilical cord, muscle, skin, other issues, and that is important, but the number of studies that have come out that have shown significant scientific results from embryonic stem cells is zero.

So I hope that this panel will look at these issues as ones that are important to review and that we cannot, no matter how hard we might use tactics to dismiss it as political, we cannot dismiss ourselves from the obligation of carefully, carefully reviewing each thing we do. Life does have value, saving lives has value, and scientific research cannot be made distinct from ethical oversight of that same research.

I yield back.

Mr. PALLONE. I think we have time for one more, so I recognize Ms. DeGette for an opening statement.

Ms. DEGETTE. Thank you, Mr. Chairman. I would ask unanimous consent to put my full opening statement in the record.

Mr. PALLONE. Without objection, so ordered.

OPENING STATEMENT OF HON. DIANA D. DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DEGETTE. Thank you, and I want to thank you for holding this very first ever hearing on stem cell research in the Energy and

Commerce Committee. It is an incredibly important topic, and I want to thank Dr. Zerhouni for coming and rearranging his schedule today.

It is particularly important that we have this hearing because over the past year we have had many developments in the field of cell-based scientific research. We saw breakthroughs and accomplishments that could not have been predicted even months before they happened: insulin-producing islet cells created from embryonic stem cells, induced pluripotent stem cells developed from adult skin cells, and primate embryonic stem cells generated through somatic cell nuclear transfer. All of this proves that one can rarely predict the outcomes of scientific research and it underscores what the other members have been saying, that it is crucial to make the investment in all ethical forms of research to begin with.

That is what we are going to explore during this hearing: where we are now and where we are going with stem cell research. Every time there has been some new discovery in some other type of research besides embryonic stem cells, the Bush Administration and opponents of this research try to claim it is a substitute for embryonic stem cell research, yet as every researcher tells me, all of these forms of cell-based research are complementary and they all aid future developments of cures for patients, which we see so eloquently here in the front row. It simply does not make sense to remove one avenue of research from the equation, especially one that is relatively well developed. We should continue pursuing all forms of ethical research.

It makes me particularly angry when people try to claim that adult stem cells can substitute cures for diseases for which adult stem cells have shown no clinical promise whatsoever. I know that these wonderful patients who are here today who have been cured by adult stem cells, mostly for blood-related diseases, would never say that somebody with diabetes or somebody with Parkinson's or somebody with nerve damage or somebody with macular degeneration, all diseases for which embryonic stem cell research has shown promise and adult stem cells have shown no clinical promise, no one would say those people should not be cured, and that is the whole issue here today. I pray every day that my 14-year-old daughter will be cured of diabetes and I frankly don't care if she is cured by embryonic stem cell research or adult stem cell research or ethical somatic cell nuclear transfer. I don't really care and I don't think the rest of the parents in this country care either.

But what we do need to do as a government is we need to take our responsibility seriously and we need to say we are going to expand this research in an ethical way, we are going to make a national commitment to doing it, and we are not going to play politics with it. That is why I want to introduce and congratulate my friend, Mike Castle, who has snuck into the back of the room, who has been my compadre and fellow fighter on this issue. Mike and I are developing new legislation which I hope this hearing will help us begin to get evidence for, and what we believe our new legislation should do is obviously lift the ban on Federal funding for research on embryonic stem cell lines developed after August 2001, construct a framework for ethical oversight of all cell-based research developed by the National Institutes of Health and with the

NIH as a key player, and make the national commitment to this research that we should have had for the last 10 years. We expect to be introducing this legislation soon and are looking forward to input from the experts in the field.

And just one last note, Mr. Chairman. Absent in this whole discussion today and absent in the Bush Administration's national discussion is the fact that there is no Federal ethical oversight over the research that is going on either among the States with the limited Federal dollars that are available right now or perhaps most disturbing to me, with private entities that are doing the research. We need to both make the commitment to all ethical cell-based research but we also need to make the commitment to ethical oversight because some of this research is on the edge of bioethics and we need to make sure that we get it right for the patients of tomorrow.

With that, Mr. Chairman, I appreciate your comity and I yield back.

[The prepared statement of Ms. DeGette follows:]

STATEMENT OF DIANA DEGETTE

Mr. Chairman, I want to thank you for holding today's hearing on the future of stem cell research. Over the past year there have been many important developments in the field of cell-based scientific research. We saw breakthroughs and accomplishments that couldn't have been predicted even months before they happened—insulin producing islet cells created from embryonic stem cells, induced pluripotent stem cells (IPS) developed from adult skin cells, and primate embryonic stem cells generated through somatic cell nuclear transfer (SCNT). All of this proves that one can rarely predict the outcomes of scientific research and underscores why it is crucial to make the investment in all ethical forms of research to begin with. This is what we are going to explore during this hearing: where we are now and where we are going with stem cell research.

Everytime there has been a new discovery in some type of research besides embryonic stem cells, the Bush Administration tries to claim that it is a substitute for embryonic stem cell research. Yet, in actuality the numerous types of cell-based research are all complementary—they aide future developments or provide the background necessary for some yet-to-be-discovered breakthrough. It simply does not make sense to remove one avenue of research from the equation—we should continue pursuing all forms of ethical research and see where the science takes us.

It is important that we still pursue embryonic stem cell research, for example, since it remains the most promising avenue of research for certain debilitating diseases like diabetes, Parkinson's, and Multiple Sclerosis. However, there is still plenty to learn about both embryonic and induced pluripotent stem cells. Embryonic stem cells, as the vast majority of scientists agree, are currently the gold-standard for stem-cell research, and are the basis upon which to measure the success of IPS cells. The goal of IPS cell research is to make them mimic embryonic stem cells. But, how are we ever going to know whether the IPS cells are acting like embryonic stem cells if we haven't done enough research on embryonic cells to even know what we are looking for?

None of the recent progress in the adult stem cell field would have even been possible without the original embryonic stem cell research. Looking forward, we simply do not know where the advances will come from for each of the many diseases that we need to address-we do not know which will come from embryonic stem cell research and which will come from IPS research. We need to support both embryonic stem cell research and IPS research and let the science decide which is more promising over the long-run.

We do not yet fully know what the recent IPS stem cell breakthrough means in terms of application. It seems as though it will likely prove to be a significant scientific advance. However, we do not yet know whether it will prove to be a significant medical advance. For example, IPS cells currently remain far too dangerous for actual treatment, and we do not know whether they will ever be safe for humans. Cutting off funding for other promising avenues of research in the meantime would be about the most short-sighted things we can do. When we develop new tools, we

don't throw out the old ones that still serve a valuable and unique purpose. Why should it be any different when it comes to medical research?

Although we are making great progress in the field of stem cell research, it has not progressed as far as it might have had the Administration instituted a cohesive federal policy for ethical oversight of stem cell research, rather than simply banning the use of federal funding for research on embryonic stem cell lines developed after August 9, 2001. Progress has been even further hindered because of inadequate resources for all research at NIH.

With all the new research coming down the pipeline, much of which we have yet to even imagine, it is clear to me that we need a comprehensive, ethical oversight framework for all cell-based research, as well as a national commitment to a robust research program in the United States.

So, in light of these issues, I have been working to develop new stem cell legislation with my dear friend Mr. Castle, who was kind enough to join us here today. We know that NIH is best-suited to overseeing and coordinating all forms of ethical stem cell research. It is best positioned to ensure that all research meets high ethical standards, as it has long experience overseeing cutting edge research and establishing regulations that ensure the research is done ethically. So, the new legislation will:

- Construct a framework for ethical oversight of all cell-based research, with NIH as a key player;
- Ban certain unethical activities,
- Lift the ban on federal funding for research on embryonic stem cell lines developed after August, 2001.

Input from the experts in the fields is key to crafting quality legislation, which is also part of the reason we are holding this hearing. I look forward to a vigorous discussion here today with our witnesses about where the science is currently, where the science is likely to go in the future, and what we, as federal lawmakers, should do in order to best support and promote all the promising new research that our scientists are working on.

Thank you, Mr. Chairman. I yield back the balance of my time.

Mr. PALLONE. Thank you.

The subcommittee will stand in recess until the votes are completed, about an hour, maybe a little less.

[Recess.]

Mr. PALLONE. The subcommittee will reconvene. We were I guess longer than we expected. We left off with Congresswoman DeGette, and next I recognize the gentlewoman from Tennessee, Ms. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Ms. BLACKBURN. Thank you, Mr. Chairman. I thank our witnesses for their patience today. As the chairman said, we were a little longer than we had anticipated being, but we do appreciate that you are here. We are looking forward to what you have to say.

We all know that embryonic stem cell research continues to be a controversial issue. In my opinion, it does implicate ethical and moral standards within scientific progress and has the potential to offend millions of our constituents. It is my understanding that no journals have shown any treatment trials in human beings to have been successful using embryonic stem cells but there has been successful stem cell research, most definitely yes, from adult stem cells. In almost all cases, adult stem cells are equivalent or superior to embryonic stem cells and there are plenty of sources of adult stem cells, amniotic and placental fluid, cord blood, bone marrow—and none of these sources require any destruction of precious human embryos.

But many organizations continue to push for funding for embryonic stem cell research, claiming that it is the holy grail for cures of many diseases. One particular disease that is touted for support of embryonic stem cell research is diabetes, but since 2002, published studies in stem cells in diabetes journals concluded that trials using these cells showed no cures, and most of the time the treatments resulted in tumors, and I hope we will hear a little more about that.

Significant progress, however, has been made on treating diabetes with adult stem cells, and since 2003, studies in the same journal showed adult stem cells successfully treated diabetes in mice, and when human trials conducted in Brazil and Europe began to use adult stem cells for treatment, many of the patients were insulin free after the stem cell transplant. The Federal Government should not be funding research that is showing no results and forcing Americans to pay for research that requires the destruction of human embryos, research that offends their moral and ethical sensibilities. Adult stem cells have a proven track record, and the NIH should be focusing, in my opinion, much of their research effort on this. I urge my colleagues to consider what is laid before us today, to ask good questions and to inquire about science that actually works and shows results.

Thank you, Mr. Chairman. I yield back the balance of my time.

Mr. PALLONE. Thank you.

Next is the gentlewoman from Wisconsin, Ms. Baldwin, recognized for an opening statement.

OPENING STATEMENT OF HON. TAMMY BALDWIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WISCONSIN

Ms. BALDWIN. Thank you, Mr. Chairman. I really appreciate the fact that you are holding this very important hearing today.

I am a strong supporter of embryonic stem cell research. I am fortunate to represent the University of Wisconsin, Madison campus, where Dr. Jamie Thomson and his team were the first to derive and culture human embryonic stem cells in a lab, and I have had the opportunity to tour Dr. Thomson's lab and review the work that happens in that lab, and the field is truly groundbreaking.

Embryonic stem cells open the possibility of dramatic new medical treatments, transplantation therapies, and cures, but at 9 p.m. on August 9, 2001, the hope and promise of this embryonic stem cell research was greatly curtailed by this Administration's restrictions on the Federal research dollars for embryonic stem cells. The President's policy that limits Federal funding for embryonic stem cell research to those stem cell lines that were created before a certain time and date is arbitrary and irrational, and it needlessly ties the hands of our scientists as they search for cures and treatments to diseases and conditions like diabetes, Parkinson's disease, Alzheimer's disease, and spinal cord injury. It also sends a very negative message to young, upcoming scientists that this is not the field to enter if you hope to secure Federal grant funding to support your research efforts.

But despite the President turning his back on the promise of embryonic stem cell research, I am pleased that many States, univer-

sities and private research foundations have stepped in to fill that role and the research has continued. Late last year, the same Dr. Thomson that I referenced earlier announced that he had discovered a way to reprogram skin cells into stem cells that seem to act like embryonic stem cells. While this development is very exciting, we must continue to support embryonic stem cell research and explore all the possibilities that this science holds. Whether we are talking about embryonic stem cells, adult stem cells, cord blood stem cells, or these new reprogrammed cells, we must explore all avenues of research. We owe it to the millions of Americans who suffer from diabetes, Parkinson's disease, paralysis, and countless other conditions to realize the potential of all of this research.

And I just want to close by associating myself with Congresswoman DeGette's frustration, she said anger, over the confusion between adult and embryonic stem cells and the arguments that have been proffered. These stem cells have different properties. I can't say with scientific accuracy that it is like comparing apples to oranges but I can say that we need to clarify the properties and why we need to pursue both lines of research, and I hope that our expert witnesses will help educate the members of Congress on this committee on the different properties that those stem cells have.

Thank you, Mr. Chairman, and I yield back.

Mr. PALLONE. Thank you.

Mr. Ferguson of New Jersey.

OPENING STATEMENT OF HON. MIKE FERGUSON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. FERGUSON. Thank you, Mr. Chairman. Thanks for holding this hearing.

I am sure many people are aware, as we have heard already, that there have been great strides that scientists have been making in the past several years in stem cell research, in treating and even curing patients that have life-altering diseases. Research has produced very exciting developments such as the development that Ms. Baldwin was talking about, the induced pluripotent stem, or iPS, cells, which are derived from nonpluripotent cells by inserting genes to create the pluripotent stem cell. In 2006, Shinya Yamanaka of Kyoto University published the first article concerning iPS cells in mice, and 16 months later, his group and a group led by, as was said, Dr. James Thomson at the University of Wisconsin-Madison, reported the creation of human iPS cells.

But I have to say, as Dr. Thomson himself has said, if human embryonic—I quote, "If human embryonic stem cell research does not make you at least a little bit uncomfortable, you have not thought about it enough." He is right. And fortunately, there are better alternatives. There are more promising alternatives. There are alternatives that are showing treatments and progress in human beings today. Carol France is sitting in front of us. She suffers from multiple myeloma. Five years ago, my mother died from multiple myeloma. When she was first diagnosed at age 52, she was told she probably had a year to live. She lived 6 years because she had a similar treatment that is extending Carol's life today. One of our children was able to—when my mother was first diag-

nosed, she had no grandchildren. Three of our kids were born in the 6 years that her life was extended because of this stem cell treatment, not an embryonic stem cell treatment where there are no treatments, no humans that are benefiting from that today, but a treatment that is benefiting Carol and countless other people today, not just in cancers, but yes, there is progress in Parkinson's disease. Yes, there is progress in diabetes as was shown in the Brazilian study. It is true.

So when we are looking at where we spend scarce taxpayer dollars on Federal research, let us look at what is working, where the promise is, and not spinning our wheels going elsewhere. You know, I think citizens are rightly concerned about where their tax dollars are going, and in fact, my home State, the chairman and my home State of New Jersey, just last year, in New Jersey, embryonic stem cell research is done privately. We don't even have a law against human cloning in New Jersey so we are pretty so-called progressive State when it comes to scientific research. But last year, voters in our State rejected a $450 million embryonic stem cell research center. Now, in the State of New Jersey, a ballot test hasn't been defeated in 17 years, and in fact, there was another ballot question on the ballot at the same time that would have funded something else that passed. This is the only one in 17 years that failed. I think voters and citizens as they look at the scientific evidence, I think as they look at the progress and they see the great progress of adult stem cell research and the people that it is benefiting today and they look at the alternatives, I think they are seeing that our—the question is not what is legal, the question is, where should we be spending taxpayer money? Where are we going to get the most bang from our buck? And I think people are beginning to see more and more clearly, particularly because of the research of Dr. Thomson and others, that there are very promising, very ethical opportunities for this research and we don't have to go down a route that frankly has a lot of the ethical baggage that embryonic stem cell research has.

Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you, Mr. Ferguson.

Our vice chair, Mr. Green, recognized for an opening statement.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman. I am shocked that New Jersey doesn't have a ban on human cloning.

Mr. FERGUSON. Me too.

Mr. GREEN. My concern is that some of my colleagues may want to put that ban in effect in Texas and we would have no Texans that sound like me here.

But be that as it may, there is not anyone in this room or in our country who has a friend or family member or a neighbor that hasn't suffered from diabetes, Alzheimer's, or Parkinson's disease or a spinal cord injury, and how difficult that struggle is. But the issue, and you hear it today, the diversity of opinion is we can do what we need to do with adult stem cell research and there has been some great strides, but there is a substantial difference between adult stem cells and embryonic stem cells, and that is why

we need both. We don't need to say we can only do it with adult, and that is what frustrating about this debate.

Embryonic stem cells can actually divide indefinitely and evolve into any cell type in our body, and that is the big difference. We need to research it all and not just artificially say we are not going to do something, and that is what is frustrating. I have seen poll after poll the last number of years since the President set his criteria that 70 to 80 percent of the people support embryonic stem cell research, just because why we would put our head in the ground when we shouldn't—when there is some potential for that. And I would hope the next Congress, if not this one, would pass the legislation again because it has been overwhelmingly passed in the House and the Senate, obviously not enough to override a veto, but hopefully we will pass it during the next Congress, if not this one.

Mr. Chairman, I would like to ask my statement be placed in the record, and thank our witnesses for their patience for all our votes we had on the floor.

[Mr. Green did not submit a prepared statement for the record.]

Mr. PALLONE. Without objection, so ordered, and I think we have completed our opening statements, so we will turn to our witness, who has been waiting patiently here for 2 hours or so.

First of all, welcome. Dr. Elias Zerhouni is director of the National Institutes of Health, and we appreciate your being here today. We have 5-minute opening statements. They become part of the hearing record, and you may in the discretion of the Committee submit additional statements in writing for inclusion in the record, and I now recognize you for 5 minutes. Thank you for being here.

STATEMENT OF ELIAS A. ZERHOUNI, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Dr. ZERHOUNI. Well, thank you, Mr. Chairman. It is worth waiting 2 hours to discuss stem cell research, and thank you, members of the subcommittee.

I am really pleased to appear before you today to testify about the current state of stem cell research science and its significance, its current prospects, and its likely future. But let me start by saying that from the scientific standpoint, this is one of the most important, if not the most important, areas of medical research today. It has the potential to not only treat millions of individuals but also allow us to discover some of the fundamental findings and discoveries that we need to make in this century if we are going to be effective as a society in lessening the burden of disease.

The central issue which I would like to go over in my oral statement and submit my total written statement for the record is the significance of this research from the standpoint of science. Why is it important that stem cell research be pursued very aggressively? I have a panel that I would like to share with you and I think we have distributed copies of that to each member. But let me just tell you what the real mystery is for us as doctors or scientists. It is the mystery of how DNA, which is exactly the same in every one cell of our body, goes from what we call a totipotent cell with the exact same DNA, to then form a complete organism with over 260 different cell types in what we know as ourselves. This is a funda-

mental mystery that we need to unravel in this century. Why? Because we know also that DNA has been sequenced. We know how the DNA code is written. We know all the letters of the DNA code. What we do not know is how it is played, how it is programmed. So we know the hardware of how cells do this; we don't know the software. And the whole field of stem cell research cannot be separated from our standpoint into components of adult or intermediate because they are all part of the same continuum, and let me explain that for you. Clearly, when a totipotent cell evolves, it plays a program, a program of molecular factors that are timed to change the characteristics of the DNA and how the DNA is played out. That then leads to a pluripotent cell. That pluripotent cell has a very interesting characteristic. It can self-renew. It can stay, in other words, idle until it goes forward in development and then can create through a second set of programs a program to create three precursors of our body systems. One is a line called the endodermal line. The internal organs, the guts, for example, arise from that line. The second is the mesodermal mid layer which really gives rise to muscles and bones and heart and blood. And then there is the ectodermal line, the epilayer, the outer layer, which gives rise to the nervous system and all of the neurons and all of the superficial layers of the skin.

Now, we know that we can evolve a pluripotent cell into one of these, and this is the discovery that Jamie Thomson was credited for, finding that in fact you can cultivate these pluripotent cells, these embryonic stem cell lines, and then program them in different directions. This is where the research has been very active.

Now, as we also learned, this is not the only program that is played. You still need to go from this line, from this cell, for example, the mesodermal precursor, and then you go through a different series of what we call adult stem cells. So you may have adult stem cells through multiple programs, many of which are completely unknown to us. We know some; we don't know many of them. And then these will then give elements of the blood, for example, the white blood cells or the muscle, the deep layers of the skin, the skin fibroblast.

Now, why is it important to understand that when we talk about adult stem cells, embryonic stem cells, committed precursors, it is very important to understand that this is a whole, that in fact, when we look at embryonic stem cell research, what we are looking at is to look forward in the programming from a totally unprogrammed cell to a fully programmed cell. Now, adult stem cells are partially programmed cells, which are able to evolve into different end points. Now, the therapies in adult stem cells have been developed for over 40 years, and the first one to be developed was the idea of replacing the bone marrow in patients who had blood cancers like myeloma or leukemias and so on, and the idea was to eradicate the cancer cells and then fish from the bone marrow some of these stem cell precursors to replace the bone marrow in a healthy way.

So for most of the past 40 years, we have used that therapy to treat many cancers, and over the past 10 years there has been another line of research, which is to replace the immune system. We have many autoimmune diseases—multiple sclerosis, type 1 diabe-

tes, lupus, scleroderma—and so doctors have had the idea of using the technique that was developed for cancer to use it to treat autoimmune disease where your own immune system goes awry and attacks your own tissues. So the idea there is to change that immune system, actually destroy it with radiation and chemotherapy, and replace it with a healthy bone marrow precursor that would then replace that. So fundamentally, if you think about the central issue, the central issue is, how is the software of DNA organized? We know the hardware; we don't now the software. How do we discover how that is organized in health and disease is the central scientific question.

Now, when you look at this, as you know, scientists have been looking at all angles of this research, and two things happened between 2001 and today as we were able to fund for the first time embryonic stem cell research. Researchers tried to look for what is it that makes a pluripotent cell a stem cell, and what they started to describe are DNA factors, genes, that were active at that time and then they defined culture conditions which allowed those cells to expand. Now, the thing that is very important to understand is that embryonic stem cells can be expanded many times and adult stem cells, up to today are not something that is frequent in the body and that we can expand as well as we do embryonic stem cells. So researchers have been thinking, can we create a new source of pluripotent stem cells, and this is the discovery that Dr. Yamanaka made, Dr. Thomson. Dr. Daley, who is one of your witnesses today, also showed the same thing, and that is that you can take a skin fibroblast and with these same factors that were discovered during embryonic stem cell research, apply them to a fully programmed cell, and lo and behold, you can deprogram the cell, erase the program, the software that was there and bring that cell back to what seems to be the exact same potency as the stem cell. It looks very similar but we know already they are not identical. But they have the same potential of being reprogrammed into the first three precursors. Now, here is another important issue, and that is that if you were able to cross-program these cells from a blood cell to a neural cell to a pancreatic cell, you would have made a great breakthrough. To this date, we have absolutely no evidence that once you have a precursor, you can reprogram it.

So in summary, what I would like to say is that from the scientific standpoint, adult stem cell research, embryonic stem cell research, and induced pluripotent stem cell research are the faces of the same coin. They are intrinsically interrelated. They are related to the fundamental program of learning how to program, reprogram, deprogram DNA so that we can use these cells for therapies.

So I will stop here, Mr. Chairman, and I would be happy to take your questions.

[The prepared statement of Dr. Zerhouni follows:]

Testimony
Before the
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives

Stem Cell Science: The Foundation of Future Cures

Statement of
Elias A. Zerhouni, M.D.
Director
National Institutes of Health
U.S. Department of Health and Human Services

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Good morning, Mr. Chairman, Ranking Member Deal and Members of the Subcommittee. I am Elias Zerhouni, the Director of the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services (HHS), and I am pleased to appear before you today to testify about the science of stem cell research. I look forward to discussing ongoing federal support of both embryonic and non-embryonic stem cell research and scientific progress, including the recently published findings on induced pluripotent stem cells and other updates provided during the NIH Symposium on Cell-Based Therapies, which we hosted just two days ago.

Stem cell research has the potential to lead to therapies for injuries and illnesses that could not even have been imagined when I first began studying medicine. As this new field of discovery advances, nothing we have learned has dissuaded us from the belief that these cells, representing the building blocks of life itself, offer the possibility of becoming a renewable source of replacement cells and tissues to treat such common diseases and disorders as Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

A great deal of progress has already occurred. When I first became the Director of NIH, scientists were still struggling with learning how to grow embryonic stem cell lines. Since then, experiments have occurred in animals where embryonic stem cells actually replaced damaged cells and tissues. But we have a very long way to go.

The Need for Research to Explore the Potential of Human Stem Cells

Stem cells can multiply without changing – that is, self-renew – or can differentiate to produce specialized cell types. This ability to renew and eventually replace damaged cells and tissues fuels the excitement of stem cell researchers across the world. But all stem cells do not come from the same source; they have different characteristics and are difficult to harness and grow. Stem cells have been derived from both embryonic and non-embryonic tissues, and these cell types have different properties. Both pluripotent and nonpluripotent types show potential for developing treatments for human diseases and injuries, and there are many ways in which they might be used in basic and clinical research. We are still early in the learning process. This is an exciting but new field of discovery, and additional research is needed to realize the potential of stem cells and their uses. Before we reach the promised land of stem cell therapies, scientists must learn to reliably manipulate the cells so that they possess the necessary characteristics for successful differentiation, transplantation, and engraftment.

To be useful for transplant purposes, differentiated stem cells must:

- Proliferate extensively and generate sufficient quantities of specialized cells;
- Differentiate into the desired cell type(s);
- Survive in the recipient after transplant;
- Integrate into the surrounding tissue after transplant;
- Function appropriately for extended periods of time; and

- Avoid harming the recipient.

As this field of research advances, stem cells will yield still unknown information about the complex events that occur during the initial stages of human development. At present, a primary goal of this research is to identify the molecular mechanisms that allow undifferentiated stem cells to differentiate into one of the several hundred different cell types that make up the human body. Scientists have learned that turning genes on and off is central to this process. But we do not yet fully understand the signals that turn specific genes on and off to influence the differentiation of the stem cell into a specialized cell with a specific function, such as a nerve cell. This knowledge will not only offer the opportunity to learn how to control stem cells from both embryonic and non-embryonic sources, but also provide better understanding of the causes of a number of serious diseases, including those that affect infants and children, which in turn could lead to new and more effective intervention strategies and treatments.

Human stem cells are also being used to speed the development of new drugs. Initially testing thousands of potential drugs on cells in cell culture is typically far more efficient and informative than testing drugs in live animals. *In vitro* systems are useful in predicting *in vivo* responses and provide the benefits of requiring fewer animals, requiring less test material, and enabling higher throughput. New medications can be tested for safety on the specific types of human cells that are affected in disease by deriving these cells from human stem cell lines. Other kinds of cell lines are similarly used in this way. Cancer cell lines, for example, are used to screen potential

anti-tumor drugs. The availability of useful stem cell lines would allow drug testing in a wider range of cell types. Potentially, stem cell research will result in a more efficient, effective, safer and faster way of developing drug treatments for a vast array of illnesses, but not until we produce the fundamental discoveries that will pave the way for the widespread use of stem cells in this manner.

Advances in Stem Cell Research

Over the past year, scientists have made remarkable discoveries about the potential of stem cells. For example, NIH-funded scientists have developed a method to coax human embryonic stem cells (hESCs) into becoming cells that resemble lung epithelial cells. The scientists engineered a virus (modified to eliminate its disease-transmitting function) to infect cells with two genes simultaneously, one that drives them into becoming a specialized type of lung cell and another that enables them to resist being killed by a drug (neomycin). Only those cells that express the two genes survived when the scientists treated the culture dish with neomycin. In this way, they were able to generate a pure population of lung-like cells, with no contaminating cells. The surviving cells had the appearance and shape of lung-lining cells called alveolar type 2 cells, which help maximize air exchange, remove fluid from the lungs, serve as a pool of repair cells, and fight airborne diseases. (*Proceedings of the National Academy of Sciences of the USA* 104(11):4449–4454, laboratory of R.A. Wetsel. 2007 March.)

In another experiment, NIH-funded investigators developed a new technique to generate large numbers of pure cardiomyocytes (heart muscle cells) from hESCs. They also formulated a

"prosurvival" cocktail (PSC) of factors designed to overcome several known causes of transplanted cell death. The scientists then induced heart attacks in rats and injected the rat hearts with either hESC-derived human cardiomyocytes plus PSC (treatment group) or one of several control preparations. Four weeks later, the scientists identified human cardiomyocytes being supported by rat blood vessels in the treated rat hearts. The treated rat hearts also demonstrated an improved ability to pump blood. The control animals presented no improvement in heart function. This work demonstrates that hESC-derived cardiomyocytes can survive and improve function in damaged rat hearts. Scientists now hope to learn how the human cells improved the rat hearts, and eventually to test this method to treat human heart disease. (*Nature Biotechnology* 25(9):1015–1024, laboratory of CE Murry. 2007 Sept.)

In a significant advance, Japanese scientists and a team of NIH-supported scientists reported that they each succeeded at reprogramming adult human skin cells to behave like hESCs. The Japanese team forced adult skin cells to express the proteins *Oct3/4, Sox2, Klf4,* and *c-Myc,* while the NIH-supported team forced adult skin cells to express *OCT4, SOX2, NANOG,* and *LIN28.* The genes were all chosen for their known importance in maintaining the so-called "stemness" properties of stem cells. In both reports, the adult skin cells are thus reprogrammed into human induced pluripotent stem (iPS) cells that demonstrate important characteristics of pluripotency. The techniques reported by these research teams will enable scientists to generate patient-specific and disease-specific human stem cell lines for laboratory study, and to test potential drugs on human cells in culture. However, these human iPS cells are not yet suitable for use in transplantation medicine. The current techniques use viruses that could generate tumors or other undesirable mutations in cells derived from iPS cells. Scientists are now

working to accomplish reprogramming in adult human cells without using potentially dangerous viruses. (*Cell* 131:861–72, laboratory of S. Yamanaka, 2007 Nov 30; *Science* 318:1917–1920, laboratory of J. Thomson, 2007 Dec 21

Researchers from Japan were the first to successfully generate germ cells (the cells that give rise to sperm or eggs) from mouse iPS cells, and their results were verified and extended by another independent laboratory (Rudolf Jaenisch) in the United States. Recent publications from the same Japanese scientists, a team of NIH-supported scientists from University of Wisconsin-Madison, and the Harvard Stem Cell Institute report that they have each succeeded at reprogramming adult human skin cells to become human iPS cells.

There is no doubt that this finding is a remarkable scientific achievement, providing non-embryonic sources of pluripotent cells. Human ESCs and iPS cells are excellent tools to study differentiation, reversal of differentiation, and re-differentiation. In addition, both types of pluripotent cells may be useful for studying the cell biologic changes that accompany human disease. However, from a purely scientific view, it is essential to pursue all types of stem cell research simultaneously, including hESC research, since we cannot predict which type of stem cell will lead to the best possible therapeutic application.

In addition, reprogramming adult human cells would not have been possible without years of prior research studying the properties of hESCs. Two fundamental factors critical to the development of human iPS cells are based upon the knowledge gained from studying hESCs: knowledge of "stemness" genes whose expression or repression is essential to maintain

pluripotency; and hESC culture conditions. NIH is proud of the role it has played in supporting this work since 2001 and advancing non-embryonic sources of pluripotent cells.

Scientists must now focus on understanding the mechanism by which retroviral transduction and consequent expression of "stemness" genes induce pluripotency in somatic cells. The consequences of using retroviral vectors to induce pluripotentiality for normal cell functions are unclear, and because the retroviral vectors integrate into the genome of the somatic cell, it can cause the cell to function abnormally. Scientists are now looking for safer methods to reprogram adult cells to a pluripotent state that do not disrupt the genome.

NIH Stem Cell Symposium on Cell-Based Therapies

Two days ago, on May 6, the NIH hosted a symposium entitled "Challenges and Promise of Cell-Based Therapies." Notable stem cell researcher Dr. Stuart Orkin opened the symposium by explaining how 25 years of active research using blood stem cells has led to their successful use in the treatment of blood cancers and other blood disorders. He described the critical characteristics of blood-forming stem cells that have enabled their use in therapies, and how this knowledge will help scientists understand ways to use these and other types of stem cells for treating human diseases. Prominent scientists then discussed how they are developing stem cells as therapies for diseases of the nervous system, heart, muscle and bone, and metabolic disorders. The scientists shared their research results, the technical hurdles they must overcome, and what they ultimately hope to achieve with stem cells. Dr. George Daley of the Harvard Stem Cell Institute gave the final presentation on patient-specific pluripotent stem cells, also known as induced pluripotent stem cells.

Federal Funding of Stem Cell Research

NIH has acted quickly and aggressively to provide support for this research in accordance with the President's 2001 stem cell policy. Since 2001, NIH has invested approximately $3.7 billion on all types of stem cell research. Within this total, NIH has funded: more than $174 million in research studying human embryonic stem cells; more than $1.3 billion on research using human non-embryonic stem cells; more than $628 million on nonhuman embryonic stem cells; and more than $1.5 billion on nonhuman non-embryonic stem cells.

Additionally, in FY 2009, it is projected that NIH will spend approximately $41 million on human embryonic stem cell research and about $203 million on human non-embryonic stem cell research, while also investing approximately $105 million on nonhuman embryonic stem cell research and nearly $306 million on nonhuman non-embryonic stem cell research.

In addition, NIH is conducting activities under the President's July 2007 directive in Executive Order 13435, which directs HHS and NIH to ensure that the human pluripotent stem cell lines on research that it conducts or supports are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus. The order expands the NIH Embryonic Stem Cell registry to include all types of ethically produced human pluripotent stem cells, and renames the registry as the Human Pluripotent Stem Cell Registry. The order invites scientists to work with the NIH, so we can add new ethically derived stem cell lines to the list of those eligible for federal funding.

Further, NIH has encouraged stem cell research through the establishment of an NIH Stem Cell Task Force, a Stem Cell Information Web Site, an Embryonic Stem Cell Characterization Unit, training courses in the culturing of human embryonic stem cells, support for multidisciplinary teams of stem cell investigators, and a National Stem Cell Bank and Centers of Excellence in Translational Human Stem Cell Research, as well as through extensive investigator initiated research. NIH determined that obtaining access to hESC lines listed on the Human Pluripotent Stem Cell Registry and the lack of trained scientists with the ability to culture hESCs were obstacles to moving this field of research forward. To remove these potential barriers, the National Stem Cell Bank and the providers on the Human Pluripotent Stem Cell Registry together have currently made over 1400 shipments of the hESC cell lines that are eligible for federal funding, as posted on the Human Pluripotent Stem Cell Registry web site. In addition, the NIH-supported hESC training courses have taught several hundred scientists the techniques necessary to culture these cells. We plan to continue to aggressively fund this exciting area of science.

Thank you for the opportunity to present these exciting developments to you. I will be happy to try to answer any questions.

Mr. PALLONE. Thank you, Doctor, and we have questions now. I will start and recognize myself for 5 minutes.

My colleague—this is just a quick one. My colleague, Representative Blackburn, commented in her opening statement that embryonic stem cells have not produced any results and that adult stem cells have shown more promise. You know, can you just respond to that? I mean, just in general.

Dr. ZERHOUNI. I think it is correct that if you look at clinical applications, because we started in adult stem cells a long time ago, 1956 was the first animal bone marrow transplant—we have learned a lot more about this and how to use that in many other diseases, primarily in two conditions: cancer and autoimmune diseases. Most of the diseases that are today helped by adult stem cells fit into these two categories. So it is absolutely clear that it takes about 17 years for the development of an idea to the first trial. We have had a lot more time in adult stem cells, a lot more funding——

Mr. PALLONE. But what about the promise of the embryonic? In other words, she said they haven't produced any results but is there still promise out there for embryonic?

Dr. ZERHOUNI. I think absolutely. I think that it is true that if you look at the snapshot of today, that we have made more clinical applications available. If you look at the scientific question, as I described, discovering the program that will make those things happen, it is very premature to say that one has promise and the other one doesn't.

Mr. PALLONE. Now, one of the witnesses—I hate to do this when I ask you about something the next panel is going to say before they have said it, but one of our witnesses on the next panel, Dr. John Fraser, asserts, and I quote, "that increasing funding to embryonic stem cell research means a decrease in funding to other stem cell research. Increasing funding to embryonic stem cell research at the expense of funding adult stem cell research means that valuable clinical opportunities that are serving patients today and others that appear on the cusp of doing so will be sacrificed for a technology and approach that while scientifically interesting contains enormous obstacles before responsible clinical application can be contemplated." Did you want to comment on that as well?

Dr. FRASER. That has been removed from my testimony. That is an old version that is not part of my testimony today.

Mr. PALLONE. All right. Let me say for the record that I appreciate what you said, but his comments are not part of the record until he gets up here and testifies later. But if you would just—all right. Let me—it is a little bizarre. You are saying you didn't say this?

Dr. FRASER. I am saying that I amended—the document that I sent was amended, and you have an older version.

Mr. PALLONE. Oh, OK. Well, you can comment on the older version then.

Dr. ZERHOUNI. I have to tell you, I think it is premature to make statements as to the ultimate potential of one or another. It is all interconnected. It is all the same problem. I don't know where the breakthroughs are going to come from, and if I don't know, then I don't want to close a door without thinking about the con-

sequences of doing that. There are ways of doing it ethically, and I think we need to really think about those. There is no doubt that our scientists are just as concerned as anybody else in finding solutions that are ethical, but I think we can't just completely shut a door with the knowledge that we have today. As the director of NIH, we do not know enough to know where to stop, when to stop one kind of research or another.

Mr. PALLONE. OK. If we could just stop the clock a minute, I just don't want the reporter to have difficulty. We have never had that before in my experience where somebody talked who wasn't part of the panel. Are you able to handle that?

The REPORTER. Yes, sir.

Mr. PALLONE. OK. So you have his comment, both of his comments?

The REPORTER. Yes, sir.

Mr. PALLONE. Then let me ask you, let us go back, Dr. Zerhouni. Can you explain to me the significance of this date, August 9, 2001, that the President has chosen? You know, he says no Federal funding for research on stem cell lines derived after August 9, 2001. What is the significance of the date? I mean, does it relate in any way to research or the scientific evidence?

Dr. ZERHOUNI. I remember that the Federal Government could not fund any research deriving embryonic stem cells because of the Dickey-Wicker amendment. There is an amendment on the books which prevented NIH to fund any embryonic stem cell research deriving embryonic stem cells. The President made a decision to allow research to proceed and be funded for cell lines that had already been derived so that there would be no further destruction of embryos. That is what I understand the logic of the decision to be. I wasn't involved in the decision. But the 2001 date was a date which the President made a decision to fund what was developed prior to this, including Dr. Thomson's lines and so on and many others, but not any further.

Mr. PALLONE. But there wasn't any scientific significance to the date?

Dr. ZERHOUNI. No, I don't think that the decision was based on purely scientific considerations.

Mr. PALLONE. OK. Now, do you believe that NIH is in danger of falling behind other countries with respect to biomedical research due to the restrictions that are based on that August 9, 2001, date?

Dr. ZERHOUNI. It is very difficult to state categorically one way or the other. There is no doubt that about 50 percent of all the research that is published is currently published with results that are coming from NIH funding of this research. But there is no doubt that the rest of the world is also advancing. Fifty percent is published by the rest of the world. So I don't think that it would be—it is hard to predict but I don't think it would be in our best interests, if you will, to not continue to proceed in understanding the DNA programming, reprogramming issue that I think is core to biology in the 21st century.

Mr. PALLONE. Thank you.

Mr. Pitts.

Mr. PITTS. Thank you, Mr. Chairman.

Thank you, Dr. Zerhouni, for your testimony. First, how much NIH funding has gone toward human adult stem cell clinical trials beyond bone marrow transplants?

Dr. ZERHOUNI. Total funding for human non-embryonic stem cells is $203 million.

Mr. PITTS. Does that include the bone marrow transplants?

Dr. ZERHOUNI. I would think it does on all applications of adult stem cells.

Mr. PITTS. How much funding has NIH provided for human embryonic stem cell research and animal embryonic stem cell research?

Dr. ZERHOUNI. On a yearly basis, $203 million is a yearly number. We have been funding human non-embryonic stem cells at about $203 million, human embryonic stem cells at about $41 million a year, and non-human embryonic stem cells probably $150 million but I will check that number for you.

Mr. PITTS. How much NIH funding has gone toward the new human iPS research?

Dr. ZERHOUNI. The new iPS research, if you looked at many of the funding, for example, Dr. Daley, who is here, was funded by NIH as a Pioneer Award winner from the NIH, but the total before the discoveries were made is about $4 million. But we have, as you know, launched a program to encourage this area of research. and we are currently looking at proposals. It is a recent discovery, so you couldn't fund it as much until it was discovered.

Mr. PITTS. Now, how many vials of stem cells does NIH have available?

Dr. ZERHOUNI. I don't know the exact number but I can tell you that we have shipped about 1,400 vials of human embryonic stem cells from our stem cell bank. I don't know how many are available in the stem cell bank.

Mr. PITTS. Have you ever turned down requests for a sample of the approved lines due to lack of availability?

Dr. ZERHOUNI. I am not aware of that, but I know that scientists will tell you that there are lines that they wish not to use because there have been changes in the quality of those lines. So they tend to use fewer lines than all 21 lines because some of them don't necessarily function as they wish.

Mr. PITTS. Of the approved lines, how many have not yet been developed for research?

Dr. ZERHOUNI. So we had initially 71 unique derivations, and about 21 have been developed and expanded and are available for research. About the same number were attempted to be developed but failed. The failure rate is quite high in developing these lines. And there are about 25 or 30 which have not been developed, have not been expanded for various reasons.

Mr. PITTS. Is it possible that some of those lines were not developed on mouse feeder cells?

Dr. ZERHOUNI. It is possible. Most of the—all the lines we have currently expanded have been developed on mouse feeder cells, which was the technology at the time.

Mr. PITTS. Do you have any idea of how many were not developed on mouse feeder cells?

Dr. ZERHOUNI. I think we know that the Goteborg University in Sweden has 16 derivations which have not been developed at all and are attempted to be developed on human—on non-mouse feeder cells.

Mr. PITTS. Now, you have stated before that the Bush-approved human embryonic stem cells are contaminated. However, Dr. James Thomson has stated that these cells can be washed and the contamination is not a problem. Are you aware of the study published by Dr. Thomson?

Dr. ZERHOUNI. So we looked at that several years—I don't know I declared that but we did look at this very carefully, and we have pointed out in testimony as well as in written statements that the fact that something is grown in mouse feeder cells makes applications much more difficult and FDA approval more difficult but not impossible. We do have other products like vaccines that have been developed in that way. So our testimony does not say it cannot be done, but it is a lot more difficult to do.

Mr. PITTS. Now, you said you weren't aware of any patient being successfully treated with embryonic stem cells. When is the soonest that you would anticipate clinical applications using embryonic stem cells?

Dr. ZERHOUNI. The one current clinical application at the FDA is one by a company, Geron I think is the name, G-e-r-o-n, for using human embryonic stem cells for spinal cord injuries. That is the only one that is near clinical application, has not yet been approved by FDA for trials.

Mr. PITTS. And how would treatments be affected by their propensity for tumor formation?

Dr. ZERHOUNI. That is a problem you need to resolve before you can implant human embryonic stem cells. This is why most of the researchers working with human embryonic stem cells need to continue to work on these programs so that they can move the cell to a point where it will no longer develop a tumor.

Mr. PITTS. Thank you, Mr. Chairman. I think my time is up. It is hard to see.

Mr. PALLONE. You still have another 25 seconds if you want to use them.

Mr. PITTS. Well, I will ask one more. Why did NIH not fund clinical trials for Harvard researcher Denise Faustman even though she reversed diabetes in mice and was FDA approved to start trials?

Dr. ZERHOUNI. I am a little stumped on this one. I don't know the details of this particular researcher and the particular trial. so I will get back to you on the record for that.

Mr. PITTS. All right. Thank you, Mr. Chairman.

Mr. PALLONE. Ms. DeGette.

Ms. DEGETTE. Thank you very much, Mr. Chairman.

Dr. Zerhouni, I want to ask you, you said in your opening statement that this type of research, the general category of cell-based research, is one of the most important, if not the most important, forms of research we can do going forward in the future. What is the entire NIH budget?

Dr. ZERHOUNI. About $29 billion.

Ms. DEGETTE. Twenty-nine billion dollars. What is the total budget for the cell-based research including embryonic and non-embryonic?

Dr. ZERHOUNI. About $655 million a year.

Ms. DEGETTE. Six hundred and fifty-five million dollars a year. So I think probably if Congress were willing to authorize and appropriate a substantially higher research budget for all of these types of research, the NIH could probably find some people who would—some researchers who would be willing to take those grants and to make them into some promising discoveries, don't you?

Dr. ZERHOUNI. Definitely.

Ms. DEGETTE. Do you think the NIH would need to have more research to really make this kind of——

Dr. ZERHOUNI. If we could have more resources, we could accelerate this research much faster.

Ms. DEGETTE. And if we accelerated the research faster without predicting specific advances, what kinds of things do you think could happen?

Dr. ZERHOUNI. Well, clearly, as I said, the scientific community is making rapid progress in understanding these factors, these molecular programming factors. Every week, every 2 weeks, we get a report of scientists, for example, developing a very potent capable line, both in humans as well as in animal systems. The question though is going to be, how fast can you do this. Now, this deprogramming advance, this breakthrough, happened because we learned of the factors that were in this first program. Now, we are going to learn more and go forward into this route, as we can fund scientists to do that.

Ms. DEGETTE. Will the current embryonic stem cell lines, the 21, give or take a little, lines that still are allowed to be used with Federal dollars by federally-funded labs be sufficient to sustain this type of future research?

Dr. ZERHOUNI. Scientists will tell you that they need access to more cell lines that are earlier in their history. What happens is, as you cultivate a cell line, over time it accumulates changes, both genetic changes and software changes, program changes, which makes a lot of scientists say I would rather have a cell which is early in this development right here so I can understand the——

Ms. DEGETTE. Not to cut you off but what you are saying is these cell lines that existed as of August 2001 are now getting old from a research standpoint and the researchers would like to have newer stem cell lines?

Dr. ZERHOUNI. Many researchers can use them, they are using them, but many cannot.

Ms. DEGETTE. Now, the way it works, both with approved lines at the NIH and also private researchers is, they take cell lines that are developed from embryos which were created for in vitro fertilization clinics and not used by the patients and then slated to be thrown away, correct? I mean, these embryos are——

Dr. ZERHOUNI. I would assume that is true, but I don't know all the details of every case.

Ms. DEGETTE. OK. I will ask the researchers. I wanted to ask you if you are familiar with this Brazilian diabetes study that some have referred to today, and whether or not in fact that study

showed U.S. researchers that diabetes was curable by adult stem cells.

Dr. ZERHOUNI. I am familiar with that study, and this is the study that I think Congressman Pitts was mentioning. Actually the study was conceived by a researcher at Northwestern University and the idea there was this: type 1 diabetes is probably an autoimmune disease where your own immune system is destroying your own cells. So again, along the line of what I described where you use bone marrow stem cells, adult stem cells to replace the immune system. The idea then was, why don't we use the treatment that was developed for cancer patients into young type 1 diabetes patients to prevent the destruction of their stem cells. When that science was reviewed by our ethics experts and by experts in bone marrow transplants, it was felt that this would be unethical because the mortality rate is 5 percent in these diseases. Now, you can take that risk when you are dealing with a cancer that has a life expectancy of a year, like leukemia, but the problem is, type 1 diabetes is manageable today. We have patients who live almost normal lives. So the risk-benefit ratio as assessed by the ethical boards, the institutional review board said this isn't something that should be started in children, we should start it in adults perhaps or with a different risk ratio and not go forward with——

Ms. DEGETTE. So that was never really in clinical trials in the United States, correct?

Dr. ZERHOUNI. Not that I know of because of the ethics issues.

Ms. DEGETTE. I have one last question. Right now does the NIH have ethical oversight over the embryonic stem cell research that is conducted at the State level or by private firms?

Dr. ZERHOUNI. Well, as you know, we can only use Federal funds for the approved uses of embryonic stem cells so we cannot really have that oversight responsibility. I think that this is something that I wish common ground could be found over time. I think NIH has always played the harmonizing role and prevented in fact unethical uses as well as promoted the good use of science, so I would say that no, we do not, and I wish we did.

Ms. DEGETTE. And do you think that the NIH would have the capability of developing such ethical oversight over cell-based research?

Dr. ZERHOUNI. Definitely I think NIH should have an enhanced role in that. I think we have shown over the years that we can do this. We have regulated, for example, gene therapy through the Recombinant DNAAdvisory Committee for over 30 years. It has worked very well. And the same thing is true now with biosecurity issues. I think we have the talent and frankly, I don't know of any other organization in the world that could do a better job than NIH.

Ms. DEGETTE. Thank you very much, and thank you for joining us, Dr. Zerhouni.

Dr. ZERHOUNI. Thank you.

Mr. PALLONE. Mr. Deal.

Mr. DEAL. Thank you.

Dr. Zerhouni, let me first of all begin by thanking you for the excellent job you do in managing and directing NIH. I think political party affiliations and politics aside, I think everybody feels com-

fortable with your leadership and your knowledge of issues as you expressed on one of the more difficult issue that all of us are confronted with, this one that this hearing is about today, and I continue to be impressed by your leadership and thank you for that.

Dr. ZERHOUNI. Thank you.

Mr. DEAL. Let me ask you about one aspect. I wasn't here but I was listening to you over my computer in my office as I was doing some other things, and one of the things that is interesting, at least to me, and I wish you would expound upon it a little more, and that is the new human iPS research. Would you expound on that a little bit more? What is the degree of enthusiasm about this at NIH? Is it something that really has great potential, do you think?

Dr. ZERHOUNI. I think it is one of the biggest breakthroughs in stem cell research in recent years. We are very excited about it. We want to explore it. Because the idea that you can take a cell that has gone through full programming and then using four factors, you can deprogram it to be able to do other things, that is a venue that is extraordinarily exciting. We are putting out requests for proposals. I know we have received 29 proposals just in the first submission, the majority of which are on iPS cells. And remember that iPS cells are not just to replace cells in your body. They are also tools to make progress in other areas. For example, if you have a patient with a disease and you developed a pluripotent cell from that patient, think about what you can do to discover new treatments, new drugs, new therapies. Pharmaceutical companies are very excited about this potential. You could reduce the toxicity of drugs that today hurt patients because of heart toxicity or liver toxicity. So you could create liver cells or you can create heart cells and test the drug in vitro and prevent the toxicity. So there are many more uses than just the typical we are going to replace neurons or we are going to replace diabetic cells, much more exciting than—and I have to commend the scientists. Remember that what they did is, they learned from embryonic stem cells and immediately applied it in a way that will allow us to all go forward without the concerns that many of us have about this research.

Mr. DEAL. Well, thank you. I can see you have enthusiasm on this.

Dr. ZERHOUNI. I surely do.

Mr. DEAL. I think rightfully so, apparently. Although you do not control all of the research that is being done, especially on embryonic stem cell research, could you give us some idea from your perspective the magnitude of research that is being done that is not NIH-funded in this entire area?

Dr. ZERHOUNI. If you are referring to embryonic stem cell research alone, we feel that, because of initiatives in several States that the rest of the country spends more than we do at NIH for the $40 million that we spend. If you look at the totality though of what we do in this entire spectrum that I described, which is really a continuum, it is all sides of the same coin. When we look at that, we spend $655 million total, which is higher than any other actor out there. California just this week announced a $225 million investment in this type of research. So I would say that if you look at non-Federal sources, it probably equals the Federal in-

vestment, but I can't really tell you because I don't know what is happening in industry or in private entities.

Mr. DEAL. Well, Mr. Chairman, I am going to yield back my time, but again, thank you very much, Dr. Zerhouni, for being here.

Mr. PALLONE. Thank you, Mr. Deal.

Ms. Capps is recognized for questions.

Ms. CAPPS. Thank you very much for your patience with our proceedings in the House, and I want to first of all say since I didn't get to make an opening statement, how proud I am of the National Institutes of Health. I am bragging about all the—people know all the things that are wrong about Congress and I say but there is at least one good thing that is happening that really impacts lives in this country but it is also our biggest gift to the world that we are able to do all of that. That happens on the campus and other places as well.

I have a lot of questions I would like to ask you but I want to start with one that was touched upon in the opening remarks, and someone else may have asked you this. One of the things we are clearly missing in the national policy on stem cell research is a standard that we need that can be provided for us in the way of ethical standards, an ethical framework. We have now seen in my State of California and other States and other private entities a lot of push forward because of the lack of support from the Federal government. That is in one of the best natures of our country as well. But what is clearly missing from all of this from my perspective, but I would like to learn from you, how do you regard the importance of an ethical framework to guide both private and public research and endeavors into all stem cell research?

Dr. ZERHOUNI. Without harmonious and coherent oversight, which historically NIH has provided and is the best organization in the world to provide, you can see a world where different standards are going to be used. FDA will have real trouble finding out whether the research in California is more valid than the research in Washington or somewhere else. It will slow down progress for all stem cell research, not just embryonic stem cell research, because we need to characterize exactly what those cells do. There is the risk of tumor development. We need to control that. You cannot do that well at the speed you need to do it. It is hard enough when it is well overseen. It is, in my view, very shortsighted not to oversee it at the Federal level.

Ms. CAPPS. So if we were able to pass legislation that authorized Federal involvement, it wouldn't just be funding for research through NIH, it would also be to provide that ethical framework and guidelines for all of the research that is going on?

Dr. ZERHOUNI. I think some common ground has to be found. I really believe it is in the best interests of our millions of patients and the best interest of our country to act in unison when it comes to ethical oversight of any area of medical research.

Ms. CAPPS. OK. In whatever time I have left, and you may have touched on this before, but if there has been anything left out, there were efforts underway before 2001 and advances have been outside the Federal government's purview, both through States and through private enterprise. What is missing apart from that ethical framework? What could be the contribution of providing funds for

research specifically through the Federal government? What would you do?

Dr. ZERHOUNI. There was no Federal funding of human embryonic stem cell research before 2001.

Ms. CAPPS. Oh, I know that.

Dr. ZERHOUNI. And so we have had this 6 years experience of how to do this. I think what in my view would be very important is to get over in some fashion or another in a good way the issue of providing scientists with avenues of exploration with strong safeguards, strong ability for us to prevent some of the rightly scary scenarios that could develop. So we need to have that now because it wasn't that important in 2001 since the science wasn't advanced, but I can tell you, it is advancing at an enormous speed, and I think we owe it to ourselves to create a new framework to oversee this research over time. Now, it could be that you can separate funding from oversight. I mean, there are many ways that can be done, but we cannot just say stop this and do this and no oversight.

Ms. CAPPS. So in this vacuum, you say that some dangerous or unintended consequence could be developing, putting some of our citizens at risk?

Dr. ZERHOUNI. Well, let me just be frank here.

Ms. CAPPS. Yes.

Dr. ZERHOUNI. I get e-mails from clinics in various countries that do not have the oversight structure we do about promising treatments for stroke patients in the Dominican Republic, other treatments in countries that just don't have the oversight infrastructure we have. I am very concerned. As a physician I am concerned. I know the despair of patients who need treatment, and that can be abused and used. We have this in cancer therapies, and we are seeing it in stem cell therapies. Why would we let our citizens go in an unregulated, not-overseen environment with the risks we know about this research and say, go ahead, it is much better there than it is here? It is not correct to say that, and I am very worried that there will be people harmed by this.

Ms. CAPPS. So there is a moral component to this in terms of our leadership, and these are our citizens, many of them who are flocking to places because they have been promised certain things?

Dr. ZERHOUNI. Absolutely. I mean, look, hope is hope, and as you know, we need to really understand that.

Ms. CAPPS. Thank you.

Mr. PALLONE. Thank you.

Our ranking member, Mr. Barton, recognized for questions.

Mr. BARTON. Thank you, Mr. Chairman. I will be very brief.

I want to welcome you, Dr. Zerhouni. It is good to see you. I haven't seen you in person in a while though we have talked by telephone several times. I know the purpose of today's hearing is an update on stem cell research, but I can't pass up the opportunity to ask you to give us a brief review of the NIH reform bill that this committee passed on a bipartisan basis at the end of the last Congress. Could you kind of tell us where that is and what, if anything, we need to do to help you implement it?

Dr. ZERHOUNI. Well, first of all, let me thank you, Mr. Chairman. I think you have accomplished what NIH needed to have for many, many years. As you know, there had not been a reauthorization of

NIH for many years, and you have been able to do this with your colleagues on a bipartisan basis and I am very, very pleased and proud of the fact that both sides came together in authorizing the NIH Reform Act of 2006.

The main impact of the reauthorization, in my view, is that it has institutionalized the concept that as science is becoming more complex, as science is also converging between different Institutes, the NIH Reform Act has allowed us to have cross-collaborations with a Common Fund so that no one is being taxed, if you will, for doing the right thing across diseases. Now, we know, as you just heard, that many diseases, for example, multiple sclerosis or diabetes, are treated with the same approach because they are all autoimmune diseases. Well, those diseases obviously are taken care of by multiple Institutes. So I would say that the fact that also in the same year, the bill passed in 2006 and the Joint Resolution of Congress, the appropriators then decided to fund the Common Fund as a separate entity so that Institutes will no longer have to contribute to that, I thought that was a great statement of support. We appreciate it, and I think that you will see results of that on a going-forward basis that I think you would be surprised at the change in the ability of NIH to address cross-cutting issues that go beyond any one Institute's mission or Institute's focus.

Mr. BARTON. Well, I have asked Chairman Dingell to hold an oversight hearing where we could go into detail on it, so hopefully he will do that in the near future.

Ms. DEGETTE. Will the ranking member yield?

Mr. BARTON. Yes.

Ms. DEGETTE. As the Vice Chairman of the Committee, I will tell you, and a big supporter of that bill, I also want to thank you, Mr. Barton, for that legislation. I think it has been great. And I have also spoken with Mr. Dingell about doing oversight hearings and I expect we will be doing that this year.

Mr. BARTON. Anyway, it is good to see you, Doctor, and we will hopefully welcome you back soon to talk on some other issues.

I yield back, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Barton. I was going to say that now that you asked that question, we didn't need to have the hearing, but I guess—I am just kidding.

Next we have Ms. Baldwin recognized for questions.

Ms. BALDWIN. Thank you, Mr. Chairman, and I want to add my words of support for the incredible and unique role that the NIH plays in the world and in the United States. Following on Ranking Member Barton's comments, I feel like my constituents are beneficiaries in so many different ways, whether it is the results of the research that is funded, the funding that comes into research universities like the University of Wisconsin-Madison or in my own case having been raised by my grandparents, my grandfather was an NIH-funded scientist at the university, so I am a beneficiary in yet another unique way of NIH funding.

I want to talk about a couple of things sort of pivoting off the questions that you have gotten about ethical concerns and needing to have a harmonious oversight process. There is another role that NIH plays, which is priority setting through the process of reviewing the grant proposals, and because a part of the overall stem cell

research that is not being conducted through NIH, I am wondering what comments you might have of the role that NIH plays in priority setting in this overall endeavor.

Dr. ZERHOUNI. Well, again, I think as you have seen through history, NIH since 1945 has basically been the tempo maker for science in many ways. The first treatments, for example, for leukemia that changed the mortality in children from 95 percent to 5 percent were done because of that process, and we need to continue to do that. So my sense is that the more we have an open understanding of how to run this forward, given the fact that it is getting closer to clinical applications, needs to be enhanced.

Ms. BALDWIN. Now, I mentioned in my opening statement one of many concerns I have about the current funding policy for embryonic stem cell research is the message it sends to young, upcoming scientists in terms of what direction they should go in, but I am additionally concerned about the consequence of the current Federal policy because in many ways, it seems like we are maintaining two separate structures. I know in many research institutions, they have to build and equip two sets of labs, one that conducts NIH-funded research, a parallel, oftentimes a whole building is constructed and lab equipment is acquired. Do you have any sense of what sort of costs are involved in this sort of dual structure that is occurring all over the country?

Dr. ZERHOUNI. In all fairness, NIH does not impose separation of physical facilities. We have been extremely clear that you cannot use Federal funds for unapproved uses but you can account separately within your own laboratory for that. It is difficult to do though. Most of our researchers say, you know, I don't want to get in trouble, I would rather separate the two completely.

Ms. BALDWIN. That has certainly been my reflection in my home community.

Dr. ZERHOUNI. Right. So it is an impediment to the researchers, who really want to do risk management in the institutions. From our standpoint, we are satisfied with the accounting procedures that we have put in place, and we haven't had a case where there has been a significant issue that we have been concerned about. But I think at the end, the institutions, our concern about that—in California, I know that the first $225 million are actually dedicated to building separate facilities. I know that this is a concern out there.

Ms. BALDWIN. Lastly, we have had some discussion about how much funding has been devoted to the new iPS findings. Going forward, what sort of growth do you expect in terms of contributing funding to that?

Dr. ZERHOUNI. I cannot be precise, but I can see exponential growth in the field of induced pluripotent stem cells for the reasons that I mentioned. One, it is much more practical, easier to do. It also highlights different ways of programming DNA, as I said at the beginning. It has multiple uses other than just the clinical use, because right now these cells are not ready for clinical use. They are generated using viruses that carry these factors, so we have to do more research on them to find a way to use them safely in the environment. But my sense is that already we know of many researchers—you are going to hear from Dr. Daley, who is a leader

in that field—many researchers, many applications, and researchers who are currently funded by NIH, redirecting their research to that area. So you will see—I think you will see major growth in that field.

Ms. BALDWIN. Dr. Zerhouni, thank you very much for your time.

Mr. PALLONE. Thank you.

The gentleman from New Jersey, Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman.

Dr. Zerhouni, thank you again for being here today. We very much appreciate your testimony and your leadership at NIH over the years. I think you know that I personally am an admirer of yours and appreciate the dialogs that we have had over these years.

Mr. Chairman, I just wanted to submit two things for the record that I referenced in my opening statement. One is the autologous—this is a Journal of the American Medical Association study published April 11, 2007, documenting the progress that has been made with adult stem cell research in type 1 diabetes. I can give this to you. I would like to submit it for the record, please.

Mr. PALLONE. Without objection.

Mr. FERGUSON. And the other was the quotation that I mentioned from Dr. James Thomson that was in an article in the Washington Post from November 30, 2007. I would like to submit that.

Mr. PALLONE. Without objection, so ordered.

[The information follows:]

PRELIMINARY COMMUNICATION

Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

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Context Type 1 diabetes mellitus (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells. Previous animal and clinical studies suggest that moderate immunosuppression in newly diagnosed type 1 DM can prevent further loss of insulin production and can reduce insulin needs.

Objective To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 DM.

Design, Setting, and Participants A prospective phase 1/2 study of 15 patients with type 1 DM (aged 14-31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid decarboxylase. Enrollment was November 2003-July 2006 with observation until February 2007 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil. Patients with previous diabetic ketoacidosis were excluded after the first patient with diabetic ketoacidosis failed to benefit from AHST. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m^2) and granulocyte colony-stimulating factor (10 μg/kg per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (4.5 mg/kg).

Main Outcome Measures Morbidity and mortality from transplantation and temporal changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points: serum levels of hemoglobin A_{1c}, C-peptide levels during the mixed-meal tolerance test, and anti–glutamic acid decarboxylase antibody titers measured before and at different times following AHST.

Results During a 7- to 36-month follow-up (mean 18.8), 14 patients became insulin-free (1 for 35 months, 4 for at least 21 months, 7 for at least 6 months; and 2 with late response were insulin-free for 1 and 5 months, respectively). Among those, 1 patient resumed insulin use 1 year after AHST. At 6 months after AHST, mean total area under the C-peptide response curve was significantly greater than the pretreatment values, and at 12 and 24 months it did not change. Anti–glutamic acid decarboxylase antibody levels decreased after 6 months and stabilized at 12 and 24 months. Serum levels of hemoglobin A_{1c} were maintained at less than 7% in 13 of 14 patients. The only acute severe adverse effect was culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others. There was no mortality.

Conclusions High-dose immunosuppression and AHST were performed with acceptable toxicity in a small number of patients with newly diagnosed type 1 DM. With AHST, beta cell function was increased in all but 1 patient and induced prolonged insulin independence in the majority of the patients.

Trial Registration clinicaltrials.gov Identifier: NCT00315133

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TYPE 1 DIABETES MELLITUS (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells.[1] The course of autodestruction is subclinical until the amount of beta-cell mass is insufficient to maintain glucose homeostasis. Thus, at the time of clinical diagnosis, approximately 60% to 80% of the beta-cell mass has been destroyed.[2]

Type 1 DM comprises only 5% to 10% of all diabetic etiologies but is associated with a high frequency of vascular complications and compromises quality and expectancy of life.[3,4] Patients with type 1 DM depend on exogenous insulin administration for survival and for control of long-term complications. The best-established treatment is tight control of blood glucose achieved by frequent daily injections or continuous subcutaneous in-

For editorial comment see p 1599.

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fusion of insulin, ie, intensive insulin therapy. This treatment reduces the risk of retinopathy, nephropathy, and neuropathy by 35% to 90% when compared with conventional therapy with 1 to 2 injections per day.[5]

Subgroup analysis of the Diabetes Control and Complications Trial showed that patients with a larger beta cell reserve demonstrable by serum C-peptide levels presented a slower decline of these levels during the study and experienced fewer microvascular complications than patients with low or undetectable C-peptide concentrations. Therefore, beta cell preservation is another important target in the management of type 1 DM and in the prevention of its related complications.[6]

Many clinical trials have evaluated the role of immunointervention in preventing residual beta cell loss by blocking the autoimmune response with prednisone,[7] azathioprine,[8,9] prednisone plus azathioprine,[10] cyclosporine,[11] antibodies against CD3,[12,13] heat shock protein,[14] and rabbit antithymocyte globulin.[15] These therapies were shown to induce a slower decline or some improvement in C-peptide levels when compared with placebo groups. However, almost all patients required exogenous insulin use.

Since 1996, organ-threatening systemic lupus erythematosus[16] and other autoimmune diseases[17] have been successfully treated with high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST). Organ function was salvaged and in many cases improved following AHST. In animal models, allogeneic bone marrow transplantation prevents both insulitis and the development of type 1 DM in susceptible strains of mice.[18]

On the basis of these observations, we initiated a phase 1/2 study in November 2003 analyzing the safety, metabolic effects, and ability of AHST to preserve beta cell function in patients with newly diagnosed type 1 DM. Here we report the first prospective trial, to our knowledge, of stem cell therapy in human DM. We describe 15 patients with type 1 DM, submitted to AHST, and observed from 7 to 36 months (mean 18.8 months) after treatment.

METHODS

Patients

Inclusion criteria were patients of both sexes, aged 12 to 35 years, with a diagnosis of type 1 DM during the previous 6 weeks confirmed by measurement of serum levels of anti–glutamic acid decarboxylase (anti-GAD) antibodies. From September 2003 to February 2007, more than 100 patients were offered screening for enrollment (most by e-mail or telephone interviews). Of those patients, 52 fulfilled the inclusion criteria and were personally interviewed, 15 patients opted to participate, and all 15 were subsequently enrolled between November 2003 and July 2006 and observed until February 2007 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil.

The main reasons for not fitting the inclusion criteria were the duration of type 1 DM longer than 6 weeks or previous episodes of diabetic ketoacidosis. Concerns about the probable adverse effects related to the immunosuppression were the main cause of refusing study participation. The first patient enrolled was diagnosed with diabetic ketoacidosis and received hydrocortisone (200 mg) and methylprednisolone (125 mg) to prevent rabbit antithymocyte globulin reactions. This patient's continued insulin dependence after AHST (see Results section) resulted in modification of the protocol to exclude patients with diabetic ketoacidosis-onset diabetes and to remove glucocorticoids from the immunosuppression regimen. Other exclusion criteria were positive serology for human immunodeficiency virus, hepatitis B or C, and underlying hematologic, nephrologic, cardiac, psychiatric or hepatic disease. Serum levels of β-human chorionic gonadotropin were determined in all women to exclude pregnancy.

Participants were initially treated by their own physicians until admission to the present study. Race/ethnicity was self-reported and was assessed because of the diversity of the Brazilian population along with its prevalence of black/white biracialiy. HLA class II typing was performed at low/medium resolution using reverse sequence-specific oligonucleotide probes (RSSOP-One Lambda, Canoga Park, Calif), and at high resolution using sequence–specific primers (SSP, One Lambda). The study protocol was approved by the research ethics committees of both the University Hospital of the School of Medicine of Ribeirão Preto and the Brazilian Ministry of Health. An informed consent according to the Declaration of Helsinki was signed by patients or their parents.

Study Design

Key end points of the study were morbidity and mortality from transplantation and temporal changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points were serum levels of hemoglobin A_{1c}, C-peptide levels during the mixed-meal tolerance test, and anti-GAD antibody titers measured before and at different times following transplantation.

Blood samples for hemoglobin A_{1c} determination were collected after an 8-hour fast at pretreatment and every 3 months thereafter. Blood samples for the determination of C-peptide, an indirect measure of endogenous insulin secretion, were collected in the fasting state and every 30 minutes during a 2-hour mixed-meal tolerance test. The morning and evening doses of insulin were withheld the day before the test at pretreatment, 6 months, 1 year and then yearly following AHST. Serum anti-GAD antibodies were titrated at the same intervals.

All patients were encouraged to self-monitor blood glucose at least twice daily (before and 2 hours after different meals and/or at 3 AM) between mobilization and the conditioning phase and then indefinitely after discharge from the hospital. During hospitalization, blood glucose monitoring was performed before meals and at bedtime. Insulin titration was based on fasting before meals and

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2 hours after meals with target blood glucose levels of less than 120 mg/dL (6.7 mmol/L) and less than 140 mg/dL (7.7 mmol/L), respectively. The dose of insulin was reduced by 1-2 IU/mL if patients presented clinical findings of hypoglycemia and/or blood glucose levels less than 4.9 mmol/L (90 mg/dL).

Standard recommendations for lifestyle modification (performing physical activities and a low-sugar diet) after AHST were made to all patients irrespective of exogenous insulin use. Intensive insulin therapy was the treatment of choice for all patients who needed exogenous insulin. All changes in insulin doses were ordered by one of the endocrinologists of the team (C.E.B.C.).

Stem Cell Mobilization Regimen

Peripheral hematopoietic stem cells were mobilized with cyclophosphamide and granulocyte colony-stimulating factor (Leucin, Laboratory Bergamo, São Paulo, SP, Brazil). Cyclophosphamide (2 g/m^2) was infused in 2 doses 12 hours apart in 250 mL of saline solution over 1 hour. Uroprotection was achieved with intravenous saline infusion at 250 mL/h, initiated 4 hours before cyclophosphamide infusion and continued for 16 hours. Mesna (sodium 2-mercaptoethanesulfonate), 4 g/m^2, was infused over 24 hours to bind toxic cyclophosphamide metabolites in the bladder. Granulocyte colony-stimulating factor (10 µg/kg per day) was injected subcutaneously starting 1 day after cyclophosphamide infusion and continuing until leukapheresis was completed.

Leukapheresis using a continuous-flow blood cell separator was initiated when the rebounding CD34$^+$ cells reached 10 cells/µL. Apheresis was continued daily until the number of harvested progenitor cells reached a minimum of 3.0×10^6 CD34$^+$ cells/kg body weight. Unmanipulated peripheral blood stem cells were frozen in 10% dimethyl sulfoxide in a rate-controlled freezer and stored in the vapor phase of liquid nitrogen.

Conditioning (Immune Ablative) Regimen

Conditioning was achieved with cyclophosphamide and antithymocyte globulin. Cyclophosphamide was given intravenously in divided doses of 50 mg/kg per day over 1 hour on days 5, 4, 3, and 2 before stem cell infusion. Rabbit antithymocyte globulin (thymoglobulin, IMTIX Sangstat, Lyon, France) was administered at a dose of 0.5 mg/kg per day on day 5 before, and at a dose of 1 mg/kg per day on days 4, 3, 2, and 1 before stem cell infusion. Except for the first patient, prophylaxis of antithymocyte globulin reactions was done with dexchlorpheniramine (6 mg by mouth) avoiding the use of glucocorticoids. Stem cell infusion was performed on day 0 and granulocyte colony-stimulating factor (5 µg/kg per day) was administered subcutaneously from day 5 after stem cell infusion until neutrophil count was greater than 1000/µL.

Supportive Care

Patients were isolated in rooms equipped with high-efficiency particulate air filters. After hospital admittance for conditioning, antimicrobial prophylaxis was started with ciprofloxacin (500 mg every 12 hours intravenously), acyclovir (250 mg/m^2 every 8 hours by mouth until day 35), amphotericin B (0.2 mg/kg per day intravenously and 10 mg/d aerosolized). Ciprofloxacin was replaced by cefepime (2 g every 12 hours intravenously) during febrile episodes. After engraftment, antifungal prophylaxis was changed to fluconazole (400 mg/d by mouth until day 60) and sulfamethoxazole/trimethoprim (800/160 mg every 12 hours by mouth 2 times per week) or dapsone (100 mg 3 times per week) was given through day 60 for prevention of *Pneumocystis jiroveci* pneumonia. Weekly monitoring of cytomegalovirus antigenemia in circulating neutrophils was performed until day 60.

During pretreatment evaluation, semen samples were collected and frozen in liquid nitrogen. Leuprolide acetate depot (3.75 mg by intramuscular injection) was given to female patients to prevent menstrual bleeding and to protect ovarian function. All women opted to use oral contraceptive methods after AHST.

Laboratory Assessment of Diabetic Status

Serum C-peptide levels were measured by radioimmunoassay using commercial kits (Diagnostic Systems Laboratories Inc, Webster, Tex). The lower limit of detection was 0.1 ng/mL and undetected values were reported as 0.1 ng/mL. Serum levels of anti-GAD antibodies were measured by radioimmunoassay using commercial kits (RSR Limited, Cardiff, UK) and the results were considered positive if greater than 1 U/mL. Hemoglobin A_{1c} was measured by low-pressure liquid chromatography.

Statistical Analysis

Multiple comparisons of total area under the curve of serum C-peptide measured during the mixed-meal tolerance test (during fasting and at 30, 60, 90, and 120 minutes) were made using a model of multiple regression of mixed effects for periods 0, 6, 12, and 24 months posttransplantation. The same model was used to test anti-GAD titers. To present the mean variation of hemoglobin A_{1c} levels with time, a model of linear regression of random effects was constructed using the following equation: $y = \beta_0 + \beta_1 \times \log(\text{time}) + \beta_2 \times [\log(\text{time})]^2$, in which each parameter represents a random effect in each patient. These models are characterized to present residuals that are normally distributed. Data analysis was completed using PROC MIXED, SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

Fifteen patients aged 14 to 31 years (mean 19.2 years) were enrolled in the study between November 2003 and July 2006. Individual demographic characteristics and follow-up variables are listed in TABLE 1 and TABLE 2. Mean body mass index (calculated as weight in kilograms divided by height in meters

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squared) at diagnosis was 19.8 (range, 16.6-23.4) and mean plasma glucose was 391 mg/dL (21.7 mmol/L) (range, 130-612 mg/dL [7.2-33.9 mmol/L]). All patients presented symptoms of hyperglycemia (polyuria, polydipsia, and weight loss) at diagnosis. Six patients presented both HLA haplotypes characteristic of high risk for type 1 DM, 7 patients presented 1 of those haplotypes and 2 patients presented 0.

Time from diagnosis to mobilization ranged from 25 to 56 days (mean, 38.4) and mean duration of hospital stay for transplantation (from conditioning to discharge) was 19.2 days (range, 15-24). Mean number of infused $CD34^+$ cells was 11.0×10^6/kg (range, 5.8-23.1×10^6/kg). Neutrophil engraftment (>500/μL) occurred between days 8 and 10 after transplantation (mean 9.1 days) and platelet engraftment (>20 000/μL) was detected between day 0 and day 15 after transplantation (mean 11.4 days).

Most patients had febrile neutropenia, nausea, vomiting, alopecia, and

Table 1. Pretreatment and Follow-up Variables of Patients With Type 1 Diabetic Mellitus Undergoing Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation (Patient Demographics, HLA Type, Blood Glucose, Hemoglobin A_{1c}, Weight Loss, Hyperglycemia Symptoms, Body Mass Index)

Patient No./Sex	Age, y	Race	HLA Type	Blood Glucose at Diagnosis, mg/dL	Hemoglobin A_{1c} at Pre-transplantation, %	Weight Loss at Diagnosis, %	Duration of Symptoms of Hyperglycemia, d	Follow-up, mo†	Body Mass Index‡			
									Pre-treatment	Pre-mobilization	Pre-conditioning	Last Visit
1/M	24	Biracial§	DRB1*03, *04/DQB1 *0201,*0302	477	7.6	14.0	35	12	22.6	21.8	22.5	21.9
2/M	27	Black	DRB1*03, *04/DQB1 *0201,*0302	589	7.5	2.8	2	36	22.9	24.1	23.4	21.8
3/M	21	Biracial§	DRB1*03, *04/DQB1 *0201,*0302	381	9.3	3.0	5	32	19.0	19.6	19.6	19.9
4/M	15	White	DRB1*01, *07/DQB1 *0201,*0501	321	8.0	9.0	10	32	23.0	22.4	22.3	22.3
5/M	16	White	DRB1*04,*10/ DQB1*0302, *0501	404	7.7	14.5	21	25	17.5	19.0	19.0	18.6
6/M	14	White	DRB1*01,*03/ DQB1*0201, *0501	504	7.3	15.0	7	22	23.4	23.3	23.4	21.5
7/F	20	White	DRB1*04,*12/ DQB1*0302, *0301	391	10.0	11.0	20	21	16.8	20.7	20.9	19.3
8/M	16	Biracial§	DRB1*03,*04/ DQB1*0201, *0302	314	5.4	16.0	50	18	17.6	18.9	17.9	18.0
9/F	18	White	DRB1*03,*13/ DQB1*0201, *0602	330	6.7	7.0	14	18	19.1	20.4	19.1	19.2
10/F	17	White	DRB1*01/ DQB1*0501	612	8.9	5.0	30	17	20.1	20.7	19.6	21.9
11/M	16	Biracial§	DRB1*03,*04/ DQB1*0201, *0302	130	5.4	5.0	5	15	17.8	17.8	17.6	17.8
12/F	14	Biracial§	DRB1*01,*04/ DQB1*0302, *0501	581	8.1	7.0	7	10	19.8	19.7	20.3	21.6
13/M	24	White	DRB1*03/ DQB1*0201	269	8.1	9.1	14	9	18.4	18.9	18.2	18.3
14/M	31	White	DRB1*04,*04/ DQB1*0302, *0402	273	7.8	7.1	14	8	22.1	21.5	21.5	22.1
15/M	16	White	DRB1*01,*03/ DQB1*0201, *0501	291	10.1	12.7	30	7	16.6	17.6	17.8	17.2
Mean (SD)	19.2 (5.1)			391.1 (137.8)	7.86 (1.38)	9.2 (4.4)	17.6 (13.5)	18.8 (9.2)	19.8 (2.4)	20.4 (1.9)	20.2 (2.0)	20.1 (1.8)

SI conversion factor: to convert glucose to mmol/L, multiply by 0.0555.
†Months since mobilization regimen.
‡Calculated as weight in kilograms divided by height in meters squared.
§Denotes patients who self-identified as having both black and white racial parentage.

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other common transplantation-related complications due to the drugs used in the mobilization and conditioning (TABLE 3). Bilateral pneumonia of unidentified etiology that required supplementary oxygen therapy and responded completely to broad-spectrum antibiotics occurred in patient 2 and was the only severe acute complication of AHST. During long-term follow-up, patient 3 developed autoimmune hypothyroidism and transient renal dysfunction associated with rhabdomyolysis, a complication that was treated successfully with levothyroxine. Measurements of gonadal function (follicle-stimulating hormone and lutenizing hormone in both sexes, testosterone in men, and estradiol in women) were in the normal range in 14 of 15 patients. Patient 2 fathered a child 2 years after transplantation (by natural means) and patient 10 presented mild hypergonadotropic hypogonadism at 12 months following transplantation. There was no mortality.

The first patient enrolled in the study presented few minor complications of transplantation (Table 3). However, this patient's insulin requirements increased progressively and at 12 months following transplantation when he abandoned follow-up, he was using a dose 250% higher than his initial requirement (1.7 IU/kg per day). His hemoglobin A_{1c} levels were 7.6%, 8.2%, 8.9%, 9.7%, and 11.1% at 0, 3, 6, 9, and 12 months following transplantation, respectively, and his C-peptide levels were low at study entry (basal level, 0.4 ng/mL; peak stimulated level, not available) and did not increase after 1 year (basal, 0.3 ng/mL; peak stimulated level, 0.4 ng/mL) (Table 1 and Table 2). Anti-GAD antibody levels were 36.0, 9.9, and 7.7 U/mL at 0, 6, and 12 months following transplantation, respectively. Since the protocol was changed after treating this patient, his data were not included in the statistical analysis. Thus, hemoglobin A_{1c} (FIGURE 1) and results of C-peptide levels (FIGURE 2) refers to 14 patients fulfilling the same selection criteria and receiving the same conditioning regimen.

Before the mobilization regimen, all patients required exogenous insulin (mean, 0.38 IU/kg per day, range, 0.13-0.58). By February 2007, 13 patients were free from exogenous insulin for 1 to 35 months (mean, 16.2) (Table 2). Patient 7 used a fraction of the initial insulin dose for 20 months and discontinued insulin use in January 2007. Patient 10 discontinued insulin transiently during transplantation (from 2 days before to 7 days after), then resumed insulin use (0.34 IU/kg per day) and after progressive reduction in its dose discontinued insulin again 1 year after transplantation. Patient 11 was free from insulin from 3 days before trans-

Table 2. Pretreatment and Follow-up Variables of Type 1 Diabetic Patients Undergoing Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation (Anti–Glutamic Acid Decarboxylase, C-Peptide, Insulin Dose, Insulin-Discontinuation Time, Insulin-Free Time)

Patient No.	Anti–Glutamic Acid Decarboxylase, U/mL*†					C-Peptide Fasting/ Peak Stimulated, ng/mL†					Insulin Dose, IU/kg per Day			Time of Insulin Discontinuation, d†	Time Free From Insulin, mo
	Diagnosis	6 mo	12 mo	24 mo	36 mo	Pretreatment	6 mo	12 mo	24 mo	36 mo	Pretreatment	Premobilization	Preconditioning		
1	36.0	9.9	7.7			0.4/NA	0.4/0.4	0.3/0.4			0.48	0.51	0.79	Not discontinued	0
2	49.0	19.0	20.0	17.0	23	0.3/0.6	0.3/0.7	0.5/1.2	0.5/1.1	2.0/4.6	0.29	0.34	0.20	+6	35
3	1.1	0.0	0.0	0.0	‡	0.3/1.0	0.9/1.6	1.6/6.2	1.7/1.8		0.39	0.27	0.21	+34	30
4	22.0	20.0	20.0	17.0		1.0/2.8	1.3/2.4	1.8/8.2	3.2/6.9		0.35	0.23	0.18	+2	31
5	51.0	51.0	24.0	41		0.6/3.1	2.7/12.3	0.9/5.0	2.4/8.4		0.52	0.38	0.27	−1	24
6	17.0	4.6	1.6			0.8/1.8	2.1/8.0	0.6/1.5			0.26	0.42	0.42	−6	21
7	4.0	14.0	9.0			0.09/0.09	0.3/2.6	1.6/2.5			0.48	0.44	0.17	+610	1
8	48.0	9.5	6.4			0.3/0.4	0.7/2.0	1.3/4.8			0.35	0.55	0.34	0	17
9	102.0	31.0	30.0			0.06/0.4	0.6/2.5	1.1/6.8			0.42	0.35	0.29	−1	17
10§	44.0	19.0	13.0			0.4/1.3	0.3/1.7	0.3/3.5			0.61	0.29	0.25	−2	5
11‖	11.0	4.4	6.5			0.9/0.4	0.3/1.7	0.8/0.7			0.10	0.13	0.20	−3	12
12	11.0	10.0				0.09/0.3	2.0/7.9				0.22	0.45	0.58	0	9
13	24.0	21				0.5/3.1	0.5/2.9				0.28	0.58	0.28	−2	8
14	37.0	29				0.1/1.6	3.0/9.2				0.32	0.37	0.05	−3	7
15	21.1					0.5/0.8					0.66	0.44	0.67	−1	6
Mean (SD)	31.8 (25.5)	17.3 (13.2)	12.5 (9.6)	18.7 (16.8)		0.4/1.3 (0.3/1.0)	1.1/4.0 (0.9/3.7)	1.0/3.7 (0.5/2.6)	1.9/4.5 (1.1/3.7)		0.38 (0.14)	0.30 (0.12)	0.32 (0.20)	1.7 (10)¶	14.8 (11.2)

Abbreviation: NA, not available.
SI conversion factor: to convert C-peptide to nmol/L, multiply by 0.331.
*Statistical analysis of mean anti-glutamic acid decarboxylase values: $P = .02$ between pretreatment and 6 mo; $P = .13$ between 6 and 12 mo; $P = .46$ between 12 and 24 mo.
†Times related to stem cell infusion.
‡Empty cells denote follow-up times not yet reached by the respective patient.
§This patient had transient insulin discontinuation from 2 days prior until 7 days following stem cell infusion and insulin was discontinued again after 1 year (see Results).
‖This patient was free from exogenous insulin from 3 days prior until 360 days following stem cell infusion and then resumed insulin use at the dose of 0.43 IU/kg per day (see Results).
¶Excluding patient 7.

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plantation until 360 days after, when insulin use was resumed (0.43 IU/kg per day) after an upper respiratory tract viral infection. The time course of individual insulin doses in different phases is presented in Table 2.

All 14 patients treated according to the same protocol (patients 2-15) complied with blood glucose self-monitoring and scheduled medical appointments. The time course of hemoglobin A_{1c} concentrations of those patients is presented in Figure 1. There was a statistically significant reduction of hemoglobin A_{1c} levels after transplantation. At entry into the study, 11 of 14 patients presented values above 7% and within 3 months after AHST, hemoglobin A_{1c} values were below this level and were maintained during follow-up (except for the relapsing patient 11).

The time course of fasting and peak stimulated C-peptide levels and of the area under the curve response curve during mixed-meal tolerance test are shown in Table 2 and Figure 2. Compared with pretreatment levels, peak stimulated C-peptide levels following transplantation increased in 11 of 13 patients studied at 6 months, in 8 of 10 patients studied at 12 months, in 4 of 4 patients studied at 24 months, and in 1 patient studied at 36 months. Mean peak stimulated C-peptide levels were 1.3 ng/mL at pretreatment and following transplantation 4.0 ng/mL at 6 months, 3.7 ng/mL at 12 months, and 4.5 ng/mL at 24 months. The increase at 24 months following transplantation was statistically significant compared with all other time points (Table 2). Mean area under the curve of C-peptide levels before transplantation (92.0 ng/mL per 2 hours) showed a statistically significant increase at 6 months following transplantation (332.7 ng/mL per 2 hours), which was not different from 12 months (289.2

Table 3. Transplantation Complications and Gonadal Function Tests*

Patient No.	Mobilization Complications	Minor Conditioning Complications†	Major Conditioning Complications	Late Complications	Last Visit, mo	Follicle-Stimulating Hormone, mIU/mL‡	Luteinizing Hormone, mIU/mL§	Estradiol, pg/mL	Testosterone, ng/dL
1	Nausea, vomiting, pyoderma	Anorexia, fever, catheter infection	None	None	12	6.9	9.8		315
2	Dysuria		Bilateral pneumonia (from day −2 to day +14)	None	36	8.0	2.5		495
3	None	Diarrhea, fever, sinusitis, skin rash	None	Rhabdomyolysis, hypothyroidism (day + 360)	32	4.8	4.2		379
4	Nausea, vomiting	Fever, catheter infection, herpes simplex, right cephalic vein thrombosis	None	Leucopenia	32	13.3	8.0		475
5	None	Anorexia, fever, urticaria	None	None	25	9.0	2.8		401
6	None	Anorexia, fever, skin rash, hypokalemia, mucositis	None	None	22	7.4	5.3		364
7	None	Diarrhea, skin rash, fluid overload	None	None	21	10.3	11.0	35	
8	None	Diarrhea, skin rash	None	None	18	3.2	7.8		335
9	None	Anorexia, diarrhea, fever	None	None	18	12.0	2.5	43	
10	None	Skin rash	None	Hypogonadism (day +360)	17	31.4	14.8	38	
11	Fever	Anorexia, fever	None	None	15	7.6	3.4		372
12	None	Epistaxis	None	None	10	1.7	5.8	<20	
13	Fever	Diarrhea, skin rash	None	None	9	6.0	3.2		289
14	Sialorrhea	Fever, skin rash, fluid overload	None	None	8	9.2	2.4		676
15	Nausea, vomiting, anorexia	Fever, skin rash	None	None	7	8.6	1.8		292

SI conversion factor: to convert estradiol to pmol/L, multiply by 3.671 (normal range, >20). To convert testosterone to nmol/L, multiply by 0.0347 (normal range, >250).
*Gonadal function tests were determined at the last visit. Estradiol levels were measured only in women in the follicular phase and testosterone levels were measured in men.
†All patients except 4, 5, 7, and 8 presented with nausea; vomiting presented in all except 4 and 6; all presented with alopecia.
‡Normal range: 0.9 to 15.
§Normal range: 1.3 to 13.0.

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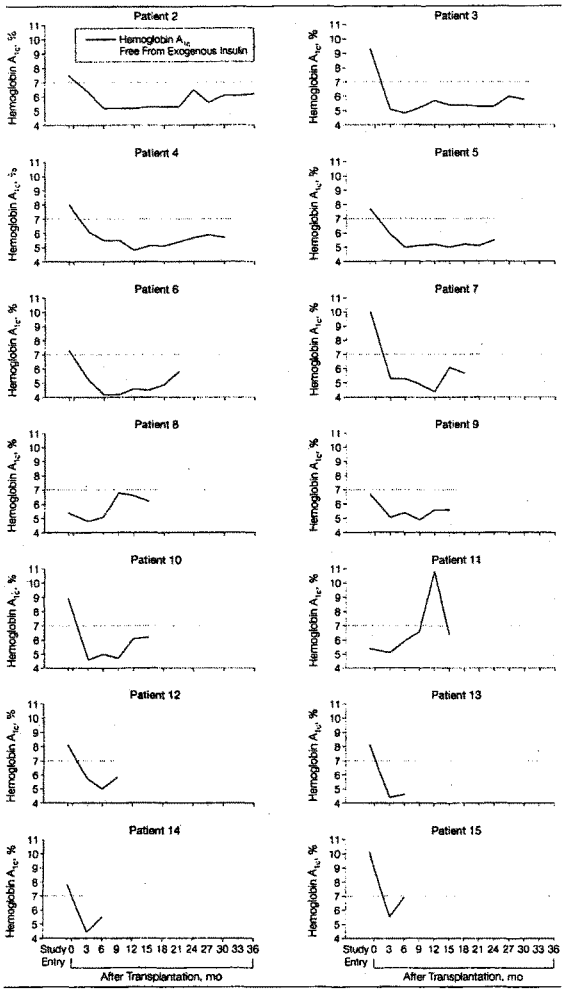
Figure 1. Hemoglobin A_{1c} Levels and Periods Free From Exogenous Insulin Requirement



Data from patient 1 were not included. Mean hemoglobin A_{1c} values were adjusted with a model of linear regression of random effects based on the following equation: $y = 7.8185 - 2.4237 \times \log(\text{time}) + 0.5512 \times [\log(\text{time})]^2$. Differences between pretransplantation and all posttransplantation levels were statistically significant ($P < .05$). Horizontal dotted lines indicate hemoglobin A_{1c} treatment goal < 7%. Gray tint indicates end of follow-up.

ng/mL per 2 hours) and 24 months (270.3 ng/mL per 2 hours) (Figure 2).

Mean values of anti-GAD antibodies at diagnosis and at 6, 12, and 24 months after treatment were 31.8 U/mL, 17.3 U/mL, 12.5 U/mL, and 18.7 U/mL, respectively (Table 2). Statistical differences were observed between pre- and and post-6-month titers but not among posttreatment times. Anti-GAD titers showed as negative in only 1 patient (patient 3) at 6 months posttreatment, and continued to show as negative at the 2-year-follow-up.

COMMENT

Many clinical trials have analyzed the effect of various immunointervention regimens in blocking autoimmune response and preserving beta-cell function. Short chronic use (≤12 months) of prednisone,[7] azathioprine,[8,9] azathioprine plus prednisone,[10] and cyclosporine[11] in randomized controlled trials produced variable degrees of improvement in C-peptide levels at the end of follow-up compared with pretreatment values. However, these effects were not maintained after immunosuppression was discontinued.[7-11]

Recent studies using short-term treatment with anti-CD3 monoclonal antibodies or heat-shock protein showed long-lasting improvements on C-peptide levels (up to 18 months), however with only partial improvement in insulin usage.[12-14] Control groups in the recent studies of immunointervention (treated with intensive insulin therapy) experienced progressive declines of C-peptide levels after study entry or after transient increase in its levels and a parallel increase in insulin needs.[12-15]

In our study, the increase of C-peptide levels and reduction of hemoglobin A_{1c} were maintained 2 years after insulin discontinuation, excluding the acute effect of insulin therapy on C-peptide concentrations and metabolic control. The natural history of type 1 DM was more altered in our study than in other immunosuppression interventions because, different from those studies, 14 of 15 or 93% of our patients experienced variable per-

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iods of insulin independence and most of them maintained this status throughout the follow-up.

Beta cell function in newly diagnosed type 1 DM is a measurable outcome that predicts long-term clinical status. Thus, preservation of beta-cell mass can be expected to provide long-term benefits.[6,19] The first patient failed to show a clinical benefit probably because of a very low beta-cell reserve at study entry, predicted by previous ketoacidosis that was further jeopardized by the beta-cell apoptotic effect of glucocorticoids used during conditioning.[20] Most of the subsequent 14 patients treated without glucocorticoids in the conditioning regimen demonstrated increased beta-cell function measured by C-peptide levels and became insulin-independent for 1 to 35 months. Two patients (identified as 7 and 10) who initially remained on insulin use shortly after transplantation developed insulin independence 20 and 12 months after AHST, respectively, probably secondary to progressive elevations in C-peptide levels over time. The reverse was seen in patient 11, who presented a decline in C-peptide levels after 1 year and resumed insulin use after that time. With the exception of patient 1, irrespective of insulin use all others achieved and maintained peak stimulated C-peptide levels greater than 0.60 ng/mL, which is known to be associated with reduced prevalence of diabetic complications.[21] Area under the curve levels of C-peptide increased significantly after transplantation and remained high up to 24 months thereafter.

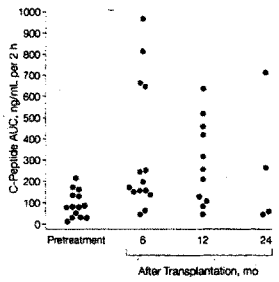
All patients experienced common transplantation-related complications of high-dose immunosuppression and only 1 patient presented a major infectious complication. The low frequency of severe acute complications after AHST is expected in a group of young patients with early-onset type 1 DM in contrast to other advanced autoimmune diseases.[16,17] On the other hand, 2 patients presented late endocrine dysfunctions that could be caused by autoimmune dysregulation associated with the transplant procedure[22] or by autoimmune polyendocrine syndrome frequently associated with type 1 DM.[23] We cannot exclude the occurrence of long-term complications related to high-dose cyclophosphamide use.

The exact mechanism of action of AHST in autoimmune disorders is not fully understood. Whether the mechanism is active or passive tolerance, ie, T-regulatory cell suppression or clonal deletion, is unknown. In multiple sclerosis, evidence supporting post-AHST immune resetting includes an increase in thymus-derived naive T cells, decreased central-memory T cells, increased output of recent thymic emigrants, and recovery of a diverse but distinct T-cell receptor repertoire following AHST.[24] Detailed studies of immune reconstitution are underway in these patients to better understand the mechanisms of action of AHST in new-onset diabetes. Preliminary data suggest a resetting of the immune system toward a tolerant phenotype beyond 1 year after transplantation, as observed in multiple sclerosis (K.C.R.M. and J.C.V., unpublished data, 2006). In the patients of this study, persistence of anti-GAD antibodies, even at low titers, shows that the conditioning regimen was not fully ablative for autoreactive B-cell clones and confirms that the magnitude of the humoral response is not predictive of beta cell reserve or clinical response.[19]

Improvement of beta-cell function after intensive immunosuppression could be explained by regeneration of beta cells from surviving beta cells or from pancreatic or bone marrow stem cells.[25,26] However, pancreatic stem cells have not been clearly demonstrated, and significant in vivo generation of islet cells from hematopoietic stem cells was not observed in animal models of type 1 DM[18] or in patients with long-term type 1 DM treated with allogeneic hematopoietic stem cell transplantation for concomitant blood disorders.[27]

This is, to our knowledge, the first report of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation for human type 1 DM. Very encouraging results were obtained in a small number of patients with early-onset disease. Ninety-three percent of patients achieved different periods of insulin independence and treatment-related toxicity was low, with no mortality. Further follow-up is necessary to confirm the duration of insulin independence and the mechanisms of action of the procedure. In addition, randomized controlled trials and further biological studies are necessary to confirm the role of this treatment in changing the natural history of type 1 DM and to evaluate the contribution of hematopoietic stem cells to this change.

Figure 2. Time Course of Total Area Under the Curve of C-Peptide Levels During Mixed-Meal Tolerance Test



Data from patient 1 were not included. Statistical analysis was performed using a model of multiple regression of mixed effects. $P<.001$ between pretreatment and 6 months; $P=.85$ between 6 and 12 months; $P=.18$ between 12 and 24 months following transplantation. SI conversion factor: to convert C-peptide to nmol/L, multiply by 0.331.

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Study concept and design: Voltarelli, Malmegrim, Foss, Squiers, Burt.
Acquisition of data: Voltarelli, Couri, Stracieri, Oliveira, Moraes, Pieroni, Coutinho, Malmegrim, Foss-Freitas, Simões, Foss, Squiers.
Analysis and interpretation of data: Voltarelli, Couri, Stracieri, Malmegrim, Foss-Freitas, Simões, Foss, Squiers, Burt.
Drafting of the manuscript: Voltarelli, Couri, Stracieri, Malmegrim, Simões, Squiers.
Critical revision of the manuscript for important intellectual content: Voltarelli, Couri, Oliveira, Moraes, Pieroni, Coutinho, Malmegrim, Foss-Freitas, Simões, Foss, Squiers, Burt.

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Washington Post
Friday, November 30
2007

Charles Krauthammer

Stem Cell Vindication

"If human embryonic stem cell research does not make you at least a little bit uncomfortable, you have not thought about it enough."

— James A. Thomson

A decade ago, Thomson was the first to isolate human embryonic stem cells. Last week, he (and Japan's Shinya Yamanaka) announced one of the great scientific breakthroughs since the discovery of DNA: an embryo-free way to produce genetically matched stem cells.

Even a scientist who cares not a whit about the morality of embryo destruction will adopt this technique because it is so simple and powerful. The embryonic stem cell debate is over.

Which allows a bit of reflection on the storm that has raged ever since the August 2001 announcement of President Bush's stem cell policy. The verdict is clear: Rarely has a president — so vilified for a moral stance — been so thoroughly vindicated.

Why? Precisely because he took a moral stance. Precisely because, to borrow Thomson's phrase, Bush was made "a little bit uncomfortable" by the implications of embryonic experimentation. Precisely because he therefore decided that some moral line had to be drawn.

In doing so, he invited unrelenting demagoguery by an unholy trinity of Democratic politicians, research scientists and patient advocates who insisted that anyone who would put any restriction on the destruction of human embryos could be acting only for reasons of cynical politics rooted in dogmatic religiosity — a "moral syntolish," as Sen. Tom Harkin so scornfully put it.

Bush got it right. Not because he necessarily drew the line in the right place. I have long argued that a better line might have been drawn — between using doomed and discarded fertility-clinic embryos created originally for reproduction (permitted) and using embryos created solely to be disassembled for their parts, as in research cloning (prohibited). But what Bush got right was to insist, in the face of enormous popular and scientific opposition, on drawing a line at all, on requiring that scientific imperative be balanced by moral considerations.

History will look at Bush's 2001 speech and be surprised how balanced and measured it was, how much respect it gave to the other side. Read it. Here was a presidential policy pronouncement that so finely and fairly drew out the case for both sides that until the final few minutes of his speech, you had no idea where the policy would end up.

Bush finally ended up doing nothing to hamper private research into embryonic stem cells and pledging federal monies to support the study of existing stem cell lines — but refusing federal monies for research on stem cell lines produced by newly destroyed embryos.

The president's policy recognized that this might cause problems. The existing lines might dry up, prove inadequate or become corrupted. Bush therefore appointed a President's Council on Bioethics to oversee ongoing stem cell research and evaluate how his restrictions were affecting research and what means might be found to circumvent ethical obstacles.

More vilification. The mainstream media and the scientific establishment saw this as a smoke screen to cover his fundamentalist, obscurantist, anti-scientific — the list of adjectives was endless — tracks. "Some observers," wrote The Post's Rick Weiss, "say the president's council is politically stacked."

I sat on the council for five years. It was one of the most ideologically-balanced bioethics commissions in the history of this country. It consisted of scientists, ethicists, theologians, philosophers, physicians — and others (James Q. Wilson, Francis Fukuyama and me among them) of a secular bent not committed to one school or the other.

That balance of composition was reflected in the balance in the reports issued by the council — documents of sophistication and nuance that reflected the divisions both within the council and within the nation in a way that respectfully presented the views of all sides. One recommendation was to support research that might produce stem cells through "de-differentiation" of adult cells, thus bypassing the creation of human embryos.

That Holy Grail has now been achieved. Largely because of the genius of Thomson and Yamanaka. And also because of the astonishing good fortune that nature requires only four injected genes to turn an ordinary adult skin cell into a magical stem cell that can become bone or brain or heart or liver.

But for one more reason as well. Because the moral discomfiture James Thomson always felt — and that George Bush forced the country to confront — helped lead him and others to find some ethically neutral way to produce stem cells. Providence then saw to it that the technique be so elegant and beautiful that scientific reasons alone will now incline even the most willful researchers to leave the human embryo alone.

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Mr. FERGUSON. Thank you.

Dr. Zerhouni, I think you are familiar with Celgene Cellular Therapeutics. They are a biotech company in my district in New Jersey. They do—really one of the leaders in stem cell research. They do really extraordinary work and they have developed a clinical application to create blood stem cells by using human placenta-derived stem cells along with umbilical cord blood cells. The first application of this particular technology was completed at Louisiana State University Health Sciences Center, the Health Sciences Center at Children's Hospital on March 28, 2008, just not very long ago. It was big news. They treated a pediatric patient who was suffering from acute lymphoblastic leukemia, which is a cancer of the bone marrow and the blood.

Mr. BURGESS. I think he knows.

Mr. FERGUSON. Yes, I am sure he knows, but I want to have it on the record. Thanks, Mike.

I think I began my statement by saying I am sure he knows, but in any event, yet another example of remarkable progress and potential treatments that are coming from again not an embryonic stem cell source but a different source, in this case placental stem cells and cord blood stem cells. It just further highlights for me, we were talking about these essentially two different things and I mentioned before some of the sort of ethical questions obviously that are still out there, and you have referenced many times in your discussion about the ethical considerations as we look at these different types of research, and clearly I think we would all agree that there are things that we can do but ought not do in life, right? But that is really not the question that we are talking about here today. The question that we are talking about today is, should all things that we can do be funded using taxpayer money? That is really the question that we are getting at here today, and voters in New Jersey just last fall decided embryonic stem cell research was not something they wanted their taxpayer dollars to go to fund. So that was one opportunity for voters to be heard. But we have to have that conversation all the time certainly in this committee and this subcommittee.

I wanted to pursue something you had talked about before, and clearly for many people, even obviously Dr. Thomson and others who have raised questions, certainly ethical considerations about embryonic stem cell research, and I am genuinely curious about this because I don't know where this goes. If there are ethical concerns that some people, many people have about embryonic stem cell research, the nature of that research today, my question is, I guess I don't have a good enough imagination or certainly not scientific expert enough to know, where does it go when perhaps, as you said, perhaps years down the road if some treatment or progress comes from embryonic research—I talked to the researchers in my district and in New Jersey about placental and stem cell and cord blood research, and one of the things they love about that kind of research is, when they come up with an application, as they seem to have, there is a virtually limitless supply of—I don't know what you would call it—raw material, you know. How many children are born every day? How many placentas and cord blood, you know, we have a virtually limitless source of these cells. If we were

to get to that point some years in the future, as you have said, with embryonic research, where does the raw material come from?

Dr. ZERHOUNI. You are asking extremely important and difficult questions. I think we absolutely do not want to obviate the need for a deep conversation. Likewise, scientists, as I described, believed that progress will come from our understanding at the deepest level of the molecular program that is timed to create the cells or create the appropriate neurons or that lead to understanding disease and eventually cure it. Most scientists when you talk to them, in my conversations with them, including Dr. Thomson, would say the picture 20 years down the line is that as we discover these programming factors, we probably won't need any particular one source. We will program, if you will, the software of any cell. Am I talking about science fiction? No, it has already happened in front of us; with four factors we have reprogrammed skin fibroblasts. So I think the discussion will evolve, and you are right. Is there anything that we could do that should not be done? I just gave you an example of the autologous bone marrow transplants in young type 1 diabetes patients where we know that 1 in 20 will die within 100 days of having received that transplant. That is just as important a consideration as the other consideration that you referred to, which is what is the limit, what is the barrier here. We clearly as scientists—now, I am talking from the scientific point of view—if you understand that the problem for us is to truly advance the cures that we need to implement which are dependent on our understanding of DNA programming and reprogramming and how do you modulate that, the embryonic stem cell is just unique in the sense that it can self-propagate. If it wasn't for that, I don't think scientists would be as excited about it. The fact is, you cannot get cord blood cells to multiply the way you get an embryonic stem cell to, but that doesn't mean it is not possible because we also are showing that it is doable. So, Congressman Ferguson, I know you have thought about this, and we have had these conversations. I don't know where the happy medium is, but I know that we cannot close our eyes to the fact that the progress may come from any one of these sources. So NIH wants to fund all of those areas of research, whether it be cord blood or placenta, and we do.

Mr. PALLONE. We are out of time, 3 minutes over.

Mr. FERGUSON. If I could just close on that and respond, I think that is a very thoughtful answer. I appreciate it. The researchers that I have talked to in our district and in——

Mr. PALLONE. Mr. Ferguson, not for anything but we are 2 minutes over so we have to move on.

Mr. FERGUSON. Sorry.

Mr. PALLONE. All right. Ms. Baldwin? Oh, she is not here. Mr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. Let me just yield 30 seconds to my friend from New Jersey to finish his thought.

Mr. FERGUSON. That is extremely courteous, Dr. Burgess. Thank you.

I would just say that the researchers that I have talked to in our district have raised that question with me, and these are all folks who agree, and I think everyone would agree that all types of research, particularly as we have seen embryonic stem cell research

and these other types of research, are extremely interesting, extremely interesting and potentially valuable. I think anybody who is being honest would have to acknowledge that they are potentially valuable. The question that we are struggling with here is not whether it should exist, not whether the embryonic stem cell research should exist. That is not the question that we are dealing with today or have been dealing with. The question is, where are we going to spend scarce taxpayer dollars? On the most promising, immediately beneficial examples and research or are we going to roll the dice on other forms? That is really the question that we are after today, so I appreciate it. Thank you, Dr. Burgess.

Mr. BURGESS. You are very welcome. That is a rhetorical question. It doesn't require a response.

Let me ask you—Mr. Ferguson raised another very good point. What about just the volume of material that is going to be required to do the type of research or to provide the therapeutic benefit? There is a virtually unlimited supply of cells from amniotic fluid and cord blood and a relatively finite supply of human embryonic stem cells, regardless of whether or not any funding source is lifted.

Dr. ZERHOUNI. Well, as you know, because of the new discoveries, we have sort of bypassed this issue of being able to expand the cells that we have through the induced pluripotent stem cells. There is no doubt that when you look at placenta or cord blood, we have—we are unable to take a cord blood sample and expand it to use in patients other than young children.

Mr. BURGESS. But if I could interrupt you, what about the pluripotent cell from amniotic fluid?

Dr. ZERHOUNI. Well, there is one documented work from Dr. Atala there and we are looking forward to see what the expansion potential of that is there, but there is no doubt that scientists will explore every door. The one thing that we don't know is where the magic answer is. So everybody is really going to explore all of those avenues. We want to support them all.

Mr. BURGESS. And we talked a little bit about funding, and I wish I had a great deal of time to spend on that, but as far as Dr. Anthony Atala's work is concerned, is any of that supported by NIH funding?

Dr. ZERHOUNI. Oh, definitely, yes.

Mr. BURGESS. So he has an ongoing grant from NIH?

Dr. ZERHOUNI. Oh, yes, I think he has had it for a long time.

Mr. BURGESS. And reports are coming back to you so you are able to evaluate the work that is going on down in North Carolina?

Dr. ZERHOUNI. Absolutely. We are keeping a close eye on our investments.

Mr. BURGESS. And I am happy that you do. Let me just ask too on this, since Mr. Barton brought up the issue of the reauthorization and the $29.5 billion that was the baseline funding in the reauthorization bill and the increases were slated to be 5 percent per year. Were you able to get to that amount last year in the appropriations cycle through Congress?

Dr. ZERHOUNI. No, and it is something that we will have to consider in the long term and look at the long-term impacts. I think the increases have been below inflation, and we have managed and

tried to reorganize our priorities, but they have not been at the authorization level.

Mr. BURGESS. Correct, and the reason for that bipartisan reauthorization was to give you the certainty of that funding stream so that when you go out and hire young scientists to start new labs, you will know that you will be able to continue to fund that. I won't ask you to be a prophet here but what do you intuit about this year's appropriations cycle as far as the NIH is concerned?

Dr. ZERHOUNI. I appreciate your point, Dr. Burgess. I think you are very aware. I know from our conversations that you know, based on your own experience, that young scientists make decisions not on the basis of today but on the basis of what they see coming, and as we send a message that is discouraging, there is a definite sense out there of young scientists deciding not to go into science.

Mr. BURGESS. I would just remind those who are in the party in control that control now the appropriations process, we were criticized when we were in control for leveling off the funding for several years after a doubling and now it appear that even in spite of the hard work that was done by both sides of the dais in this committee in the last Congress that that doesn't seem to be reaching the level that any of us had intended.

Let me just ask one last line of questions, and I mean to get a response to this in writing. Currently, as far as the treatment of diabetes, the ability to implant an islet cell from a cadaveric source currently exists. Is that correct?

Dr. ZERHOUNI. That is correct.

Mr. BURGESS. And NIH is using that and that is successful, but those patients will have to take a drug to inhibit rejection from that point on. And I don't think the human embryonic stem cell has ever been able to produce insulin that would impact blood sugar, but if it did, and if that cell were then implanted like other islet cells have been implanted from a cadaveric source, would that same requirement for taking anti-rejection drugs be required for that individual?

Dr. ZERHOUNI. So it all depends on where the cell comes from. If it comes from the patient himself or herself, no.

Mr. BURGESS. Which is why the reprogramming activities——

Mr. PALLONE. We are going to have to——

Mr. BURGESS [continuing]. Are so exciting.

Mr. PALLONE. One more question and that is it because you are over too.

Mr. BURGESS. For the anti-rejection medication.

Dr. ZERHOUNI. It would make sense but I would be very careful, Dr. Burgess, because when you reprogram a cell with outside factors and viruses and so on, it is not clear that you won't have an immune response. This needs study, but in theory you are correct.

Mr. BURGESS. Very well. I will yield back, Mr. Chairman.

Mr. PALLONE. Thank you.

The gentlewoman from North Carolina, Ms. Myrick.

Ms. MYRICK. Thank you, Mr. Chairman, and I echo all the accolades that others have said. We appreciate all the hard work you do. Thank you for that.

I wanted to ask you, I was really astounded when I learned that the scientists at Wake Forest and Rutgers had actually—this was

funded by the Pentagon, by the way—but they managed to grow a human ear and it was generated from the stem cells of a badly wounded Marine, and they grew it on the back of a mouse, as I am sure you probably know, to be transplanted onto the Marine, and my question is twofold. One, can you comment on the promise of such research, and do you think that a bill like H.R. 810 alone would allow for this same sort of breakthrough, even though the embryo lines eligible for Federal funding under the bill may not actually come from the patient, and would scientists need to create or clone embryos in order to tailor-make therapies like this in the near term, I am talking; not 30 years from now but in the near term?

Dr. ZERHOUNI. As I said, I think currently the difficulty of using adult stem cells and using them clinically is less because we have had a lot more experience. We have had 40 years of experience. What you are referring to is tissue engineering, which is the specialty that you are mentioning that you are aware of, and in tissue engineering, we have learned how to grow cells, for example, vessels or skin cells, on a 3-dimensional basis. That is currently available. We have grown skin, for example, for burn patients for many, many years already. The real issue, though, is how do you change the destiny of a cell to become an islet cell? So we know how to make the same cell expand into the same cell. We don't necessarily know how to take that cell, even though it is pluripotent, into replacing a neuron. That is the prospect of what we are doing, Congresswoman.

Ms. MYRICK. I appreciate it. And Mr. Chairman, if you would allow me, I have two articles by Dr. Atala at Wake Forest that I would like to submit for the record, if I may.

Mr. PALLONE. I looked at the one Mr. Ferguson gave me and it was not easily understood, so I will ask that you give me those copies and then we will take a look at it again, if that is all right, and——

Ms. MYRICK. No, it is fine.

Mr. PALLONE. Let me take a look.

Ms. MYRICK. Thank you.

Mr. PALLONE. The gentleman from Oklahoma? No? OK. I think that completes our questions, and thank you, Dr. Zerhouni.

Dr. ZERHOUNI. You are welcome.

Mr. PALLONE. We really appreciate your testimony and all that you did and all that you continue to do. Thank you.

Dr. ZERHOUNI. Thank you very much.

Mr. PALLONE. I would ask our second panel to come forward. I want to welcome our second panel, and let me introduce everyone from left to right once we have the signs posted here. Welcome. I will start with, on my left is Dr. John Gearhart, who is the C. Michael Armstrong professor of medicine at the Institute for Cell Engineering at the Johns Hopkins University. And then we have Dr. Amit Patel, who is director of cardiac cell therapy, the Heart, Lung and Esophageal Surgery Institute Surgery at UPMC Presbyterian in Pittsburgh—I am sorry—UPMC Presbyterian, McGowan Institute of Regenerative Medicine in Pittsburgh, Pennsylvania. And then Mr. Douglas T. Rice from Spokane Valley, Washington. Dr. George Daley, associate professor of pediatrics for the Karp Family

Research—I guess that is your address, I am sorry—associate professor of pediatrics at the Children's Hospital in Boston. And then we have Mr. Weyman Johnson, Jr., who is chairman of the National Multiple Sclerosis Society, and from my own State of New Jersey, Dr. Joseph Bertino, who is interim director and chief scientific officer for the Cancer Institute of New Jersey. Good to see you again. And then we have Dr. John K. Fraser, who is principal scientist with Cytori Therapeutics—I hope I got that right—in San Diego, California.

And as I said before, we have 5-minute opening statements. They become part of the record, and you may, in the discretion of the committee, be asked to submit additional written statements for inclusion in the record, depending on the questions that we get to.

We will start with an opening statement by Dr. Gearhart.

STATEMENT OF JOHN D. GEARHART, PH.D., C. MICHAEL ARMSTRONG PROFESSOR OF MEDICINE, INSTITUTE FOR CELL ENGINEERING, JOHNS HOPKINS UNIVERSITY

Mr. GEARHART. Thank you, Mr. Chairman and members of the Committee. Ten years ago, we had our first hearing in Congress on embryonic stem cells. This was the result of the publications from two laboratories of the discovery of these cells. I had the privilege of being part of that, and Dr. Harold Varmus was here at the time as the director of the NIH and he at that time put forward what these cells could be used for, the potential of these cells, and I thought it would be interesting to the Committee to review his comments and then to tell you where I see as an active researcher in this field where our science is with embryonic stem cell research.

So the initial comment that he made was that these cells could be a boon to basic science, to understanding human biology and human development. And indeed, we see that one of the primary uses to date of these cells is to understand some of these very early events in embryogenesis for which there is no other avenue of research to understand how we go from a single cell egg up to an individual that has 200 trillion cells. What are the processes involved? And so we and others have used these cells and culture to discover new genes, new genes that are involved in the formation of the central nervous system, of the heart, and recently in our laboratory we discovered 40 new genes in the very earliest stages of the development of the circulatory system, which happens within the first few weeks of our development. There is no other way that we could have gotten this information, and these are critical genes. We can demonstrate by shutting them down, manipulating them as we do, that they are important in development. This is just but one example of the use of these cells that are going to be made in understanding how our program, the genetic program that Dr. Zerhouni mentioned, is played out so that we can get a handle on birth defects and ultimately on some of the disease processes that occur in our bodies. And this has been an extremely exciting development.

Secondly, he mentioned that these cells could be used in the testing of drugs and factors directly on human cells without having to subject patients to them, and we see this happening now, of culturing a variety of different cell types, having them in culture and

subjecting them to different types of toxins, drugs of different kinds, and see the response of the cells without going through either animal models, which sometimes aren't important, or directly a variety of different human genotypes. This is occurring.

Also, we see remarkable work being done on figuring out how we go through these lineages, how a single cell can become one of the 260 different cell types. This isn't trivial. We have a cell in culture that can form all of those cell types. How do we get it to form just a liver cell or a dopaminergic neuron? And we are figuring out these processes by trying to mimic what is occurring in an embryo and then using that information to direct the specialization of that cell. This is enormous from the standpoint of saying, well, if we are going to develop some kinds of therapies, we are going to have to get a homogenous population of cells that we know what they are that we can put into a patient. This is extremely important.

Another avenue he said would be the use of these cells in transplantation research for diseased or damaged tissue, and we now see in the published literature dozens and dozens of examples of where cells derived from human embryonic stem cells have been placed into animal models either for disease or injury. Yes, there are variable outcomes to this but it shows a great deal of promise.

So in all of these avenues, we are seeing this in research, and I just want to tell you that is going to take a while. This is something else that came out of this initial meeting, was this projection of how long it would take for us to develop these kinds of therapies for patients. It is going to take years, and much of it is safety. We don't want to place cells into a patient without knowing what their fate is going to be and how we can regulate it, and we are getting a handle on that in the modes of delivery, the types of cells we put in, whole new—we have made radiologists even richer from the standpoint that when we first went to the FDA, we were asked, if you are putting in 300,000 cells, we want to know where every one of those cells is going. We want live-time tracking of these cells. So we are delighted at the progress of this.

Now, let me tell you how I——

Mr. PALLONE. I hate to interrupt you all because what you are saying is so important but we have a long panel, so you have to wrap it up.

Mr. GEARHART. That is fine. Well, I have recently seen how policy issues can trump science and I am very disappointed. Reference was made recently to the Army's Institute of Regenerative Medicine announcement of $250 million. I think you should be aware that what was not permitted in those studies was anything dealing with embryonic stem cells, and I just feel that we are shooting ourselves in the foot by not also having that avenue explored for some of this very important regenerative medicine.

[The prepared statement of Mr. Gearhart follows:]

Testimony on Stem Cell Science: The Foundation for Future Cures

John Gearhart, Ph.D.
C. Michael Armstrong Professor, Director, Stem Cell Program,
Institute for Cell Engineering, Johns Hopkins Medicine
Baltimore, Maryland

Before the U.S. House of Representatives Subcommittee on Health of the
Committee on Energy and Commerce
May 8, 2008

Mr. Chairman and Members of the Subcommittee, I am John Gearhart, a stem cell biologist at Johns Hopkins Medicine. I am pleased to appear before you to discuss the foundation for future cures through stem cell science.

It is rare that a field of scientific research can have both an enormous potential impact of human health and quality of life and be a fount of new basic research discovery. What crystallized the scientific and medical communities' interest in stem cell research was the derivation of human embryonic stem cell lines. These cell lines are unique in that they are capable of forming all the different cell types (>220) that are present in the body (a property that is referred to as pluripotentiality) and they can produce more cells like themselves indefinitely (self-renew). This development, first reported ten years ago, has been among the most heralded as well as contentious issues of the modern scientific era. Heralded, as now we had in the laboratory a source of cells from which we could grow any and all cells of the human body for much needed replacement therapies and contentious, because embryos are destroyed to derive the cells. No wonder that stem cell research has impacted many areas of our society – science, medicine, religion, ethics, policy and economics. Seldom has a week gone by without some new revelation about stem cells reaching the front pages of the press or the top news stories of the day and what this means for our society, invariably hyped. It is recognized that stem cell research has the potential to revolutionize the practice of medicine and to improve the quality of life and in some cases, the length of life for many people suffering from devastating illnesses and injuries. Also, it is believed by many that there will be no realm of medicine that will not be impacted by stem cell research.

Research over the past ten years is setting the foundation for the use of embryonic stem cells and the knowledge derived from this research for developing and designing therapies, therapies that will be safe as well as effective. To envision what lies ahead for

the use of these cells in human therapies, it is informative to mention the progress that has been made over the past decade while keeping in mind that the progress made by US investigators has been compromised by current policy on federal funding. In the very first Congressional hearing on these stem cells (December 2, 1998, Before the Senate Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education and Related Agencies) and one in which I had participated, Harold Varmus, MD, then the Director of the National Institutes of Health (now the President of the Memorial Sloan-Kettering Cancer Center) outlined the potential uses of these cells in biomedicine and it is appropriate to use his list in evaluating what has transpired in laboratories since then.

(Varmus) At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

There is no question that we have learned a great deal about these stem cells and the molecular mechanisms underlying the bases of pluripotentiality and of cell differentiation, that is, the conversion of these cells into one of the types of specialized cells of the body. This is what we call basic science, a prerequisite first step in understanding cellular processes. We have utilized studies of other organisms to first give us insight into these mechanisms and then confirmed these mechanisms or variations on these mechanisms in the human cells. Much of our progress has been informed by such studies and as has been pointed out recently by Bruce Alberts, Ph.D., there are no shortcuts to medical progress: *But, as has been repeatedly demonstrated, the shortest path to medical breakthroughs may not come from a direct attack against a specific disease. Critical medical insights frequently arise from attempts to understand fundamental mechanisms in organisms that are much easier to study than humans; in particular, from studies of bacteria, yeasts, insects, plants, and worms. For this reason, an overemphasis on "translational" biomedical research (which focuses on a particular disease) would be counterproductive, even for those who care only about disease prevention and cures. (Bruce Alberts, Shortcuts to Medical Progress? Science Vol 319, 28 March 2008).* Embryonic stem cells provide another link in the biomedical investigation and discovery chain that leads to human application.

So, we now know a handful of the critical genes and of the regulation of the expression of these genes that enable cells to be pluripotential. This knowledge was at the basis of the most recent and exciting development in our field in which skin cells were converted to cells that had properties of embryonic stem cells by the addition of just a few genes to the cells. The skin cells had these genes but they were not being expressed. Adding exogenous version genes that were expressed caused these cells to be reprogrammed,

eventually expressing their own, endogenous genes. The embryonic stem cell-like cells are called induced pluripotent stem (iPS) cells. This is a major paradigm shift in stem cell biology and I will comment more on this later but it was through the study of embryonic stem cells that this advance was made.

There have now been hundreds of research reports on studies of in which embryonic stem cells are differentiating to specialized cells. We are learning the mechanisms involved in the earliest decisions made by cells to become neurons or gut cells or muscle cells, etc. It has been know for decades that cell-cell interactions in the embryo determine the fates of cells during development as summarized by the Noble laureate Hans Spemann (1943): *We are standing and walking with parts of our body which we could have used for thinking if they had been developed in another position in the embryo.* With these embryonic stem cells in culture, we are learning how different factors influence cell fate decisions. By experimentally manipulating these factors we can then direct cell differentiation to a desired cell type through the use of growth factors, attempting to mimic the environment of the embryo.

Personally, I have been interested in human embryology and development for decades and have felt strongly as Samuel Taylor Coleridge (1934) stated so beautifully: *The history of man for the nine months preceding his birth would probably be far more interesting and contain events of far greater moment, than all the three-score and ten years that follow.* These stem cells have provided a unique resource to learn about the biologic mechanisms underlying our development, both normal and abnormal, so that we may eventually understand the basis of birth defects and perhaps guide us in correcting these malformations, etc. We have learned much about the mechanisms of cell decision making in the early embryo, such as within the conceptus, becoming embryonic or extra-embryonic, and within the germ layers of the embryo, what determines cell fate. In our own current work with embryonic stem cells, we have recently discovered ~40 new genes that are critical to the formation of the heart and great vessels. There are many other examples for the use of these important cells in studying human development.

Recent findings have discovered and solidified the understanding that many of the same cellular mechanisms found in the development of a tissue or organ play critical roles when rebuilding or regenerating that tissue. Investigators have gone on to show that manipulation of these developmental factors, the understanding for which has been often discovered, expanded and/or validated in embryonic stem cells, can greatly influence regenerative capacity, even recovering the capacity to regenerate in animals that did not possess it. It is of the outmost importance that studies continue in order to discover these and utilize this knowledge in designing therapies for the many maladies affecting us. As all of you have observed, we humans don't regenerated body parts like some of our lower relatives in the animal kingdom. Imagine the possibility of harnessing the capacity of zebrafish, for example, who using the same families of genes that we use in the development of our heart can regrow a large part of their heart when amputated. We must determine the reasons why humans fail to display this capacity in most organs, emboldened by the knowledge that our livers can regenerate, in order to combat many common debilitating diseases such as heart attacks and strokes.

(Varmus) Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

There have now been many examples of use of what are called high throughput screens for testing the effect of various chemicals, molecules and drugs on the stem cells and their specialized derivatives. The use of this approach for studies with 'diseased' cells is just beginning as embryonic stem cells have been derived from embryos diagnosed with mutations that can lead to disease later in life.

(Varmus) Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation

There are now many reports on the use of embryonic stem cell sources of cells for grafting into animals with various injuries or that serve as models for a variety of human diseases. The results have been highly variable (as it has been using stem cells from any source, adult or embryonic) but in many cases, they are encouraging. Our laboratory has been working with cell-based therapies for the heart. Currently there are no adult stem cells that have been identified to date that have shown robust cardiac muscle formation in vivo (in the heart), or for that matter, in vitro (in the dish). We and other laboratories have identified a stem cell that gives rise to most of the cells within the heart and these cells, when grafted to infarcted rodent hearts robustly undergo cardiac muscle formation, integrate into the heart and restore function.

There are three further important points that I want to make in considering the future of providing cures or ameliorating diseases and injuries through stem cell science.

1) Time frame for developing safe and effective therapies.

2) Where disease is involved, we must determine the underlying pathogenesis of the disease and stop it. I have talked only about having a source of cells (or the knowledge of how to control cell fates) in establishing a foundation for future therapies. What is as important, is the understanding of the pathogenesis of devastating diseases for we must stop this process for grafted cells will surely succumb to the same fate.

3) How do the iPS cells factor into the future?
Quite simply I believe that they are important part of the future. They require further vetting as true embryonic stem cells. At the moment, we can only measure what can measure with embryonic stem cells and induced pluripotent stem cells. More must be learned about each. They represent a powerful example of our goal to instruct our cells to do what we want; but this is just the beginning. Is this a farewell to embryonic stem cells in research? Not at all, for they represent the gold standard. For my studies focused on human embryology, I will continue to use embryonic cells but, like many of my colleagues, I will vigorously pursue the direct reprogramming of adult cells.

Summary

Mr. Chairman, I am grateful to you for providing a forum to discuss this promising arena of science and medicine. Learning to instruct our cells to get them to do what we want is the ultimate control of our own cells and the basis of future medicine. Based on current research results with stem cells, the future is, as Yogi Berra has said, not what it used to be. We look to stem cells not only to provide cells for replacements in therapies, but also to provide us with the knowledge of how cells work and to use this information to instruct patients' cells to effect repair and regeneration of damaged or diseased tissues. We must recognize that the development therapies that are safe and effective is going to take time and resources and that circumspection is not a retreat from promise. I would be pleased to answer any questions you might have.

Mr. PALLONE. Thank you, Doctor.
Dr. Patel.

STATEMENT OF AMIT N. PATEL, M.D., M.S., DIRECTOR OF CARDIAC CELL THERAPY, THE HEART, LUNG AND ESOPHAGEAL INSTITUTE, UPMC PRESBYTERIAN, MCGOWAN INSTITUTE OF REGENERATIVE MEDICINE

Dr. PATEL. I would like to thank the Chairman and the members of the Committee for giving me this opportunity to testify before you. I just have to make a quick note that the testimony that I am giving today is of my own opinion and not necessarily that of the institution that I am currently employed by.

My career has really been developed and based on the treatment for cardiovascular disease. I am a cardiac surgeon and a translational scientist, meaning my goal is to take the science that many of the panelists here have been doing for longer than I have been alive that they first started and how can we most safely and efficiently help the patients who have the disease today, and based on that, cardiovascular disease, as we know, is the greatest cause of death in America. There are millions of patients every year who die from new heart attacks, limb ischemia, not getting enough blood supply to their legs, and the most end stage, which is about 5 million patients with heart failure. Fifty percent of those patients will die within 5 years of their diagnosis in the most severe forms. So the question that I have and I try to help my patients with is, I do bypass surgeries, I do valves, I do heart transplants, but with our limited organs, the risks of complications of anti-rejection medications, I have to find other solutions that safely can help these patients just because I can't help all of them, and every day I get calls from patients from within the United States and around the world, can you provide me a therapy, just as Dr. Zerhouni said.

But the key is, how we can do it safe and effective here in the United States. And so there are two problems that we have tried to solve and by no means have an answer to but have some early treatments for is, for heart failure, our basic problem is, we have a pump that just cannot supply enough blood by delivering enough oxygen to the entire body, and in patients with limb ischemia, these are patients that due to lack of enough oxygen and blood supply to their legs, these patients end up with amputations. So when you combine those together, the total loss that was reported by the American Heart Association in 2005 was $394 billion, $242 billion from the healthcare expenditures and $152 billion from loss in productivity from death and disability. So as we know how dramatic of an impact this has on not just the capital resources but human resources, that is the two things that we have really focused on.

So our role of stem cell therapy really has been, well, what do we want to do. It is great for these very complex diseases and disorders such as Parkinson's and other neurological or immunological problems, but our goal is very simple. We need a heart that has more ability to pump by either providing more cardiac myocytes, or heart muscle, and increasing the blood supply, developing new blood vessels. And in patients with limb ischemia, how can we develop more blood cells that will prevent these patients from getting amputation. So it sounds like a simple solution that we need to ad-

dress, so our goal has been, how can we help the patients today with the cells that we have available that have been safe, and the question of safety is always an issue.

Five years ago, when we first started some of the earlier clinical work, that was a very significant concern and we received one of the first FDA approvals to do human trials here in the United States, and a similar group in Texas also received this approval using bone marrow-derived cells, and it is not to say that that was the perfect answer or solution because before that, in France, patients had received biopsies of their muscle from their thigh, they expanded them in culture and injected them into their heart and caused significant irregular heartbeats. So translating too early from the science without knowing a lot of the answers is also not the right answer, so there has to be a safe and ethical balance. But now, when those same myoblasts in the United States were taken in a safer fashion, delivered with a catheter in heart failure patients, that is now expanded to a phase II 390-patient clinical study that is funded by industry. So it is not that the cells are bad, it is knowing the right indications for the patients and the right way to culture them.

We have been able to take bone marrow in varied forms. The earliest science and animal work showed great potential that these bone marrow cells magically will become all these different cell types. The reality is that this may happen in the dish but it is very unlikely in our patients that this will happen, but the key is, how can we most safely, effectively do this, not only for our adult cells but all the other multipotent cells that we are hoping to deliver, such as the adipose cells, which you will hear about, amniotic cells, placental, menstrual, and even the embryonic, so it is the whole litany of cells. It doesn't matter where the cell comes from, we still need to go through the same questions to how to provide the most safe, reliable delivery of cells, also issues of dosing. It is very similar to pharmacological therapies that we need to know doses, toxicities, where are all these cells going to go. I could put them in the heart. If I flush them down the arteries in the heart, greater than 90 percent of the cells end up in the lungs, liver, or spleen. The question is, what are they doing there. So when it is their own cells, there has been a level of safety now after about 8 years of treatments throughout the world in registered trials. There is probably about four times as many unregistered patients who are——

Mr. PALLONE. I am going to ask you to wrap up.

Dr. PATEL. Sure. That in the 1,000 patients that have been treated in registered trials, there has been definite safety shown with bone marrow-derived cells. There has been a modest improvement in cardiac function, and in the right selected patients, there has been a very significant improvement that has shown decreased death, decreased re-admission, and up to 5 years now the safety along with sustained improvement. There is the possibility that these patients may need redosing, but the biggest issue is, we have been benefited by the NIH. There is the center of cell therapy, center of heart failure and cardiac surgery where we could further answer a lot of these scientific questions along with providing clinical therapies for patients here in the United States today so they don't

have to go overseas and get unregulated and unscrupulous therapies where they have to pay a lot of their own money. Thank you.

The prepared statement of Dr. Patel follows:]

Testimony for "Stem Cell Science: The Foundation for Future Cures" before the Subcommittee on Health of the Committee on Energy and Commerce

Presented by Amit N Patel MD MS
Director of Cardiovascular Cell Therapies
McGowan Institute of Regenerative Medicine
University of Pittsburgh Medical Center

Chairman and members of the Committee, thank you for inviting me to testify before you. My name is Amit Patel. Please note that the testimony I am giving today is my own opinion and not necessarily that of the institution where I am currently employed. I am a translational scientist for cardiovascular diseases where my research is focused on working with regenerative therapies taking the science from the lab bench to the patients. I am also a cardiovascular surgeon who on daily basis sees patients who have exhausted all medical and surgical options available who may benefit from the science of stem cell research.

My goal today is to give both a scientific and real life perspective of the impact that cardiovascular disease has in the United States and potential use of stem cell therapies.

Cardiovascular Disease

Heart disease is the leading cause of death in the United States. Nearly 930,000 Americans die of cardiovascular diseases each year, which amounts to one death every 33 seconds. About 70 million Americans have some form of cardiovascular disease, which is responsible for more than 6 million hospitalizations each year. There are over a one million patients with heart attacks every year, along with six million patients with chronic angina (chest pain), and five millions patients with heart failure. In 2005, the cost of heart disease and stroke in the United States exceeded $394 billion: $242 billion for health care expenditures and $152 billion for lost productivity from death and disability. Patients with end-stage cardiovascular disease have over $30 billion dollars in health care expenditures per year. Also, up to 20% of patients over the age 70 have limb ischemia.

Problem: The patients with end stage cardiovascular disease have at least one of two major problems:

1. Heart failure, where there is inadequate pumping function of heart due to decreased blood supply or lack of sufficient muscle.
2. Critical limb ischemia, where there is inadequate blood supply to the leg.

Current Treatment Options: Heart failure management involves optimal treatment with oral and/or intravenous medications along with surgical therapies. As patients continue to deteriorate the use of artificial hearts and heart transplantation remain the gold standard for end-stage therapy. There are many problems with the surgical options such as infection, stroke, rejection, and the overall costs associated with treatment. However,

even with all these options there are limited organs for transplant and fifty percent of end-stage heart failure patients die within five years.

Critical limb ischemia management involves oral medical therapy followed by surgical revascularization by bypass grafts. If the graft fails and further reoperative therapy is not possible, then amputation of the leg is performed. This problem is more severe in patients who also have diabetes.

The Role of Stem Cells:

Based on the current science, human stem cells have been shown both in a lab dish and in the pre-human work to make new blood vessels and in rare cases new heart muscle.

Current Clinical Therapies

Human stem cell therapies for cardiovascular disease have been performed under legitimate clinical trials since early 2000. The first group of patients had cells from thigh muscle (skeletal myoblasts) injected into their heart at the time of coronary bypass surgery hoping to grow new heart muscle in Europe. The early data demonstrated some issues with the therapy but larger trials were performed which also did not show significant improvement in heart function. This was truly an example of too rapid translation which could have destroyed the field. However, when these cells where used in a heart failure population and delivered via a catheter in U.S., the results where positive and have led to a large scale clinical trial. Also, using bone marrow cell therapy for the same patient population, both surgically and catheter based delivery has been performed in over one thousand patients in registered trials demonstrating no safety issues. This is the most important issue when performing translational therapies even though all the mechanisms of action have not been defined. As patient safety has been established, the next goal is to identify the patient population which may benefit the most from this therapy, which in the lab dish and pre-human work has shown to grow blood vessels and may improve cardiac muscle function. In these early clinical trials there has been modest improvement in heart function but there has been a significant decrease in adverse events, readmission for heart failure and new heart attacks in the randomized controlled studies. It is true that improvement in overall pumping has not been as large as most people had anticipated but that is most likely related to baseline function of the patient being enrolled in the studies. The analysis of the more severely impaired patients has shown a very dramatic increase which could not be attributed to medical therapy alone. The problem is, that most of these trials have been conducted in Europe or South America.

Similarly, the use of bone marrow stem cells for critical limb ischemia has also been studied since 2000. Most of the early clinical work was performed in Japan, with later translation to Europe and then most recently to the U.S. There has been a decrease in the rate of amputations which has been significant enough that the German government has approved certain centers of expertise which perform the therapy on patients as standard of care and obtain reimbursement from the equivalent of CMS.

Both of these examples are of the first generation of cardiovascular cell therapy. There are many other multi- and pluri-potent stem cells which also have potential for clinical use in cardiovascular disease but the safety still needs to be established before large scale clinical trials are performed such as adipose (fat), amniotic, menstrual, umbilical cord, cardiac stem cells, fetal, and embryonic. Some of these cells are in phase I safety trials both here in the U.S. and Europe. I have attached a table below which shows some of the larger cardiovascular studies in the U.S. and the rest of the world based on the international registry clinicaltrials.gov.

Phase III	Country	# Patients	Funding	Results
Acute Myocardial Infarction	Germany	200, 800 pending	Government/ Private/ Corporate	Safe, Mild improvement in heart function and decease mid term adverse events
Acute Myocardial Infarction	Brazil	300	Government	Ongoing
Heart Failure	Brazil	300	Government	Ongoing
Limb Ischemia	Germany	90	Government	Ongoing
Phase II/III				
Heart Failure-myoblasts	USA	390	Corporate	Ongoing
CABG + cells	Germany	100	Government	Pending
Phase II				
Chronic Angina	USA	120	Corporate	Completed – awaiting results

Problems in Clinical Use:
There are a number of clinical issues related to translation into reliable therapy. I have listed them below but also have attached a supplement which goes into further detail for each question: 1. What is the best source of stem cells? 2. Is a variety or combination of cells required for different types of heart disease? 3. What are the doses of cells required in humans compared to animals? 4. Are therapeutic doses available? 5. If so, what will be necessary to acquire them? 6. What is the best delivery method for the cells into the heart? 7. When is the best time after myocardial injury to deliver the cells? 8. Are the cells going to stay in the heart and, if not, where do they go and will they cause any harm? 9. How do we follow applied cells over time? 10. Will a tissue engineered scaffold be required to enhance effect? 11. Is it worth the risk to the patient?

Roles of the National Institutes of Health & Food and Drug Administration
The NIH has done a great job in terms of supporting cardiovascular cell based therapies by developing Cell Therapy Network, Heart Failure Network, and the Cardiac Surgery Network. They will all play a significant role in answering the above questions and advancing clinical cardiac cell therapy and the science that is needed to make it a reliable, safe and reproducible therapy.
The FDA has also been very helpful in approving clinical trials with adult based cell therapies. However, the use of both outside basic and clinical scientists in the field early

in the development and approval of the trials may expedite approval but more importantly help in ensuring safety to the patients, which is most important.

Summary

Cardiovascular cell therapies using the first generation adult stem cell have great potential to help our patients today. The science needs to continue to improve and help support the safety and efficacy of the therapies. Continued development of other multi-potent stem cells along with tissue engineering to make new large blood vessels, heart valves, and the entire heart are the future of cardiac cell therapy. However, significant improvement in the amount of funding is required to keep pace with other countries but most importantly help our patients here in the U.S. I am a realist that these early therapies are a treatment for cardiovascular disease and not a cure. They are experimental but without our current work, the future cures that everyone hopes for and needs will be very difficult if not impossible to achieve.

Mr. PALLONE. Thank you, Dr. Patel.
Mr. Rice.

STATEMENT OF DOUGLAS T. RICE, SPOKANE VALLEY, WASHINGTON

Mr. RICE. My name is Doug Rice and I am 62 years old. I have congestive heart disease and diabetes. I could be one of over 750,000 people that die in the United States yearly, but I am not dead, not because I shouldn't be, but there is a resolution to this problem. I am not a miracle, a phenomenon, but a living person that by the grace of God was saved from a disease that kills approximately 2,000 people daily. However, I had to travel to Bangkok, Thailand, and go in debt to do something that should be readily available in the United States. I used my own adult stem cells and a simple angioplasty procedure to have my life given back to me. Your own adult stem cells have so much more to give than we give them credit for. A lot of other diseases are being treated successfully by just using the adult stem cells.

My story is simple. In 1992, I had my first heart attack and was also diagnosed with diabetes. That same year, my mother died of congestive heart failure and diabetes, just like what I have. Also just last year, my sister died of what I have. I have had numerous heart attacks and diabetes episodes as well as having to be jump-started at least three times. I have had a TMR—that is a transmyocardial revascularization procedure—that uses a laser to drill holes in the left ventricle to get better blood flow. This did not help. In 1998, I was given only 2 years to live unless I received a heart transplant. Because of my diabetes, I did not quality for it. We tried different things that helped, and then in November of 2005 I could not walk but a few feet. I had to sleep sitting up and was just worn out. My ejection fraction, the amount of blood my heart pumps out each beat, was around 11 percent. The average is over 50 percent. My cardiologist, Dr. Canaday, said at best I had 4 months without a mechanical heart pump to survive. It was battery operated, and I decided that I did not want to be battery powered.

That night my best friend, Sheba Rice, went on the Internet looking for new heart treatments. She found Thera Vita, a company in Bangkok, Thailand, that had been having success using the adult stem cells. We contacted them, went to Bangkok in January of 2006, and other than drawing blood, shipping to Israel, then having the adult stem cells sent back and implanted in me via angioplasty, it was simple. The hardest part was the 20-hour flight. When I returned to Spokane, within a month my ejection fraction was tested. It was 28 percent and going up. I felt better than I had felt in years. I was motivated to tell the world, and that is when I found out that over 750,000 people a year die from heart disease.

These 750,000 heart patients that will die do not make the mainstream press, no newspaper articles of any significance, and certainly most politicians in Washington don't even like to discuss it. Sadly, it is a fact, if a family dies in a car wreck, children are gunned down in a school or a disgruntled person shoots or maims his or her coworkers, it is big news. But 750,000 people die at a rate of over 2,000 people a day and no one takes time to talk for

them. Not all are old. Some are very young and with families and friends to care about. Most people just don't realize that they die although almost everyone knows someone that has died or will die from this disease.

The Federal Government has spent millions of dollars on embryonic stem cells but not one person has been treated and the animals tested often get tumors.

By some estimates, over 400,000 people with various cancers and other diseases have been successfully treated and most are alive to talk about the adult stem cell treatment using their own blood cells or ones from cord blood cells. The honest experts say maybe in 10 or 20 years embryonic stem cells might have potential to treat someone, but not now, and there is something that works now. The adult stem cells work. What does it take to make people realize that a bird in the hand is worth two in the bush, especially when it comes to people's lives?

If you ask most people about stem cells, they only heard about embryonic because that is all you hear about. Education, education, education and the facts regarding adult stem cells are the only way to succeed in moving this issue to the forefront for funding and actual treatments now.

I get a lot of calls on a daily basis because I have been treated with my adult stem cells, and the most frequent question is, why did you have to go to Thailand? Because there is no treatment available in the United States. I had to pay for it myself. My insurance did not cover the costs of this treatment, though I heard that in Germany, insurance covers stem cell treatment for heart disease. I also know that much of the stem cell debate in recent years has been drastically increased funding for embryonic stem cells despite the fact they have not treated patients for any disease. Patients are being increasingly treated with adult stem cells but we need drastically more Federal funding for adult stem cell treatments. These cells aren't patentable, so private investment is far behind. The government should spend more on clinical trials so Americans like myself can have the same chance at a treatment that I had. I am just one man, and all I can do is talk to everybody I know, and it is a fact, you ask anybody what a stem cell is, and the first word out of their mouth is embryonic because that is all you ever hear. I listen to every TV station, news station and you never hear the word "adult stem cells." I am alive because of it.

Thank you.

[The prepared statement of Mr. Rice follows:]

www.douglastrice.org
ADULT STEM CELL RECIPIENT

Douglas T. Rice

Adult Stem Cell Recipient for the heart
May 8th, 2008

My name is Douglas T. Rice. I am 62 years old, have Congestive Heart Disease, and Diabetes. I could be one of over 750,000 people that die in the United States yearly, BUT I am not dead. Not because I shouldn't be, but because there is a resolution to this problem. I am not a miracle, a phenomenon, but a living person that by the grace of God was saved from a disease that kills approximately 2,000 people daily. However, I had to travel to Bangkok, Thailand and go in debt to do something that should be readily available in the United States. I used my own Adult Stem Cells, and a simple angioplasty procedure to have my life given back to me. Your own Adult Stem Cells have so much more to give than we give them credit for; a lot of other diseases are being treated successfully by just using the Adult Stem Cells.

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but a few feet, had to sleep sitting up, and was just worn out. My Ejection Fraction (the amount of blood my heart pumps out each beat) was around 11% (average is 50%+) and my Cardiologist, Dr. Donald Canaday, said at best I had 4 months without a mechanical heart pump to survive. It was battery operated and I decided I did not want to be battery powered.

That night my best friend, Sheba Rice, went on the Internet looking for new heart treatments. She found TheraVitae, a company in Bangkok, Thailand, that had been having success using the Adult Stem Cells. We contacted them, went to Bangkok in January of 2006, and other than drawing blood, shipping it to Israel, and then having the Adult Stem Cells shipped back and implanted in me via a simple angioplasty procedure, it was simple. The hardest part was the 20-hour flight there. When I returned to Spokane, within a month my Ejection Fraction was tested. It was 28% and going up. I felt better than I had felt in years. I was motivated to tell the world and that is when I found out that over 750,000 Americans die every year from Heart Disease.

These 750,000 heart patients that will die do not make the mainstream press, no newspaper articles of any significance, and certainly most politicians in Washington, D.C. don't even like to discuss it. Sadly, it is a fact, if a family dies in a car wreck, children are gunned down in a school, or a disgruntled person shoots or maims his or her co-workers, it is BIG NEWS.

BUT, 750,000 people die at a rate of over 2,000 a day and no one takes the time to talk for them. Not all are old, some very young and with families and friends to care about. Most people just don't realize that they die although almost everyone knows someone that has died or will die from this disease.

The Federal Government has spent millions of dollars on Embryonic Stem Cells, but not one person has been treated and the animals tested often get tumors.

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The honest experts say maybe in 10 or 20 years embryonic stem cells might

have potential to treat someone, but not now, and there is something that works "NOW," the Adult Stem Cells!! What does it take to make people realize that a bird in the hand is worth two in the bush, especially when it comes to people's lives?

If you ask most people about stem cells, they only know about Embryonic, because that is all they hear about. Education, Education, Education and the Facts regarding Adult Stem Cells are the only way to succeed in moving this issue to the forefront for funding and actual treatments "NOW."

I get many calls on a daily basis because I have been treated with my Adult Stem Cells, and the most frequent question is, "Why did you have to go to Thailand?" Answer: Because there were no adult stem cell clinical trials in the US that I could participate in, and FDA has been slow to approve treatments that are being conducted overseas in countries like Thailand and Germany. My insurance did not cover the cost of this treatment (though I heard that in Germany insurance covers stem cell treatments for heart disease). I also know that much of the stem cell debate in recent years has led to drastically increased funding for embryonic stem cell research despite the fact they have not treated patients for any disease. More money needs to be spent in the United States to prevent a brain drain here for treatments, and siphoning off federal funding for embryonic stem cell research has not helped patients like me. Patients are being increasingly treated with adult stem cells, but we need drastically more federal funding for adult stem cell treatments. These cells aren't patentable, so private investment is far behind. The government should spend more on clinical trials so Americans like me can have the same chance at a treatment that I had.

Listen, I am but one man, a very lucky man to have had my best friend, Sheba Rice, find the solution on the Internet while looking for new technology for heart disease. Without her efforts, I would be in an urn on the fireplace. But, she cared and wanted me alive for whatever reason. We all need to do the same for someone we know or people that need the help. We that care need to educate everyone we meet. Not because I say it, because of the 750,000 people that will die this year!

I would get down on my knees and beg if I thought that I alone could do it. I can't. I doubt if I make a difference, but you can. You Congressmen, your Doctors, News Media and friends can make a difference. I will do whatever I can do to move this forward, but I need your help! Ask me for anything

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that will help and I will do my best. I am asking everyone that reads this to do their best. One day you may be where I have been, or your mother, father, brother or sister as well as relatives and friends. This is so serious I can't imagine everyone not getting involved.

Feel free to contact me if I can be of help. dtrice@douglastrice.org

Sincerely,
Douglas T. Rice

Links for information: www.vescell.com

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Mr. PALLONE. Thank you, Mr. Rice.
Dr. Daley.

STATEMENT OF GEORGE Q. DALEY, M.D., PH.D., PRESIDENT, INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH AND ASSOCIATE PROFESSOR OF PEDIATRICS, CHILDREN'S HOSPITAL BOSTON

Dr. DALEY. Thank you, Mr. Chairman and members for the chance to testify. It is difficult to add much to what Dr. Zerhouni talked about. He really gave a very spirited and compelling argument in support of an integrated approach to stem cell research.

I am here to give the perspective of a physician scientist. I am from Children's Hospital and Harvard Medical School and I am also the current president of the International Society for Stem Cell Research. My laboratory studies blood development, blood cancers, and various experimental transplantation therapies, and in my clinical duties at the Children's Hospital I take care of kids with a variety of blood diseases and so I see firsthand the advantages and the limitations of the current therapies such as adult stem cell therapies.

All stem cells, whether they are embryonic, fetal, neonatal, adult, have great promise for medicine. However, I am concerned because the recent breakthroughs in the reprogramming of adult skin cells have renewed the calls for limitations on embryonic stem cell research, and I wish to testify unequivocally that enacting such limitations would be unwise. My organization, the International Society for Stem Cell Research, continues to assert, as do I think the vast majority of scientists, that only through an expanded support for all avenues of stem cell research can we ensure the most rapid pace of discovery.

Much excitement in stem cell research has focused on this remarkable property of embryonic stem cells, a property we call pluripotency, that was described by Dr. Zerhouni. This is the capacity for a cell to generate any tissue in the body. It is an enormously valuable property. Recently several laboratories, including my own, reported that a small set of genes which were originally discovered because of their link to pluripotency in embryonic stem cells, can be inserted into human skin cells to convert them to a cell which is like a seed for all tissues in the body, a cell that very closely resembles but may not be identical to embryonic stem cells. I can show you the scar on my forearm. We can do this with any patient, and in a matter of weeks take skin cells and turn them into pluripotent stem cells.

This is no doubt a major breakthrough in medical research and it is going to have important implications for modeling disease, and I certainly hope that one day it is going to usher in new cellular therapies. But I have to caution and reiterate the caution of Dr. Zerhouni that realizing this promise is going to take time. A major concern for this new methodology is the viruses that we use to carry the reprogramming genes. They themselves are linked to cancer. And even if we can remove viruses from this process, the genes and pathways that are activated in the cells are also associated with cancer and we don't know how these cells are going to re-

spond. We don't know what their long-term predispositions to abnormal growth or even cancer might be.

Furthermore, I want to say that even though my lab has generated these induced pluripotent stem cells, my lab will continue to vigorously study embryonic stem cells. First, we need to directly compare the properties of our embryonic stem cells against the properties of our induced pluripotent, or iPS, cells. And there are already some whispers in the community and some preliminary data that iPS cells are not as robust as embryonic stem cells for the formation of certain tissues, but it is going to take years for scientists to understand the similarities and differences.

I would also mention that even though we have iPS cells, my laboratory will continue to vigorously pursue somatic cell nuclear transfer. Reprogramming by nuclear transfer is faster than gene-based reprogramming and may entail very different mechanisms that will teach us a lot about how to make pluripotent tissues better. The iPS breakthrough is being heralded by opponents of stem cell research as a solution to the long-smoldering debate over the necessity for embryonic stem cells, and we have heard the arguments before. We heard them in 2002 when multi-potential adult progenitor stem cells were announced. We heard them later in 2004 and 2006 when fat and amniotic fluid stem cells were announced and again we are hearing them today. Congress has been wise not to yield to these arguments. I remind you that it was basic stem cell research that really led to the breakthroughs in iPS cell research.

Yesterday I gave an address to the Congressional Biomedical Research Caucus and I answered the question, "Do we still need embryonic stem cell research?" with a resounding "yes." And I would say that embryonic stem cells remain the gold standard, will remain so for the foreseeable future, and there is still real value in passing H.R. 810, the original bill put forth by Members Castle and DeGette.

I look forward to answering your questions in the Q&A period. Thank you.

[The prepared statement of Dr. Daley follows:]

STATEMENT OF GEORGE Q. DALEY

Thank you for the invitation to speak today on the subject of stem cell science. My name is George Daley and I am an Associate Professor of Biological Chemistry, Medicine, and Pediatrics at Children's Hospital Boston and Harvard Medical School, a core faculty member of the Harvard Stem Cell Institute, an investigator of the Howard Hughes Medical Institute, and the current President of the International Society for Stem Cell Research (ISSCR), the major professional organization of stem cell scientists worldwide. My laboratory studies blood development, blood cancer, and experimental transplant therapies for diseases like sickle cell anemia, immune deficiency, and leukemia. In my clinical duties at Children's Hospital, I care for patients with these devastating blood diseases, and see first hand the need for better treatments. Stem cell research offers hope.

Let me recount the stories of two patients I cared for recently at Children's Hospital that illustrate the shortcomings of current therapies. One was a young African-American boy with sickle cell anemia, suddenly struck down by what we call a pain crisis. When I saw him in the emergency room, he was writhing on the gurney and whimpering in pain. Despite powerful, high doses of intravenous morphine, I was unable to give that child adequate relief from his pain and suffering for several days. A second case was an infant who suffered repeated infections and had spent half his young life in the hospital hooked up to intravenous antibiotics. His disease

was immune-deficiency, and unfortunately he had no sibling donors for a potentially curative adult stem cell transplant. Stem cell research is laying the foundation for improved treatments for these kids and countless other children and adults with debilitating, life-threatening diseases.

All stem cells—whether from embryonic, fetal, neonatal, or adult sources—hold great promise. The crowning scientific achievement of the twentieth century was the sequencing of the human genome, and the dominant mission of twenty-first century science is to discover how that blueprint drives the formation of tissues and organs, and how tissues are sustained, repaired, and rejuvenated over time. Stem cell research goes to the core of human biology and medicine.

Much excitement in stem cell research has focused on a property of embryonic cells called pluripotency—the capacity to generate all of the tissues in an organism. Recently, several laboratories, including my own, reported that a small set of genes linked to pluripotency in embryonic stem (ES) cells can be inserted into human skin cells to induce pluripotency—to endow skin cells with this same remarkable capacity to become a seed for all tissues in the body. By using gene-based reprogramming to make these so-called induced pluripotent stem cells (called "iPS cells"), scientists can now produce customized, patient-specific stem cells in the Petri dish. In a matter of weeks, we can take cells from a patient's forearm and transform them into pluripotent stem cells that we believe closely approximate embryonic stem cells. This is a major breakthrough in medical research, empowering scientists to create cellular models of human disease. It may also mean that one day we will treat patients with rejuvenated and repaired versions of their own tissues.

Realizing this promise will take time. A key concern is that the viruses used to carry the reprogramming genes into human skin cells can cause cancer. Moreover, the genes and pathways the viruses stimulate are themselves associated with cancer, raising the concern that even if viruses can be eliminated from the process, the reprogrammed cells might remain predisposed to cancer. For these reasons, iPS cells may never be suitable for use in patients. I sincerely hope that iPS cells are the long-sought-after customized patient-specific stem cell, but much more research must be done.

Even with iPS cells in hand, my laboratory will continue to study embryonic stem cells. First, we need to directly compare the capacity of these two types of stem cells to generate specific tissues. Some very preliminary data has suggested that iPS cells may be less potent than embryonic stem cells in making blood, while others are noting a deficiency in making heart muscle cells. It will take years for scientists to understand the similarities and differences between these two valuable classes of pluripotent stem cells. Even with iPS cells in hand, my laboratory will continue to investigate somatic cell nuclear transfer as a means of generating pluripotent stem cells. Reprogramming by nuclear transfer is faster and may entail very different mechanisms than gene-based reprogramming. Learning why may lead to better methods for making iPS cells.

The iPS breakthrough is being heralded by opponents of embryonic stem cell research as a solution to the long-smoldering debate over the necessity of embryonic stem cell research. We have heard the arguments for many years, first made when multi-potential adult progenitor cells (MAPCs) were reported in 2002, and later when stem cells were isolated from Fat and Amniotic fluid; we are told that alternatives are available that preclude the need for embryonic stem cell research. Congress has been wise to not yield to such arguments. Indeed, it was embryonic stem cell research that led directly to the breakthrough in iPS cells, and my own laboratory was poised to generate iPS cells in large part because of our experience and expertise in deriving and culturing human embryonic stem cells. Today, it would again be a mistake to place limits on the tools available to biomedical scientists to pursue the next medical breakthroughs. The right course for biomedical science and ultimately the right decision for patients and our health care system, is to expand the scope of federal funding for all forms of stem cell research, including the many lines of embryonic stem cells created after the President's artificial deadline of August 9th, 2001.

Yesterday, in my address to the Congressional Biomedical Research Caucus, I was asked the question: "Do we still need research on embryonic stem cells?" to which I replied a resounding "Yes." Embryonic stem cells remain the gold standard today and will remain so for the foreseeable future. If we are to maximize the pace of scientific discovery and accelerate development of new treatments for disease, we must continue to vigorously pursue all forms of stem cell research, using ES cells derived from embryos, pluripotent stem cells generated by nuclear transfer and gene-based reprogramming, and adult stem cells. Passage of the bill H.R. 810 originally proposed by members Castle and Degette remains a worthy goal.

Mr. PALLONE. Thank you, Dr. Daley.
Mr. Johnson.

STATEMENT OF WEYMAN JOHNSON, JR., J.D., CHAIRMAN, NATIONAL MULTIPLE SCLEROSIS SOCIETY

Mr. JOHNSON. Thank you, Chairman Pallone and Ranking Member Deal. Thank you, all the members of the Committee. I am honored to be invited to speak here today among many distinguished panelists and to represent individuals who live with chronic disease.

Expanded embryonic stem cell research will advance our progress in many diseases, but today I will focus on one, multiple sclerosis, and it is not because it is more important than any disease, it is because it is the disease I know about. It is the disease that comprises my story.

I first learned close-up about multiple sclerosis when I was just a kid, 12 years old, and my father was diagnosed with multiple sclerosis. He is no longer living, but late in his life, MS affected him severely. His own sister, Allene was the first person I met with MS. She was diagnosed in the mid-1950s. I never knew Allene, unless she was in a bed or in a wheelchair. When I was a child, I was told that incidence of MS in our family was merely a coincidence. Today, through genetic research, we know that it is simply not true.

In 1989, my own sister, Lanay, who is only a few years older than I am, was diagnosed with multiple sclerosis. Today, she uses a power wheelchair to move everywhere she goes. Her hands don't work well anymore. She can no longer teach the way she did in the public school systems in Georgia for many years. She can no longer play the piano the way she did so beautifully. When I think about the sanctity of life, I include my sister's life in those thoughts.

A few years after she was diagnosed, I was diagnosed. In our family, we hate this disease. We hate its impact on our family and other families. We hate the threat it poses to future generations. While I have not been severely disabled by multiple sclerosis, I have seen its severe effects up close.

The scientific community is making progress into the genetic factors involved in multiple sclerosis. There are still more questions than answers, however. All kinds of research must continue.

I remember being told that multiple sclerosis is a disease that doesn't affect my friends in the African-American community, that it is only for white people. With scientific advance, we have found that is not true. We also used to hear that this disease did not happen to children, but that is not true either. We know now that there are thousands of children in the United States and thousands of children throughout the world who live with this disease. All kinds of research must continue.

Before 1993, there were no treatments at all for multiple sclerosis. Now we have six. But there is a wide spectrum of disability among people living with multiple sclerosis. Most of the available therapies work only for those on the lucky end of the spectrum, like me. For people like my sister on the more unlucky end, there are still few remedies. All kinds of research must continue.

Every hour, somebody new is diagnosed with multiple sclerosis. It is an unpredictable, often disabling disease of the central nervous system. The progress, the severity, the specific symptoms of MS in any one person still cannot be predicted. The cause is unknown, and there is no cure. But embryonic stem cell research holds unique promise to repair nerve cells to slow the progression of MS and to find a cure. I am just one person living with a chronic disease, but I am also privileged to serve as the chair of the board of the National Multiple Sclerosis Society. At the National MS Society, we believe that all promising avenues of research that could lead to new ways to prevent, repair, slow the progression or cure MS must be pursued with adherence to the strictest legal and procedural guidelines.

I salute Congresswoman Capps. She was chosen last year as our organization's legislator of the year. We thank her for her support for people with MS. I salute in absentia Dr. Burgess, who is a member of the MS Caucus of the House of Representatives. He and I might not agree categorically on every issue but I appreciate his support and the support of other Congresspersons for people with MS.

I am asking you today to expand Federal policy in embryonic stem cell research and to ensure that research continues for the more than 400,000 other Americans who live with MS and the 100 million Americans with other diseases and conditions. Research on all kinds of stem cells is critical because we have no way of knowing now which kind of stem cell will be of the most value for MS, for Parkinson's, for Alzheimer's, for cancer, for heart disease, for many other conditions. Just as with genetics and race and age, there is much left to learn about how to treat and cure MS, about how to treat and cure other diseases. Expanding our embryonic stem cell research is just one avenue.

As I close, I will note one side note. Our organization in January of 2007, along with our sister organization, the MS International Federation, sponsored an embryonic stem cell symposium in San Francisco. The heartening part of that symposium was that there was new research about repair that was available. The disheartening part was that there were not very many American scientists leading on the cutting edges. I think that is a shame that we may have abdicated our leadership role in the intellectual and scientific progress in the world. We ask for your commitment not to give up on legislation like the Stem Cell Research Enhancement Act. We don't have the luxury of time. Like many others who live with a chronic disease, I know that maybe not today, maybe not next week but I pray soon with patience and continued research, there will be a world without multiple sclerosis and a world of decreased disease.

Thank you very much for helping move us closer, and thank you for your time.

[The prepared statement of Mr. Johnson follows:]

STATEMENT OF WEYMAN JOHNSON

SUMMARY

• Summary of my personal and family experiences with a chronic, disabling disease.

• Speak to a patient perspective on my own diagnosis with multiple sclerosis.
• Speak to the position of a national voluntary health organization, as chairman of the board of the National Multiple Sclerosis Society.
• Speak to the need for continued research and the hope it brings for people living with chronic diseases and conditions nationwide.
• Support the need for the Committee and Congress to remain committed to legislation like the Stem Cell Research Enhancement Act.
• Embryonic stem cell research holds an incredibly unique promise for people living with chronic diseases and conditions, and the progress made to date on embryonic stem cell lines should not be abandoned.

TESTIMONY

Thank you Chairman Pallone and Ranking Member Deal. Thank you members of the Committee. I am honored to be invited to speak here today among many distinguished panelists and to represent patients who live with chronic disease.

Many diseases could benefit from expanded embryonic stem cell research. But today I will focus on one—multiple sclerosis. Not because it is more important than others, but because I know multiple sclerosis.

I remember multiple sclerosis and how it entered my life as a child, in 1964, just barely 13 years old. My father received a diagnosis of MS suddenly. He died in 2001. His sister, my aunt Allene, also had MS. Research into this disease, into genetics was just starting to evolve in the 1960s.

There were good doctors then, but they did not recognize a genetic connection. They said MS in my family was a mere coincidence. Because of research, we now know that is not true.

My own sister, who's only a few years older than I, lives with MS. She uses a power wheelchair, her hands don't work well anymore, she can no longer teach the way she did, or play the piano the way she did. A few years after she was diagnosed, so was I. We hate this disease, its impact on our family, and the threat it poses to our future generations.

We are making progress into the genetic factors involved in multiple sclerosis. However there are still more questions than answers. The research must continue.

I remember being told that MS is a disease that doesn't affect my friends in the African American community. This is only for white people from Minnesota. With good science, we have found that's not true. The research must continue.

We also used to hear that this disease does not happen to children. But that is not true either. We now know there are thousands of children in the United States, thousands of children throughout the world, who live with this disease. The research must continue.

Before 1993, there were no treatments at all for multiple sclerosis. Now we have six. But there is a wide spectrum among people living with MS. Most of the therapies will only work for those of us on the lucky end of the spectrum like me. But for people like my sister, on the more unlucky end, there's still not much out there that provides effective treatment. So the research must continue.

Every hour, someone new is diagnosed with MS. It's an unpredictable, often disabling disease of the central nervous system. The progress, severity, and specific symptoms of MS in any one person still cannot be predicted. The cause is unknown, and there is no cure. But embryonic stem cell research holds an incredibly unique promise to repair nerve cells, to slow the progression of MS, to help find a cure.

One area that holds great promise, but is often misunderstood, is Somatic Cell Nuclear Transfer. We have seen some exciting breakthroughs. But as with all science, this research takes time. We are still exploring this avenue for medical research. I have hope that SCNT will succeed because of its promise to repair nerve cells, creating new tissues, and more. I know that researchers are focused on the idea of creating cells and tissues for transplantation and research. They are trying to understand how different genes are turned on and off. They are not focused on cloning. I know that as we explore somatic cell nuclear transfer research more, we will see greater potential for developing individualized cell and tissue therapies. That holds great promise for people living with MS like me, whose body's own defense system is attacking the myelin surrounding and protecting our central nervous system.

I am but one person living with a chronic disease. But I am also fortunate to serve as chairman of the board of the National Multiple Sclerosis Society. We believe that all promising avenues of research that could lead to new ways to prevent, repair, slow the progression, or cure MS must be explored, with adherence to the strictest ethical and procedural guidelines. The National Multiple Sclerosis Society believes that all promising avenues of research that could lead to the cure or prevention of

multiple sclerosis or relieve its symptoms must be explored. The Society supports the Stem Cell Research Enhancement Act to expand the number of approved stem cell lines that are available for federally funded research. The Society supports the conduct of scientifically meritorious medical research, including research using human cells, in accordance with Federal, State, and local laws and with adherence to the strictest ethical and procedural guidelines. Research on all types of stem cells is critical because we have no way of knowing which type of stem cell will be of the most value in MS research. Stem cells—adult or embryonic—could have the potential to be used to protect and rebuild tissues that are damaged by MS, and to deliver molecules that foster repair or protect vulnerable tissues from further injury.

So I ask you to expand the federal policy on embryonic stem cell research and ensure that research continues —for the more than 400,000 other Americans who live with MS and 100 million Americans with other diseases and conditions. Research on all types of stem cells is critical because we have no way of knowing at this point which type of stem cell will be of the most value—for multiple sclerosis, for Parkinson's, for Alzheimer's, for cancer, for heart disease, for spinal cord and brain injuries, for many other conditions.

Just like with genetics and race and age, there is so much left to learn about how to treat and cure MS, about how to treat and cure other diseases. Expanding our embryonic stem cell research is just one avenue. But it is an avenue of research that must continue. Federal barriers must be lifted.

You might see that I am not the only person living with MS on Capitol Hill today. Hundreds of MS activists are visiting with their legislators on the Hill right now, talking about the need to advance medical research.

Embryonic stem cell research remains one of the most promising avenues of research to cure diseases and end suffering. I am not a scientist, but I am an observer of science. And I know that science is a matter that requires some patience. That's why we must expand the important work done to date with embryonic stem cell lines. The research must continue. So we can improve the lives of people with chronic diseases and conditions. So we can improve the lives of families for generations to come. For my grandchildren and for yours.

We need your commitment to not give up on legislation like the Stem Cell Research Enhancement Act. We don't have the luxury of time. Like many others who live with a chronic disease, I know, maybe not today, maybe not next week, but I pray soon, with patience and continued research, that there will be no more disease. Thank you for helping us move closer, and thank you for your time.

NATIONAL MULTIPLE SCLEROSIS SOCIETY

POLICY POSITION

EMBRYONIC STEM CELL LINES AVAILABLE FOR FEDERALLY-FUNDED RESEARCH

Position: The National Multiple Sclerosis Society believes that all promising avenues of research that could lead to the cure or prevention of multiple sclerosis or relieve its symptoms must be explored. The Society supports the Stem Cell Research Enhancement Act (H.R. 3 and S. 5) to expand the number of approved stem cell lines that are available for federally funded research.

The Society supports the conduct of scientifically meritorious medical research, including research using human cells, in accordance with federal, state, and local laws and with adherence to the strictest ethical and procedural guidelines. Research on all types of stem cells is critical because we have no way of knowing which type of stem cell will be of the most value in MS research. Stem cells—adult or embryonic—could have the potential to be used to protect and rebuild tissues that are damaged by MS, and to deliver molecules that foster repair or protect vulnerable tissues from further injury.

Request: We urge Congress to support the Stem Cell Research Enhancement Act of 2007 (H.R. 3 and S. 5) at all levels of the legislative process. This legislation would increase the number of approved embryonic stem cell lines that can be used in federally-funded research by allowing new lines to be generated from embryos that have been donated for research purposes by people using the services of in vitro fertilization clinics, while establishing important ethical protections.

Supporting Rationale: There is broad agreement that the policy limiting the number of stem cell lines available for federally funded research is flawed.

• An insufficient supply of stem cell lines currently exists, as only 22 of the 70 approved lines are available to researchers. In addition, all of the available lines are contaminated by nutrients from mouse feeder cells. Many in the scientific community believe that these stem cell lines are unsuitable for research and hinder U.S.

scientists' ability to capitalize on the potential breakthroughs from embryonic stem cell research.

• At the same time, it has become increasingly clear that stem cell research holds tremendous promise for MS and many other diseases and disorders. Research suggests that stem cells might have many uses: for delivery of growth factors and drugs, for tissue culture systems for drug and gene discovery, for understanding and modeling MS, and for repairing or protecting brain tissue.

• However, our scientific advisors have told us that we still don't know which type of stem cells will be most valuable for MS research, and thus we must support policies that promote the conduct of research using all types of stem cells.

Mr. PALLONE. Thank you, Mr. Johnson.

Dr. Bertino.

STATEMENT OF JOSEPH R. BERTINO, M.D., INTERIM DIRECTOR AND CHIEF SCIENTIFIC OFFICER, THE CANCER INSTITUTE OF NEW JERSEY

Dr. BERTINO. Mr. Chairman, members of the Committee, thank you for inviting me to present my testimony today.

New Jersey has been a leader in supporting stem cell research. In 2004, the Stem Cell Institute of New Jersey was created by a memorandum of understanding between Rutgers, the State University of New Jersey, and UMDNJ-Robert Wood Johnson Medical School. The State then committed $8.5 million to support work at the Stem Cell Institute, including $5.5 million in capital funds to Robert Wood Johnson Medical School and Rutgers University for laboratory renovations and GMP facilities.

In December 2005, New Jersey became the first State to finance stem cell research that included research on human embryonic stem cells. The Commission on Science and Technology awarded a total of $5 million to 17 research teams.

In 2006, the finance committee of the General Assembly passed a $250 million bill to build stem cell research facilities in New Brunswick, Camden, and Newark. One hundred fifty million dollars of this was for a joint Rutgers-Robert Wood Johnson Stem Cell Institute in New Brunswick. And just last year, New Jersey awarded grants totaling $10 million to stem cell researchers, including two grants to fund core laboratories for embryonic stem cell research.

Despite polls that show that the majority of New Jerseyans were in favor of supporting embryonic stem cell research, a referendum was defeated in 2007 that would have provided $450 million over 10 years to support all stem cell research, not only embryonic stem cell research. The major reasons for defeat of the referendum were believed to be the off-year election, with fewer than 30 percent of voters coming to the polls, and the concern that this would add to the public's tax burden.

Governor Corzine continues to be a strong supporter of stem cell research and the building of the joint Robert Wood Johnson-Rutgers Stem Cell Institute in New Brunswick. Key members of the New Jersey legislature also continue to strongly support stem cell research.

For the past 2 years, over 50 investigators from academia and pharmaceutical companies in New Jersey have been meeting monthly to report their work in stem cell research, to discuss progress in the field and to plan collaborative experiments. Two

types of stem cells are found in the bone marrow: hematopoietic stem cells, that form blood cells; and mesenchymal stem cells, capable of differentiating or forming, for example, bone or cartilage or nerve cells. Hematopoietic stem cells are now used at Robert Wood Johnson Hospital and throughout the world to treat patients with cancer following chemotherapy or immune diseases. Mesenchymal stem cells from bone marrow or cord blood are being tested for their ability to prevent graft vs. host disease after marrow transplantation, and other uses under study by New Jersey investigators include targeting tumors with mesenchymal stem cells carrying toxins, and use in regenerative medicine, in particular spinal cord injury and damaged hearts.

Researchers at both Rutgers and UMDNJ have special expertise and interest in neural stem cells that have the potential for treatment of brain disorders as well as to serve as models to promote drug discovery.

We know that cord blood, placenta, and amniotic fluid are also a rich source of stem cells. Clinical trials are in progress, for example, by Wise Young from Rutgers, with collaboration of investigators in China using a subset of cord blood cells to treat spinal cord injury. The characterization of stem cells from placenta is under study by Robert Wood Johnson Medical School investigators in collaboration with Celgene, a New Jersey-based biotech company.

Work on human embryonic stem cells, as you heard, has been hampered by Federal guidelines that limit studies to 20 cell lines that have been around for several years and have limitations. Rutgers and Robert Wood Johnson Medical School stem cell researchers with New Jersey State funding have been able to expand research activities using newly established embryonic stem cell lines, and importantly, the completion of a GMP facility at the Cancer Institute/Stem Cell Institute which allow stem cells to be produced in quantities necessary for clinical studies.

The funding provided by the State of New Jersey has provided key support for both the research outlined above and additional research focused on a variety of important disease conditions including multiple sclerosis, Parkinson's disease, Alzheimer's disease, and diabetes, and a key part of our efforts has been the establishment of stem cell banking of umbilical cord blood and other stem cells. In New Jersey, stem cell banks are leaders in this field.

I would be happy to answer any of the committee's questions. Thank you very much.

[The prepared statement of Dr. Bertino follows:]

Testimony to be presented to the House Committee on Energy and Commerce's Subcommittee on Health by Joseph R. Bertino, M.D.
May 8, 2008

Good Morning, Mr. Chairman, Members of the Committee. Thank you for inviting me to present my testimony today.

"Stem Cells" are defined as cells capable of self-renewal as well as differentiation. The investigators funded by the New Jersey State Commission on Science are exploring every type of stem cell for the purpose of understanding function, regulation, and potential therapeutic benefit. These studies range from very basic studies to studies that will soon be translated into the clinic.

The promise of stem cell research is compelling and far-reaching. No other line of scientific inquiry offers better hope for curing intractable medical conditions. Indeed, therapies based on stem cells are a paradigm shift in the modern medical revolution. The potential to treat currently incurable conditions is both real and achievable in our lifetimes.

As a society, we have an obligation to pursue scientific discoveries that offer a clear potential to help those living with devastating illnesses. At the same, we recognize the legitimate moral, social and religious concerns raised by new technologies.

To address such concerns, nationally respected science associations, federal agencies and the State of New Jersey have set forth policies and procedures that ensure stem cell research meets the highest scientific and ethical standards. The Stem Cell Institute of New Jersey is committed to conducting responsible research that complies fully with these stringent requirements.

History of stem cell Research in New Jersey:

On May 12, 2004, the Stem Cell Institute of New Jersey was created by a memorandum of understanding between Rutgers, the State University of New Jersey and UMDNJ-Robert Wood Johnson Medical School.

The State committed $8.5 million in state funds to support work at the Stem Cell Institute in financial year 2006, including $5.5 million in capital funds to Robert Wood Johnson Medical School and Rutgers University to support laboratory renovation and GMP facilities to support stem cell research, as well as two clinical trials using umbilical cord-derived stem cells.

In December 2005, NJ became the first state to finance research using human embryonic stem cells. The Commission on Science and Technology awarded a total of $5 million to 17 research teams.

On October 19, 2006, the finance committee of the General Assembly passed a $250 million bill to support stem cell research facilities in New Brunswick, Camden, and Newark.

In October 2006, monthly meetings of investigators interested in stem cell research were initiated at Rutgers and Robert Wood Johnson Medical School. Over fifty investigators from academic and pharmaceutical companies have been meeting to report their work in stem cell research, to discuss progress in the field and to plan collaborative experiments.

In 2007, New Jersey awarded 17 grants, totaling $10 million to stem cell researchers, including two grants to fund core laboratories for embryonic stem cell research.

Despite polls that showed that the majority of New Jerseyans were in favor of supporting embryonic stem cell research, a referendum was defeated in November 2007 that would have provided $450 million dollars, for ten years in support of stem cell research. Major reasons for the defeat of the referendum were the off-year election, with fewer than 30% of voters coming to the polls, and the concern that this would add to the public's tax burden, as well as put New Jersey even further in the red.

Governor Corzine continues to be a strong supporter of stem cell research and the building of the joint Rutgers/UMDNJ-RWJMS Stem Cell Institute in New Brunswick. Key members of the NJ legislature also continue to strongly support stem cell research.

In June 2008, an additional 10 million dollars will be made available for investigators in New Jersey from the State for stem cell research via a peer-reviewed grant program.

Examples of studies in progress are as follows below:

Two types of stem cells are found in the bone marrow: hematopoetic stem cells, that form blood cells, and mesenchymal stem cells, capable of differentiating or forming bone, cartilage, nerve cells, fat cells, etc. Hematopoeitic stem cells are now used at the RWJUH and throughout the world to treat patients with cancer following chemotherapy. Mesenchymal stem cells from bone marrow or cord blood are being tested for their ability to prevent graft vs. host disease, after marrow transplantation. Other uses for mesenchymal stem cells under study by NJ investigators include targeting tumors with mesenchymal stem cells carrying toxins, and use in regenerative medicine (spinal cord injury, heart injury and brain disorders (Parkinson's, Alzheimer's)).

Researchers at both Rutgers and UMDNJ have special expertise and interest in neural stem cells that may have important implications for brain disorders as well as serve as models to promote drug discovery.

Cord blood, placenta and amniotic fluid are also a rich source of stem cells. Clinical trials are in progress in collaboration with investigators in China, using a subset of these cells to treat spinal cord injury (Dr. Wise Young). The characterization of stem cells from placenta is under study by RJWMS investigators in collaboration with Celgene, a NJ-based biotech company.

Work on human embryonic stem cells has been hampered by Federal guidelines that limit studies to 20 cell lines that have been around for several years. The two core laboratories at

Rutgers and RWJMS, established with NJ State funding, have allowed investigators to expand research activities using newly established embryonic cell lines.

Importantly, the completion of a GMP facility at the Cancer Institute/Stem Cell Institute will allow stem cells to be produced in quantities necessary for clinical studies.

The funding provided by the State of New Jersey has provided key support for both the research outlined above and additional research programs focused on a variety of important disease conditions including multiple sclerosis, Parkinson's disease, Alzheimer's disease and diabetes. A key part of our efforts has been the establishment of stem cell banking of umbilical cord blood and other stem cells. New Jersey's stem cell banks are leaders in this field.

I would be happy to answer the committee's questions. Thank you.

Mr. PALLONE. Thank you, Dr. Bertino.
Dr. Fraser.

STATEMENT OF JOHN K. FRASER, PH.D., PRINCIPAL SCIENTIST, CYTORI THERAPEUTICS

Dr. FRASER. Good morning, Mr. Chairman, members of the Committee. Thank you for this opportunity.

My name is John Fraser, and I am principal scientist at Cytori Therapeutics, Inc., a publicly traded adult stem cell company based in San Diego, California. Cytori is at the forefront of bringing adult stem cells to patients as we are currently selling a stem cell-based product in Europe, conducting three separate clinical trials and have a technology which has now been used in over 200 patient procedures. From my graduate studies in New Zealand through to a post-doctoral and faculty appointment to UCLA, my entire research career has been in the field of adult stem cells.

The topic of today's meeting is consideration of stem cells as the future of medicine, and indeed, stem cells will be an important part of the clinical armamentarium going forward. But as we have heard, this is nothing new. Hematopoietic stem cells have been used in medicine for at least 50 years, and we referred earlier to the pioneering work performed in the late 1950s by Dr. E. Donnall Thomas, who performed bone marrow transplant studies that ultimately led to his award of the Nobel Prize for Medicine in 1990. Like many, I consider 1961 as the birth date of the stem cell field as that was the year that James Till and Ernest McCulloch published research that led to the description of the very first stem cell, the hematopoietic stem cell, still widely considered to be the model for all adult stem cell types.

Hematopoietic stem cells make bone marrow transplants possible. This is because they have the ability to regenerate the entire blood system of the recipient for the rest of that person's life. Simply put, hematopoietic stem cells are the regenerative engine of the blood system. In my opinion, this is a key point of distinction between adult stem cells and embryonic stem cells. Embryonic stem cells are capable of immense proliferation and essentially universal plasticity. This is because they are, first and foremost, developmental cells. They are derived from a cell mass from which the entire organism develops.

By contrast, adult stem cells are, first and foremost, regenerative cells responsible for maintaining and healing organs and tissues in the face of daily wear and tear, injury and disease. They are, by their nature, repair cells. They act in response to a need and they shut off once that need is completed. One way to look at this is to view embryonic stem cells as responsible for generating all the tissues of an organism while adult stem cells are responsible for maintaining and healing them.

The natural role of adult stem cells in repair and regeneration makes them ideally suited to clinical use. This has been proven in tens of thousands of bone marrow transplant patients over the last 40 years. This paradigm, as you have heard, is now increasingly being repeated as other adult cell types associated with repair and regeneration are being applied in different diseases.

In our own case, Cytori has initiated several clinical studies using cells obtained from the patient's own fat, adipose tissue, which is recognized as one of the richest and most accessible sources of adult stem cells. The goal of these studies is to bring forth new treatments for the millions of patients suffering from heart disease as well as other issues such as reconstructing the breast following partial mastectomy. We also intend to start studies in intervertebral disc repair.

Other researchers have published case reports and small clinical studies using fat tissue-derived stem cells and treating certain kinds of wound complications with bone marrow, GHVD, and in bone defects. Published preclinical studies have indicated potential in treating renal damage associated with chemotherapy, preserving dopaminergic neurons in a Parkinson's disease model, treatment of liver damage, ischemic, and hemorrhagic stroke, and in tissues as disparate as the cornea, the lung, and the vocal fold.

Published clinical studies with other types of adult stem cells have shown improvement in cardiac function, in inherited brittle bone disease, liver disease, and peripheral vascular disease, to name but a few.

However, as you have heard, there are still many unanswered questions, and clearly, additional science is needed. In certain settings, the mechanism through which adult stem cells provide benefit is not well understood. It is also not yet clear which adult stem cells provide greatest efficacy in which diseases. These are important questions that companies such as Cytori have neither the resources nor oftentimes the incentive to address.

For example, certain potentially beneficial populations fall outside of patent protections, providing limited incentive for companies to invest their resources in proving a technology that may then be applied without their participation. Without Federal support, much of this promise could be left to wither on the vine.

Cytori believes that ultimately science and the marketplace will determine which technologies will succeed. We have looked at the field of regenerative medicine, performed our own basic science, preclinical, and now clinical research, and we are optimistic regarding the ability of our approach to harness the natural role of adult stem and regenerative cells to provide clinically effective and cost-effective treatments for a range of human diseases in the near future.

We urge your continuing support of adult stem cell research. Thank you.

[The prepared statement of Dr. Fraser follows:]

Testimony of John K. Fraser Ph.D.; Principal Scientist, Cytori Therapeutics

Good morning, my name is John Fraser, and I am Principal Scientist at Cytori Therapeutics Inc, a publically-traded stem cell company in San Diego, California. Cytori is at the forefront of brining adult stem cells to patients, as we are currently selling a stem cell-based product in Europe, are conducting three separate clinical trials, and have a technology, which has been used in over 200 patient procedures.

From my graduate studies in New Zealand, through to a postdoctoral and then faculty appointment at UCLA, and now at Cytori, my entire research career has been centered on adult stem cells.

The topic of today's meeting is consideration of stem cells as the future of medicine. Indeed, stem cells will be an important part of the clinical armamentarium going forward. But this is nothing new; hematopoietic stem cells have been used in medicine for at least 50 years. In pioneering work started in the late 1950's E. Donnall Thomas performed bone marrow transplant studies that ultimately led to the award of the Nobel Prize for Medicine in 1990 (1-3). Many consider 1961 as the birth date of the stem cell field as that was the year that James E Till and Ernest A McCulloch published research (4) that led to the description of the first stem cell (5), the hematopoietic stem cell; which is still widely considered to be the model for all adult stem cells (6).

Hematopoietic stem cells make bone marrow transplantation possible. This is because they have the ability to regenerate the entire blood system of the recipient for the rest of that person's life. Simply put, hematopoietic stem cells are the regenerative engine of the blood system.

In my opinion, this is a key point of distinction between adult stem cells and embryonic stem cells. Embryonic stem cells are capable of immense proliferation and essentially universal

plasticity. This is because they are, first and foremost, developmental cells; they are derived from a cell mass from which the entire organism develops.

By contrast, adult stem cells are, first and foremost, regenerative cells, responsible for maintaining and healing organs and tissues in the face of daily wear and tear, injury, and disease. They are, by their nature, repair cells; they activate in response to a need and shut off once healing is completed. One way to look at this is to view embryonic stem cells as responsible for generating all the tissues of an organism, while adult stem cells are responsible for maintaining and healing them.

The natural role of adult stem cells in repair and regeneration makes them ideally suited for clinical use. This has been proven in tens of thousands of bone marrow transplant patients in the last 40 years. This paradigm is now increasingly being repeated as other adult cell types associated with repair and regeneration are being applied in different diseases.

For example, Cytori has initiated several clinical studies using cells obtained from the patient's own fat tissue, which is recognized as one of the richest and most accessible sources for adult stem cells. The goal of these studies is to bring forth new treatments for the millions of patients suffering from heart disease as well as to help reconstruction breast defects in women who have undergone partial mastectomy. We also intend to start studies in intervertebral disc repair and potentially several other clinical applications, which look promising.

Other researchers have published case reports and clinical studies using fat tissue-derived stem cells in treating certain types of wound (7-9), in treating complications associated with bone marrow transplantation (10-14), and in bone defects (15). Published preclinical studies have indicated potential in treating renal damage associated with chemotherapy (16), preserving dopaminergic neurons in a Parkinson's disease model (17), treating liver damage (18), ischemic

(19) and hemorrhagic (20) stroke, and in tissues as disparate as the cornea (21), the lung (22,23), and the vocal fold (24).

Published clinical studies with other types of adult stem cell have shown improvement in cardiac function (25-27), in an inherited brittle bone disease (28-30), in liver disease (31-33), and peripheral vascular disease (34) to name but a few.

However, there are still many unanswered questions and clearly additional science is needed. In certain settings, the mechanisms through which adult stem cells provide benefit are not well understood. It is also not yet clear which adult stem cell sources provide greatest clinical efficacy in which diseases. These are important questions that companies such as Cytori have neither the resources nor oftentimes the incentive to address.

For example, certain potentially beneficial cell populations fall outside of patent protections limiting the incentive of companies to invest resources in proving a technology that may then be applied without their participation. Without federal support much of this promise could be left to wither on the vine.

Cytori believes that ultimately science and the marketplace will determine which technologies will succeed. We have looked at the field of regenerative medicine, performed our own basic science, pre-clinical and now clinical research and we are very optimistic regarding the ability of our approach to harness the natural role of adult stem and regenerative cells to provide clinically and cost-effective treatments for a range of human diseases in the near future. We urge your continuing support of adult stem cell research.

Thank you.

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NIH Research Contract and Grant Funding Received by Dr Fraser

1R44HL076045 "Adipose Derived Cell Therapy for Myocardial Infarction" awarded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. January 2004 to July 2006: Total $950,000

1R43HL088871-01 "Adipose Tissue-Derived Cells for Vascular Cell Therapy" awarded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. September 2007 to August 2008: Total $250,000

1N01HB067142 "Collection and Storage Centers for Clinical Research on Umbilical Cord Blood Stem and Progenitor Cell Transplantation". September 1996 – September 2001: Total ~$11 million.

Mr. PALLONE. Thank you, Dr. Fraser.

We will take questions now, and I will recognize myself for 5 minutes initially.

I have to start with you, Dr. Fraser, because of what you said originally, and I noticed that you didn't make any reference in your statement now to the fact that—and I will go back to what you said in the previous one, that increasing funding to embryonic stem cell research means a decrease in funding to other stem cell research. I don't want to get into it, but basically we had one statement earlier in the evening and then it was revised, you know, based on what you said today, and I don't see any more reference to this idea that increasing funding to embryonic means a decrease in funding to others. So why did you take that out?

Dr. FRASER. Sir, I received my formal invitation to attend this meeting while I was at the airport in San Diego on my way here. At that time there was a version of my testimony which was under review and was sent to committee staff before it had been completed. I contacted committee staff——

Mr. PALLONE. Well, no, you are more than welcome to change it. I am just asking why. Why is it no longer——

Dr. FRASER. I think the initial comments that I made overstated the position. I think the point that was made there and which is no longer is that you have to make difficult decisions. You can't find everything, and for every dollar you take away—sorry—every dollar you add somewhere else, you have to take it away from somewhere else, and I——

Mr. PALLONE. Well, not necessarily, but——

Dr. FRASER. Well, that would be nice, but we all know the realities of the current fiscal and economic situation. I am simply encouraging you not to take away funding from adult stem cell research.

Mr. PALLONE. Well, I don't think we are suggesting that, but I mean, do you support embryonic stem cell research?

Dr. FRASER. The company has an official position which says we have no official position regarding embryonic stem cell research.

Mr. PALLONE. What about you personally?

Dr. FRASER. I am not here as an individual, I am here representing the company.

Mr. PALLONE. So you just basically have no response to that question?

Dr. FRASER. Well, sir, I have spent my entire career in adult stem cells. That was not a conscious decision. That was pretty much an accident when I was in graduate school. I am very happy with where I am. I am certainly not saying——

Mr. PALLONE. I am just trying to find out whether you support——

Dr. FRASER. I am not——

Mr. PALLONE [continuing]. Support embryonic stem cell, and you don't want to answer that?

Dr. FRASER. Embryonic stem cells are valuable, and research that has been performed under the NIH funding with the current situation has produced valuable insights.

Mr. PALLONE. All right. I will leave it at that. Thank you.

Let me ask Dr. Bertino a couple of questions, and thank you again for being here today. I am obviously proud of my home State in that we were the first to publicly finance embryonic stem cell research, and of course, the new Stem Cell Institute, which is going to be in my district in New Brunswick, but given what our State and many other States are doing in terms of taking the initiative on their own to advance embryonic stem cell research, some have argued that there is no need for additional Federal funding, you know, the States and private sector can do it on their own. But can you speak to this? Do you believe that New Jersey and other States with similar initiatives have enough financial resources to achieve the full potential that stem cells may hold, or do you think there is a need for additional Federal funds?

Dr. BERTINO. I think there is clearly a need for additional Federal funds.

Mr. PALLONE. I think the mic is not on, Doctor. There you go.

Dr. BERTINO. What we are seeing already is that more and more investigators are becoming interested in stem cell research because of the tremendous impact this paradigm shift is having on medicine, and as we attract the youngest and most talented researchers in this area, we have to provide them with funds, and the State at this level cannot take care of all the exciting research that is possible. I think if the stem cell bill was approved and we did get the $450 million over 10 years, I think that would have been a major step in supporting all the good research in the State, but that didn't happen.

Mr. PALLONE. And what about the money that is being spent in stem cell research in the United States versus, you know, in other parts of the world? Is the United States on par with other countries; are we falling behind? Is that going to imperil our ability to recruit top researchers unless we spend more money by comparison to other countries?

Dr. BERTINO. I don't know the details and I can't really answer that question. There are pockets of good research money for stem cell research from different States,—I think Connecticut, New Jersey, California—but there are many States that have not stepped up to the plate.

Mr. PALLONE. Well, let me ask Dr. Daley, if you don't mind, in terms of United States versus other countries and whether we are doing enough and may fall behind and not maybe get researchers to come here.

Dr. DALEY. I think one of the real issues is the supply and demand. The real question is, how many—we have a huge number of very, very gifted scientists here in the United States, many of whom I think have been scared off from the embryonic stem cell field because of the political concerns and the lack of funding. In other parts of the world, and I think about Singapore and China, they have specifically invested in this area because of the vacuum left by the Federal policy in the United States. I have heard that directly from representatives of the Economic Development Board of Singapore. They want to know what we are not able to do because they want to invest in that, because that gives them a competitive advantage. So I think, you know, it is always hard to say what might have been but I can tell you that had we had a more

expansive Federal policy, the kinds of breakthroughs we are seeing today might have happened years ago. We might have been even further along. I think the United States—I am still very, very bullish on what the United States can do and contribute in stem cells and I hope that the Federal policy will get behind the scientists because we enjoy the greatest community of scientists in the world.

Mr. PALLONE. Thank you. Thank you to all of you.

Mr. Deal.

Mr. DEAL. Thank you.

I thank all of you for being here today. You certainly have some varied points of view here. As I listened to all of you, though, I think I detected at least three examples of successful clinical applications of adult stem cells, I think Dr. Patel, Mr. Rice, and Dr. Fraser specifically. Maybe I missed it, but did any of you suggest that there are successful clinical applications of embryonic stem cells?

Dr. DALEY. This is really an interesting question that keeps coming up. There is no way that a cell which was discovered only 10 years ago would be able to compete with the clinical results of hematopoietic stem cells, which were introduced into therapy in the 1950s. It took 30 years before the discoverer of bone marrow transplant, E. Donnall Thomas, was actually recognized with the Nobel Prize for that. I think it is really unfair to hold embryonic stem cells to the same kind of standard. They are new. This is a new technology.

Mr. DEAL. I wasn't questioning whether it was fair or not. I was questioning about what the facts are.

Dr. DALEY. Well, the facts are that this is a fresh, new technology which is finding its way into the laboratories and will ultimately find its way into having a clinical impact. I think we have a responsibility to educate the public that scientific cures don't happen overnight, that this is a very long and tedious path and it involves basic investments. The NIH has been tremendous for supporting basic research and we enjoy the tremendous benefits in our healthcare system, we enjoy the tremendous benefits in our biotechnology industry, but we are at risk of not taking advantage of the tremendous possibility of embryonic research because of a Federal policy which has limited investments in that very exciting area.

Mr. DEAL. Well, I think the answer was, I did not hear any, and the second question then, Dr. Daley, since you have taken it on in the context of——

Dr. DALEY. I think you need to ask that question in another 10 years.

Mr. DEAL. All right. Well, that is my next question——

Dr. DALEY. And then we will see how things stand.

Mr. DEAL. —if you will let me ask it. How soon do you expect clinical applications from embryonic stem cell research to be used?

Dr. DALEY. So I want to say that it is very important that we educate the public about the nature of medical discovery. After I leave this hearing, I am flying to Chicago where the International Society for Stem Cell Research is convening its clinical translation task force. We have a group of 30 scientists, and bioethicists from all over the world who are tackling the question of what is a prudent approach to translate this new science of stem cells into real

clinical therapies. We already know there are companies that are attempting to commercialize both adult and embryonic stem cells. You heard reference to the Geron Corporation, which may in fact introduce the first clinical trial of an embryonic stem cell-derived cell to treat spinal cord injury. There is a big difference and a delay between the first introduction of a treatment into human patients and realizing real clinical benefit. If you look back at the history of medical technology, whether we are thinking about therapeutic antibodies or drugs, there is often a 20-year time lag. I would anticipate that we have to take another 10 years, so 20 years after the original introduction of embryonic stem cells, before we start to see therapies based on stem cells.

Now, in the much nearer term, we are already benefiting from 25 years of understanding mouse embryonic stem cells. In 1981, mouse embryonic stem cells were first isolated, won the Nobel Prize for Martin Evans this past year. There have been countless numbers of mouse models of human disease that have been generated, funded by the NIH which have revolutionized our understanding of cardiovascular disease, neurodegenerative disease, cancer and the like. So in indirect ways, that investment in basic research is translating into cures.

Mr. DEAL. Well, you are not suggesting, though, that we should not continue research and investment in adult stem cell research, are you?

Dr. DALEY. I think my testimony clearly stipulates that we need a vigorous and increased support for all forms of stem cell research. We are having a very difficult time as scientists right now through the NIH because the budget has been kept flat. We had a doubling, and it created a tremendous infusion of talent, great, high-caliber talent into American science, and now we are seeing a receding because we can't support all that momentum.

Mr. DEAL. We are very proud of our side for being able to double that budget on our side, so join with us to get some pressure on these folks to make sure we keep that 5 percent as a minimum increase every year.

I think my time is probably expired. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Deal.

I recognize the gentlewoman from Colorado, Ms. DeGette.

Ms. DEGETTE. Thank you very much, Mr. Chairman. Before I question, I have two unanimous-consent requests. The first one is that I be allowed to submit testimony of Dr. Debra Mathews on the ethics of stem cell research. We have cleared this with the Minority. For the record, we tried to get Dr. Mathews to come but because of the short notice, we were unable to. And my second UC request is to submit Dr. Zerhouni's chart that he referred to in his testimony for the record.

Mr. PALLONE. Let me also mention that I have the copies of the documents that the gentlewoman from North Carolina gave me. I am no less knowledgeable on the subject after having glanced at them than I was before but I would also unanimous consent that they be submitted as part of the record.

Without objection, all four documents will be submitted. So ordered.

[This information was unavailable at time of printing.]

Ms. DEGETTE. Thank you very much, Mr. Chairman.

I only have 5 minutes so I am going to ask the panel if they would mind giving short answers to my questions if possible because I have a lot of ground to cover.

I wanted to ask you first Dr. Gearhart, as a researcher, has the research community found that the restrictions on Federal funding for embryonic stem cell research that were enacted in 2001 affected research in the area of embryonic stem cell research?

Mr. GEARHART. Well, it has.

Ms. DEGETTE. And briefly, how has that——

Mr. GEARHART. In several ways. One Dr. Daley referred to is students and post-docs and fellows coming to the lab and looking at long-term support in this area, very problematic in this country as we look back in 2001, we didn't know where it was going, and this was before there was a big——

Ms. DEGETTE. And so it is limiting the number of people who want to go into that type of research?

Mr. GEARHART. Well, yes. They have to be practical and look to see what kind of a future there is.

Ms. DEGETTE. And do you think that the research itself would benefit if a greater number of embryonic stem cell lines were allowed under the Federal——

Mr. GEARHART. Oh, absolutely. I think we have arguments for utility, performance and safety that trump all of that, and there are many experiments that we don't want to do with some of the existing lines. It is not worth the effort.

Ms. DEGETTE. And someone, I think Ms. Capps, asked Dr. Zerhouni about the Federal funding for facilities and how people were having to build parallel labs. Are you finding that also happening in the research community where private universities or other groups are feeling like they can't use anything that has had Federal funding involved with it?

Mr. GEARHART. Well, we do. It varies from institution to institution. At Hopkins, the decision was made, not by us, that we could use the same facility but the bookkeeping from where someone's funding is coming from as either salary or supplies, we have to mark all of this as to which one is federally approved, which is not federally approved. It becomes a bookkeeping and practical nightmare under those conditions.

Ms. DEGETTE. And at other facilities, they have determined that if there is any Federal funding in those labs——

Mr. GEARHART. That is correct. They will build a separate lab.

Ms. DEGETTE. They are building separate labs.

Mr. GEARHART. Absolutely.

Dr. BERTINO. In New Jersey, we have built separate labs because it is too much of a hassle.

Ms. DEGETTE. And also in Colorado, by the way.

Dr. Daley, I wanted to ask you, you are the president of the International Society for Stem Cell Research, and someone asked you briefly about the international implications, but I have learned through talking to researchers at the international level that the U.S. restrictions are also hurting the international research because of collaboration issues. If a scientist in Singapore, for exam-

ple, wants to collaborate with a U.S. scientist, the restrictions are having an impact on that. Is that correct?

Dr. DALEY. Oh, absolutely.

Ms. DEGETTE. Could you explain briefly why that is so?

Dr. DALEY. Yes, well, it is not only international, it is interstate concerns. I mean, I have a colleague, a very respected colleague, Sean Morrison in Michigan, who can't do the kinds of research that I do in my own lab because it is restricted in Michigan so that limits the kinds of collaborations that we can have. Science is increasingly a global activity. We are about to have our international meeting, we will have 2,500 scientists from all over the world, and we have this patchwork quilt of regulations. It is not good for science.

Ms. DEGETTE. And would it also be fair to say that it would be helpful to have a national ethics oversight system for the research that is being done here, much like——

Dr. DALEY. No doubt.

Ms. DEGETTE. —in the United Kingdom and in other countries?

Dr. DALEY. No doubt.

Ms. DEGETTE. Now, it sounds like it was actually your skin cells that were used in this iPS experiment. Is that right?

Dr. DALEY. Well, I tried, but my skin cells didn't yield an iPS line.

Ms. DEGETTE. Well, the iPS research, I am assuming that hasn't led to any kind of clinical cures for anything, even though it has been touted by some as the alternative to embryonic stem cell research, has it?

Dr. DALEY. No, it hasn't.

Ms. DEGETTE. And I would also expect that since that research is 10 years behind human embryonic stem cell research and 20 or 30 years behind mouse embryonic stem cell research, the clinical applications for iPS are going to be that much farther out down the road from now, correct?

Dr. DALEY. Well, we are hopeful that we can piggyback on some of the embryonic stem cell research and accelerate that.

Ms. DEGETTE. If we expand embryonic stem cell research lines that Federal funding can be used for, would you expect that that would also help your iPS research then?

Dr. DALEY. Yes.

Ms. DEGETTE. Why is that?

Dr. DALEY. Well, I mean, we still don't know enough about these iPS cells to even know and predict with confidence we will ever be able to use them in patients. I am confident that they will be valuable for modeling disease. We are already doing that in our own laboratory, and I think it is a very important point that so much of the debate has focused on whether or not stem cells will directly cure disease, but I want to reiterate the value of basic research and the fact that these stem cells are really changing the paradigm of that research.

Ms. DEGETTE. And this is exactly what Dr. Zerhouni was talking about, isn't it?

Dr. DALEY. Actually, what Dr. Zerhouni was arguing, and it is the first time I have really heard it argued so compellingly—in fact, I would love to have him come and give that speech to my stem

cell research laboratory—is that all of the questions asked by scientists about stem cells are really the same. It is about programming of cell fates, and so we never have these kinds of disagreements at our scientific meetings about embryonic versus adult. This is a debate that happens in Congress.

Ms. DEGETTE. Thank you very much.

Mr. PALLONE. Thank you.

Mr. Pitts.

Mr. PITTS. Thank you, Mr. Chairman.

Dr. Gearhart, do you support gestating human children to later fetal stages to harvest issues to treat disease?

Mr. GEARHART. Absolutely not.

Mr. PITTS. Does anyone in the panel support that? OK.

Dr. Daley, do you think that the Federal government should fund somatic cell nuclear transfer or cloning for research?

Dr. DALEY. I do support it because I think it has enormous medical implications. The study of somatic cell nuclear transfer research, I do support that, yes.

Mr. PITTS. And so you think that should be legal?

Dr. DALEY. It is legal.

Mr. PITTS. And you think it should remain legal. Do you think that the Federal government should fund research in which animal eggs and human cells are mixed to create embryos that are part animal, part human?

Dr. DALEY. I believe that this range of experiments that you are defining are best left to the experts in the scientific community to set the priorities. I do believe that there are scientific arguments to support that area of research as has been supported by the United Kingdom. So, yes, I do believe that that is a potentially valuable area of research and it should be under the purview of the scientific community.

Mr. PITTS. And that should be legal?

Dr. DALEY. It is legal.

Mr. PITTS. It is legal and should remain legal?

Dr. DALEY. Yes.

Mr. PITTS. Dr. Patel, how many patients have you treated for heart disease with adult stem cells?

Dr. PATEL. In our team, we have treated over 100 here in the United States but we have had over 30 groups from around the world come and train and try the different techniques. The key is, we do it in a very regulated and ultimately our goal is to have it as safe as possible so now that some of the trials have evolved to phase III trials, both in Germany and in Brazil, where they are all federally-funded trials since they are mostly bone marrow-derived treatments. The problem is that even though we treat patients as still experimental, there are people who try to do these as approved or unregulated therapies, and that is our biggest concern irrespective of the cell, and we do worry that when you take the more multipotent cells, that we are going to see severe adverse events which could potentially shut down our entire field just due to the fact that patients are going to these countries and having these unregulated therapies. So we are actually very happy that the NIH has created these centers for at least cardiovascular disease where

we could offer these type of treatments in controlled trials here in the United States today.

Mr. PITTS. Do you agree that adult stem cells show promise only for blood diseases or autoimmune diseases and that they don't show as much promise as embryonic stem cells for things like Parkinson's or spinal cord injury or macular degeneration or diabetes?

Dr. PATEL. Well, my expertise is cardiovascular disease.

Mr. PITTS. What about the heart?

Dr. PATEL. So in the heart, adult stem cells show great promise and there are many different types that we need to continue to work that actually can differentiate in the lab to new heart muscle and blood vessels. The key is safely translating those therapies into patients. So in terms of other diseases, there are clinical trials for type 2 diabetes, also for Parkinson's and also for spinal cord disorders but currently they are not ongoing in the United States. These are all trials that are either in Europe or in South America that are funded by their governments, and hopefully as some of these posters and presentations are presented at the ISSCR and the ISCT, that as the academic community goes through these trials, we can hopefully bring these back to the United States and see if we can replicate them, just as the iPS cells were originally created in Japan and Dr. Daley's group along with others were able to reproduce that so that will advance the field and also keep it a very safe therapy.

Mr. PITTS. Dr. Daley, you support human cloning. You stated, I think, yesterday that human cloning is necessary to do iPS research. Since there are no human cloned embryonic stem cell lines, yet there are 124 human iPS lines including at least 15 human iPS cell lines that you have developed according to your publication online in Nature at the end of 2007, how do you justify that statement?

Dr. DALEY. Mr. Pitts, I am very pleased that you are reading my paper in Nature.

Mr. PITTS. My staff did.

Dr. DALEY. Oh, OK. Well, if you read that paper or your staff and some of my other publications, I think you would see the justification, and that I have written that there is a strong distinction between your use of cloning and the legitimate medical applications of copying cells, copying cells so that we can learn about this reprogramming process that Dr. Zerhouni described. It is a fascinating and important fundamental question in biology. We still don't know whether the reprogramming we are inducing with these candidate genes is the same process of the reprogramming that happens with nuclear transfer. We think this is a frontier of medicine with enormous potential, and I think that we should allow the scientists to explore and use all of the tools available to them subject to very rigorous and very scrupulous scientific and ethical review, and that has been done for my own experiments through at least four different institutional review committees.

Ms. DEGETTE [presiding]. The gentleman's time has expired.

The gentlelady from California.

Ms. CAPPS. Thank you, Madam Chairwoman.

I want to continue this line of thought. We need to have several more things on this, Madam Chairwoman. This is a very important

issue. To follow along the previous questioner, Dr. Daley, we are confused often here and I think the media is too, which influences us a lot. Do you support reproductive cloning?

Dr. DALEY. No, I don't.

Ms. CAPPS. And maybe you want to take a minute, this is a big issue. When you talk about human cloning, people get really scared and react with sort of blanket prohibitions. Could you just expand a little bit on that so we understand clearly? And then this harkens back to me, this need for ethical oversight, even with respect to how other countries are dealing with it and how they are filling in the vacuum, as you have said, because we have created one.

Dr. DALEY. There has been an enormous amount of public debate and some scientific discussion about the value versus the risks to society of using nuclear transfer. Nuclear transfer is the method that has been used in animal biology to perform reproductive cloning for many different mammalian types—mice and dogs—and there are legitimate scientific reasons to do this and there are issues of animal husbandry which have supported this. There is also one methodology for using nuclear transfer to establish stem cell lines. That has been enormously productive in mice. My own laboratory, together with Rudy Jaenisch, has published using nuclear transfer to treat a genetic disease in a mouse. Recently these nuclear transfer lines have been produced from primates. It has not been done from humans. And I think that much of the enthusiasm is now going to be diverted to producing these stem cell lines using the iPS methodology. So my own laboratory is performing an enormous amount of experiments on the iPS methodology, but because of the scientific value, the intrinsic scientific value of the nuclear reprogramming, we continue to pursue that. But it is very important to draw the distinction between copying cells and copying babies. No one in the scientific community—and I chaired last year the International Society's guidelines on human stem cell research, and there was a clear prohibition against productive cloning. So no legitimate scientists think that this is an area of great interest, but many scientists feel that understanding nuclear transfer so that we can reprogram individual cells is highly, highly valuable. And so you will see, I think, broad consensus for studying the various ways of reprogramming because no one knows yet which way is ultimately going to be the most valuable.

Ms. CAPPS. And doesn't this also speak to a federally-established set of guidelines that could direct the way this kind of research is done so that we can be proud and confident that our scientists will clearly be able to distinguish between the various levels of research to safeguard the threats that many people are concerned about?

Dr. DALEY. The NIH has enormous respect from all of the scientists in this country and it has always played a critical role in scientific peer review and scientific oversight, and I think it has been unfortunate that it has not been able to play its routine leadership role in this critical area of this exploding biology.

Ms. CAPPS. I want to try to get one other question in, if I can. With the description of adult stem cells coming on to the scene and they are being lauded as the end-all, then there are many, even among our colleagues, who say that well, we don't need embryonic stem cell research then, and I know you have been around this, but

clearly for the record. Also in terms of the long-term effects of it, do we really know—I think Dr. Patel has alluded to this. It is very new technology that we really don't know the end results. Maybe you would use the remaining time to distinguish there.

Dr. DALEY. It is just—it is far too premature to imagine how we are going to use embryonic, neonatal, adult in the many different indications. I am confident that we are going to find very, very valuable applications for adult stem cells and that is why we need to continue to work in those areas, but why close any doors?

Ms. CAPPS. Thank you very much.

Ms. DEGETTE. The gentleman from Texas, Mr. Hall.

Mr. HALL. I am sorry that I didn't get to hear all the testimony, and I am more sorry than that that I don't really know how to ask what I want to know. I have an illness in my family for which there is no cure, and it was illness that was treated for some time for Parkinson's 18 months to 2 years, and on my way back up here one time, I asked my wife to give me her file, and I like to read everything I can read about Parkinson's, and by the time I got up here, I wanted to go directly to a hospital or doctor's office because I had almost every symptom, but I am 85 years old. I am the oldest guy in the Congress. I am the dean of the United States Congress, and people think that is bad but it is not nearly as bad as somebody saying don't he look natural.

So I ask you this question, and it is a very important question to me and I don't know how to ask it properly, but I think Mr. Rice went overseas to have his treatment and it has been suggested that we go to India, that that was where the best available treatment was. I don't think we could stand that. Another to Mexico. I am not inclined to do that; another to Seattle, that there were some treatments there that was available. And as most acknowledge, it is not paid by insurance, and I have had price estimates all the way from $25,000 to $40,000 to $60,000, and none of those are too great if I thought it would help her for 15 minutes. The decision was made that she didn't have Parkinson's because the week I read all that, I went back and said we will go to Mayo and know what we have, and we went to Mayo, stayed 4 days, didn't want to know if she needed an appendectomy or ingrown toenail or anything else. The question was, did she have Parkinson's, and the answer after 4½ days was absolutely not. Three weeks later, a letter back saying that, however, she could have peri-Parkinson's.

Now, that would be distressing to some but it was hope to me because I understand stem cells one day might eradicate Parkinson's. I have heard that said and that may be an overstatement, but what are the facts with the effect of stem cells on Parkinson's? Who should I ask that?

Mr. GEARHART. We have done some work on this. The stem cell therapies for Parkinson's actually began by using portions of fetal brains that were obtained through abortion in northern Europe. This was a standard measure of care. Patients receiving these cells did improve over a period of time and then they lost that improvement and came back to what they were before. These cells really weren't stem cells. These were fully formed dopaminergic neurons, the cells that are lost here, and they just don't hook up appropriately when they are fully formed. There was a clinical trial in

the early 1990s here in Denver that reported the same thing pretty much. The newer technologies that are being worked on in the laboratory, and this is all through now animal modeling of Parkinson's disease, in which we can grow in great abundance and derive and grow dopaminergic neurons from embryonic stem cells. It is one of the most robust sources of these cells. These cells have been introduced into various animal models from rats to mice to monkeys in which we see very much the same thing. There was a very interesting series of experiments, summary of experiments published in Nature recently in which the evidence showed that these cells can go in, they can integrate, they can function for a long period of time.

Now, this brings up another issue. Some of these cells that were grafted in are beginning to show the cellular basis of Parkinson's disease. We know that there is a certain morphology associated and subcellular components that indicate Parkinson's disease, something we have not mentioned here. We have mentioned only that we are growing cells to replace those that are lost. We have said very little about the companion compartment of this that is so critical. We have got to learn more about the pathogenesis of disease and how to shut it down. We mentioned autoimmune for many of the diseases that are at the basis of this. If we don't learn what that is about, putting new cells in isn't necessarily going to help you.

So what we are seeing, and a short answer here, is that there is an improvement in patients, well, at least in animals and in the patients that had the fetal tissue grafts, but it is not of long standing.

Mr. HALL. Let me ask you this, and I note that some asked whether or not we were aware that the leading experts on embryonic stem cell research now says treatments from that source may be one or two decades or more away. Is that what you are saying?

Mr. GEARHART. Yes. At the moment, we are going through proof of concept experiments. These are laboratory-based animals.

Mr. HALL. I am getting close to my 5 minutes.

Mr. GEARHART. Right. So——

Ms. DEGETTE. You are over 5 minutes, so if Dr. Gearhart could——

Mr. HALL. May I ask one more question?

Ms. DEGETTE. Sure.

Mr. HALL. If we do avail ourselves of this thrust for stem cells, and it has been told to me so simple that you put two stem cells in, one finds and destroys and the other takes it place, well, I am willing to accept that but I know it is much more than that. But is there any danger if the stem cells do not help?

Mr. GEARHART. Oh, absolutely.

Mr. HALL. That they will do damage?

Mr. GEARHART. Yes, absolutely. There is——

Mr. HALL. Briefly tell me yes or no.

Mr. GEARHART. Yes. I would be happy to give you lots of data on that.

Mr. HALL. And I will take that up with the folks that I am talking to. Thank you for that.

Ms. DEGETTE. Thank you very much. I really want to thank this panel for coming on very short notice. It was an excellent panel, and every single witness added to our knowledge. As I mentioned at the beginning, this is the first hearing that we have had in the Energy and Commerce Committee ever on all of these cell therapies, so it has been very useful and I know on behalf of Mr. Pallone, I want to thank all of you for the Committee. This concludes all questioning.

In conclusion, I want to remind the members that you may submit additional questions for the record to be answered by the relevant witnesses. The questions should be submitted to the committee clerk within 10 days, and the clerk will notify the offices of the procedures.

Without objection, this meeting is adjourned.

[Whereupon, at 3:15 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

STATEMENT OF HON. ANNA G. ESHOO

Thank you, Chairman Pallone, for convening another hearing on the important topic of stem cell research. Congress has clearly demonstrated our commitment to expanding stem cell research in our country. We've held hearings, we've debated, and both chambers passed legislation. Unfortunately, the Administration does not share our view.

The very first veto of President Bush's was stem cell research and the expansion of Federal funding for it. We cannot overlook the necessity and potential of this research and the new treatments and discoveries that will invariably come from this exciting area of science, saving lives, and eradicating the pain and suffering of so many. I have cosponsored legislation to provide federal funds for stem cell research and continue to be a strong advocate on this issue.

We cannot continue to allow the United States to fall behind our international counterparts because of the current restrictions. Our scientists are hamstrung, able to only use federal funds on human stem cell lines derived prior to the President's ban in August 2001. As those cells lines age, they undergo biological changes that reduce their scientific potential. To be the world's leader, researchers in our country should not be reduced to using old stem cell lines that are of limited value. Our constituents who suffer from diabetes, spinal cord injuries, Parkinson's, and many other diseases are relying on us to give American researchers the tools and resources they need to develop new treatments. Stem cell research has far too much potential for us to restrict federal funding which limits the hopes and dreams of the American people.

The result of our Federal policy on stem cells today is sending our best scientists to research facilities overseas. Those who are still in the U.S. are watching from the sidelines and it is only a matter of time when the breakthroughs will occur.

Stem cells and the treatments and discoveries locked within them represent the future of health and medicine. I'm pleased that we are once again bringing attention to the issue of stem cell research. I thank the witnesses for being here today and I look forward to their testimony. My hope is that we can reverse the current federal policy and lift up the million of Americans who will benefit from an enlightened policy.

STATEMENT OF HON. BARBARA CUBIN

Thank you Mr. Chairman.

Today's hearing gives this committee a valuable opportunity to examine recent breaththroughs in stem cell science. Stem cells are literally building blocks of human life. They hold the promise of curing or treating a host of serious diseases, from Parkinson's and Alzheimer's to heart disease and diabetes.

There are several accounts of stem cell therapies that are working right now to treat disease. Doug Rice of Washington State, who will be sitting on our second panel today, will share the improvements he has experienced with his heart condition using stem cells isolated in his own bloodstream.

Blood stem cells have also been used by researchers from Northwestern University and Brazil to successfully treat type 1 diabetes. Thirteen of the fifteen patients involved in the trial became insulin-free according to the Journal of American Medical Association.

As a strong supporter of Alzheimer's research, I am particularly encouraged by research at the University of California, Irvine, in which scientists are using stem cells to restore the memory of mice. The research could lead to breakthroughs not just for Alzheimer's, but also stroke and traumatic brain injury.

Perhaps one of the more exciting stem cell advances is the development of induced pluripotent stem cells. In this astonishing process, genes are added to ordinary skin cells in order to create stems cells with potentially therapeutic applications. While the science and its application to humans is still developing, the cells are believed to be pluripotent, that is, capable of differentiating into any cell type.

All of these treatments and potential treatments have one vital characteristic in common. Their stem cells were derived in ways that did not involve the destruction of a human embryo. The induced pluripotent cells in particular hold the promise to be just as versatile as embryonic stem cells, both in treatment and for research purposes.

I cannot support Federal funding for embryonic stem cell research that harms or destroys any human life. As we work tirelessly to improve the health of the ill, this is still no justification for taking another human life. Moreover, no embryonic stem cell has been used to treat disease or injury, while adult stem cells are being used clinically at this very moment.

This hearing is entitled, "Stem Cell Science: The Foundation for Future Cures." With induced pluripotent stem cells, we have an ethical foundation for future treatments. With other adult stem cells, the future is now. The Federal Government owes it to millions of disease suffering Americans to support the development of these therapies.

With that, I welcome our panelists. Thank you Mr. Chairman. I reserve the balance of my time.

STATEMENT OF HON. LOIS CAPPS

Thank you, Chairman Pallone, for holding this hearing.

Even though our current Administration has prohibited federally funded embryonic stem cell research, America's biomedical research community has continued on with this important work.

Our Nation's leading scientists know the facts.

They know that both adult and embryonic stem cell research hold the potential to cure some of humanity's most devastating diseases:

Cancer, Diabetes, Parkinson's, Alzheimer's and I'm sure, many more.

I'm so pleased to have some of those leading scientists with us here today.

To share with us the truth about stem cell research.

About the nature of embryonic stem cell research and about the promise of adult stem cell research.

Adult stem cell research is crucial.

We need it.

But we need embryonic stem cell research, too, because one is not a replacement for the other.

They are two pieces of a large puzzle.

I am proud that my own state of California has been a leader in this field and filled in some gaps where the federal government has been absent.

But state and private funding are only pieces of the puzzle.

Federal dollars, predominantly through the NIH, are the primary source of funding for basic research—

The kind of research that identifies the fundamentals for future research that will eventually lead to cures.

It is quite frankly embarrassing to have taken this big step backward over the past few years as the rest of the world has soared ahead.

But again, I'm so thankful that we have scientists, health care professionals, patients and other advocates who have found ways to keep research going so that we won't waste any more time in our quest for those cures.

Finally, I'd like to thank my colleague, Diana DeGette, for her tireless leadership on this issue.

I look forward to hearing from today's witnesses.

I yield back.

STATEMENT OF HON. EDOLPHUS TOWNS

Let me thank you Chairman Pallone and Ranking Member Deal for holding this timely hearing on "Stem Cell Science: The Foundation for Future Cures."

Embryonic stem cells may hold the key to curing a host of debilitating conditions that affect millions of people around the globe. These diseases include Parkinson's disease, diabetes, traumatic spinal cord injury, Purkinje cell degeneration, heart disease, cancer, multiple sclerosis, vision and hearing loss, and others.

Given advancements in research, it is appropriate that we convene at this time to assess current developments in stem cell research, discuss the use of adult stem cells versus embryonic stem cells, and explore a new method known as "somatic cell nuclear transfer".

In 2007, I co-sponsored and voted in favor of Representative DeGette's bill to authorize embryonic stem cell research, and am proud of it passage in Congress. It was a dark day for all people who suffer from diseases that may be cured by this research when the President vetoed the bill, H.R. 3.

When the administration imposed additional restrictions on embryonic stem cell research with its 2001 embryonic stem cell policy and 2007 executive order, it crippled U.S. research efforts in these areas. Thankfully, Japan and Europe continued with their embryonic stem cell research and moved the world forward in the quest for cures. It is time that the U.S. resume its place as a preeminent contributor to this critical effort.

To this end, I welcome efforts to create a record of the work of NIH, FDA, the private sector, and other countries in the area of stem cell research. This database is critical to our coordinated efforts to advance stem cell research as efficiently and effectively as possible.

I wholeheartedly believe that such research can be conducted in an ethical manner. As a God-fearing man of faith, I humbly appreciate it is God who is responsible for both diseases and cures. Cures can only come about upon God's command. I believe he wants us to move forward on research and that we should let him shepherd us on this quest, and bring relief to those who suffer from terrible diseases unnecessarily.

Thank you Mr. Chairman. I respectfully yield back the remainder of my time.

Statement of Congressman John Sullivan
Hearing on
Stem Cell Science: the Foundation for Future Cures
House Energy and Commerce Committee, Subcommittee on Health
2322 Rayburn House Office Building
May 8, 2008

Mr. Chairman,

Thank you for calling this hearing to address the science of stem cell research. We have patients here today who were treated with adult stem cells for heart failure and cancer, and I look forward to hearing their testimony on this important issue.

Each day adult, pluripotent amniotic, and cord blood stem cells are demonstrating the same flexibility as embryonic stem cells, without the unethical destruction of human embryos. These cells have been used successfully in human clinical trials to treat over 70 diseases in human patients including spinal cord injuries, diabetes, and heart disease. Many of these treatments are experimental, but the progress is compelling as the number of patients treated continues to grow.

I believe by focusing our scientific research efforts on non-embryonic stem cell research, we can begin to find cures for those suffering from devastating diseases, such as Parkinson's and Alzheimer's, without the moral and ethical concerns embryonic stem cell research poses.

The science behind embryonic stem cell research is inconclusive. There is little evidence to show that embryonic stem cells can be used successfully in medical treatment. We all know that embryonic stem cell research is currently fully legal; however, I have opposed past legislative efforts to stick the American taxpayer with the bill for this scientifically inconclusive and morally troubling research.

It is an exciting time to see all of the scientific advancements in non-embryonic stem cell research. I look forward to the testimony of our witnesses and I yield back the balance of my time.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

AUG 1 4 2008

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515-6115

Dear Mr. Chairman:

Thank you for your detailed follow-up questions regarding the May 8, 2008, House Energy and Commerce Subcommittee on Health hearing entitled, "Stem Cell Science: The Foundation of Future Cures." I have enclosed responses to your questions for your review. The National Institutes of Health is committed to funding stem cell research that is conducted within the parameters of applicable law and policy. Thank you for your interest in stem cell research.

Sincerely,

Elias A. Zerhouni, M.D.
Director

Enclosure

RESPONSES TO QUESTIONS FOR THE RECORD
ELIAS A. ZERHOUNI, M.D.
DIRECTOR
NATIONAL INSTITUTES OF HEALTH
FOLLOWING MAY 8, 2008, HEARING ENTITLED
STEM CELL SCIENCE: THE FOUNDATION FOR FUTURE CURES

The Honorable Joseph R. Pitts

MR. PITTS (1):

You mentioned that a "pluripotent" stem cell can specialize into all three precursor cell types of body systems—endodermal , mesodermal, ectodermal. You then went on to highlight that embryonic stem cells are capable of this pluripotent capacity to form these three precursor cell types. Could you list other stem cell types that have shown this capacity?

DR. ZERHOUNI:

Scientists are able to derive human pluripotent stem cells from two sources. One source is the inner cell mass of a 5-day-old pre-implanted blastocyst-stage embryo. Cells derived in this manner are called human embryonic stem cells (hESCs). In late 2007, scientists reported in peer-reviewed journal articles a second source of human pluripotent stem cells. Specifically, they reprogrammed human adult skin cells to behave like hESCs. These reprogrammed human adult skin cells are known as induced pluripotent stem cells, or iPSCs. Scientists are actively pursuing a number of different ways to derive pluripotent human stem cells, and the NIH anticipates the need to continue to compare and evaluate new and existing sources of human pluripotent stem cells.

MR. PITTS (2):

Could you please list all of the human diseases, injuries, or conditions where stem cells have produced clinical benefits or improvements for human patients, as documented by published, peer-reviewed reports; categorized by source of the stem cells, i.e., (a) embryonic stem cells from fertilized human embryos, (b) embryonic stem cells from cloned (SCNT) human embryos, (c) human iPS cells, and (d) human adult stem cells (including from bone marrow, cord blood, adipose, placenta, amniotic fluid, or any other postnatal source)?

DR. ZERHOUNI:

The majority of treatments currently involving stem cells are focused on disorders of the blood. Hematopoietic (blood-forming) stem cells found in adult bone marrow, peripheral blood stem cells (circulating blood), and in umbilical cord blood are primarily used to treat blood disorders, such as leukemias, and inherited metabolic and immune system disorders.

There have been several peer-reviewed journal reports describing clinical trials using adult bone marrow-derived (blood forming) stem cells to repair cardiac tissue after myocardial infarction. However, the majority of these studies did not show improvement of cardiac function in individuals treated with their own bone marrow cells, and the improvements reported in the remainder were modest. Note that these studies are investigational, and some of these clinical studies are ongoing.

It takes years of research before a treatment can be tested in humans. Human embryonic stem cells were first derived less than 10 years ago. Before hESCs can be used in human therapy, scientists must learn how to differentiate these cells into adult cell types, and ensure that the adult cells are functional and stable and that they do not lead to formation of the stem cell-derived tumors, called teratomas.

Since blood-forming adult stem cells have been studied for over 40 years, there has been enough basic research to establish safety and efficacy for them. As a result, according to an article published on July 13, 2006, by Science Magazine, there are a number of clinical trials using hematopoietic stem cells (bone marrow, peripheral blood stem cells), to study the treatment of a number of diseases, for example, several types of leukemias. According to the article, there are 9 such ongoing trials using hematopoietic blood-forming stem cell transplantation. Experimental treatments are still being evaluated to determine safety (do they produce dangerous side-effects, or adverse events) and efficacy (do they improve symptoms of the specific disease or condition being tested).

Here is the breakdown of treatments based on information from Science/AAAS using the various types of stem cells you mention:

(a) embryonic stem cells from fertilized human embryos: None reported
(b) embryonic stem cells from cloned (SCNT) human embryos: None reported
(c) human iPS cells: None reported
(d) human adult stem cells
  i. Blood-forming cells in bone marrow and in cord blood: 9 stem cell treatments for immune and blood disorders reported
  ii. Adipose (None reported)
  iii. Placenta (None reported)
  iv. Amniotic Fluid (None reported)
  v. Other postnatal sources: Limbal Cells from the Adult Eye

The National Eye Institute reports that adult epithelial stem cells have successfully been removed from the limbus (periphery) of the cornea, expanded outside the body, and then transplanted into patients who have chemical burns in the eye (Tsubota K, et al. Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation. *New England Journal of Medicine.* 1999, 340:1697-703), and also in patients with some rare diseases, such as Stevens-Johnson syndrome, where the recipient's limbal stem cells have been destroyed (Tsubota K, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *American Journal of Ophthalmology.* 1996, 122:38-52). In both of these reports, the patients being studied would have been blind without the transplants.

With regard to section (d)(i) above, it is important to note that the primary role of many of these treatments using blood-forming stem cells is not to treat the diseases or conditions, but rather to help patients survive the treatment itself, which is chemotherapy. It is the chemotherapy (and not the adult stem cells) that destroys the "bad" cells for the multiple types of diseases/disorders listed. In some cases, blood-forming stem cells also provide therapeutic benefit by generating a graft-versus-tumor immune response. The role of blood-forming stem cells as a means to survive chemotherapy also applies in the case of immune diseases: chemotherapy destroys the aberrant

cells (immune cells in the blood and bone marrow) and then adult bone marrow or blood-forming stem cell transplants help patients survive the chemotherapy by reconstituting their bone marrow.

MR. PITTS (3):

You mentioned that with iPS cells, "It looks very similar, but we know already they're not identical, but they have the same potential of being reprogrammed into the first three precursors." If they have the "same potential" to produce these precursors, and stem cells are a continuum as you said before, do iPS cells have the same potential for treating or studying disease as embryonic stem cells?

DR. ZERHOUNI:

It will take several years to do the basic research required to determine whether human iPS cells differ or are similar in any significant way from hESCs, as well as the possible risks to human safety, which are currently unknown, from using either of these cells. These experiments will require side-by-side comparison of hESC lines and human iPS cell lines. Also, before clinical application of iPS cells can be realized, safety and efficacy studies of human diseases must be conducted in animal models.

In addition, the current protocols for generating iPS cells make them unacceptable for clinical applications. One major problem is the use of viruses to turn on "stemness" genes in previously mature, non-stem-like cells. These viruses insert genetic material into a cell's DNA, and this could cause undesirable genetic mutations at or near the point of insertion into the genome. A second major problem is that many of the genes that are important for "stemness" have also been implicated in causing cancer. Scientists are exploring alternative ways to generate iPS cells, such as the use of small molecules to turn on gene expression instead of using viral vectors.

Both embryonic and non-embryonic stem cells show promise for treating human diseases and injuries. Because we cannot predict which type of stem cells will be best for treating a given disease, the NIH believes we should support research on both embryonic and non-embryonic stem cells simultaneously to learn as much as possible about the potential of all types of stem cells to treat human disease.

MR. PITTS (4):

When were embryonic stem cells from any source (human or non-human) first discovered (not grown, but found in the embryo)?

DR. ZERHOUNI:

Stem cells were discovered from analysis of a type of cancer called a teratocarcinoma. In 1964, researchers Kleinsmith and Pierce noted that a single cell in teratocarcinomas could be isolated and remain undifferentiated in culture. These types of stem cells became known as embryonic carcinoma cells or EC cells (Kleinsmith LJ, Pierce GB. Multipotentiality of single embryonal carcinoma cells. *Cancer Res.* 1964; 24:1544–1552).

Researchers later learned that primordial embryonic germ cells, which are early pluripotent stem cells that give rise to adult gametes, could be cultured and stimulated to produce many different cell types. Embryonic stem (ES) cells were first derived from mouse embryos in 1981 by Martin Evans and Matthew Kaufman (Evans M, Kaufman M (1981). "Establishment in culture of pluripotential cells from mouse embryos." *Nature* **292** (5819): 154-6.) and independently by Gail R. Martin (Martin G (1981). "Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells." *Proc Natl Acad Sci U S A* **78** (12): 7634-8).

These cells were among the first to be shown to grow in an undifferentiated state for long periods of time and to be capable of differentiating into multiple cell types. Following this discovery, mouse ES cells rapidly became an indispensable tool for discovery in biomedical research.

MR. PITTS (4a):

For how many years have non-human embryonic stem cells been successfully grown in culture?

DR. ZERHOUNI:

As discussed above, since 1981 (or for 27 years), mouse ES cell lines have been isolated and grown in culture.

MR. PITTS (4b):

How long has NIH funded embryonic stem cell research (human or non-human)?

DR. ZERHOUNI:

The NIH started funding non-human embryonic stem cell research shortly after 1981. The NIH has funded human embryonic stem cell research since 2002.

MR. PITTS (4c):

Was non-human embryonic stem cell research funded prior to 1998? If so, what types of non-human sources were used for funded embryonic stem cell research?

DR. ZERHOUNI:

Yes. Embryonic stem cell research using cells from mice, pigs, goats, and non-human primates was funded prior to 1998.

MR. PITTS (5):

Could you please indicate, regarding adult stem cell research, how much of the funding goes to clinical trials, and how much goes to basic research? On average how much more costly are clinical trials over the cost of basic research? What is the average cost to conduct a Phase I clinical trial? Phase II? Phase III?

DR. ZERHOUNI:

The NIH has been tracking stem cell research funding for several years. Stem cell research should include research that involves stem cells, whether from embryonic, fetal, or adult sources, human or non-human. The NIH asks each Institute or Center to classify stem cell research under the following four main categories: Human embryonic stem cell research, Human non-embryonic stem cell research, Non-human embryonic stem cell research, and Non-human non-embryonic stem cell research.

In addition, since 2005, the NIH reports funding of Umbilical Cord Blood/Placenta stem cells, which is a subset of the Human Non-Embryonic and Non-Human Non-Embryonic Stem Cell research funding. The NIH does not track the amount of basic research compared to clinical research for all of the above categories. In general, 1) hESC and non-human ES cell consist of primarily basic research and 2) human non-ES cell and non-human/non-ES cell consist of both basic and clinical research. At present, clinical trials are involved in only human non-ES cells research.

Clinical trials involve both research and patient care costs. The NIH funding for clinical trials, on the whole, is also in the table below. This table displays funding levels for various diseases, conditions, and research areas, based on actual grants, contracts, research conducted at the NIH, and other mechanisms of support in FY 2004 through FY 2007. The FY 2008 and FY 2009 figures are estimates, and are based on the FY 2007 levels, the FY 2008 current rate level, and the FY 2009 Budget. http://www.nih.gov/news/fundingresearchareas.htm

	Research/Disease Areas	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009
	(Dollars in millions and rounded)	Actual	Actual	Actual	Actual	Estimate	Estimate
»	All Clinical Trials	2,877	2,863	2,767	2,949	2,954	2,958
»	Stem Cell Research	553	609	643	657	656	655
»	Stem Cell Research -- Human Embryonic	24	40	38	42	42	41
»	Stem Cell Research -- Non-Human Embryonic	89	97	110	106	105	105
»	Stem Cell Research -- Human Non-Embryonic	203	199	206	203	203	203
»	Stem Cell Research -- Non-Human Non-Embryonic	236	273	289	306	305	306
»	Stem Cell Research Involving Umbilical Cord Blood / Placenta	19	18	19	22	22	22
»	Stem Cell Research Involving Umbilical Cord Blood / Placenta -- Human	16	15	16	19	19	19
»	Stem Cell Research Involving Umbilical Cord Blood / Placenta -- Non-Human	3	3	4	2	2	2

The three types of NIH clinical trials are:

- Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

Given the scope, complexity, and variation of the phase of any clinical trial, we are unable to derive an "average" cost for a clinical trial phase.

MR. PITTS (6):

Some have argued that Dr. Shinya Yamanaka used embryonic stem cells to develop the iPS technique. Can you cite any evidence that Dr. Yamanaka ever used human embryonic stem cells in his laboratory, in his development of the iPS cell technique?

DR. ZERHOUNI:

Prior to his successful generation of iPS cells, Dr. Yamanaka published numerous scientific papers that focused on embryonic stem cells. The development of human iPS cell lines would not have been possible without years of prior research in hESCs. Two fundamental factors critical to the development of human iPS cells are based upon the knowledge gained from studying hESCs: knowledge of "stemness" genes, and hESC culture conditions. Scientists identified genes that give stem cells their abilities to self-renew and yet remain pluripotent—the so-called "stemness" genes. The two research teams that created human iPS cells drew upon this knowledge when they chose which genes to introduce into the human skin cells in order to reprogram them. Knowledge of hESC culture conditions was a second critical factor. According to Dr. James Thomson, Dr. Yamanaka initially tried to generate and grow human iPS cells under mouse embryonic stem cell culture conditions, but failed. It was only when he switched to using hESC culture conditions that Dr. Yamanaka was able to generate and grow human iPS cells. These critical factors for iPS cell development relied upon extensive studies of hESCs, and future important developments may also be based upon study of hESCs.

In 2006, Yamanaka's lab was able to reprogram adult mouse skin cells to behave like mouse embryonic stem cells, although the reprogrammed cells could not produce eggs or sperm (gametes). The scientists named the cells iPS cells, for induced pluripotent stem cells. In 2007, the Japanese researchers successfully generated gametes from iPS cells, and their results were verified and extended by another independent laboratory (Rudolf Jaenisch). In November of 2007, simultaneous publications from the Japanese scientists and a team of NIH-supported scientists from the University of Wisconsin-Madison reported that they have each succeeded at reprogramming adult human skin cells to behave like hESCs.

The Japanese team used retroviral transduction to direct adult skin cells to express the proteins Oct3/4, Sox2, Klf4, and c-Myc, while the NIH-supported team directed adult skin cells to express OCT4, SOX2, NANOG, and LIN28. The genes were all chosen for their known importance in maintaining the so-called "stemness" properties of hESCs. In both reports, the adult skin cells were thus reprogrammed into human iPS cells that demonstrated many important characteristics of pluripotency, including the ability to self-replicate and to differentiate into somatic cells characteristic of each of the three embryonic germ layers.

The techniques reported by these research teams will enable scientists to generate patient-specific and disease-specific human pluripotent stem cell lines for laboratory study, and to test potential drugs on such cells in culture. However, these human iPS cells are not yet suitable for use in transplantation medicine. As I mentioned previously, the current techniques use viruses that could cause undesirable mutations, including mutations that result in cancer, in iPS cells and their derivatives. Scientists are now working to accomplish reprogramming in adult human cells without using potentially dangerous viruses. (Takahashi et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell.* 2007, 131: 861-872; Yu J et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science*. 2007, 318(5858):1917-20.)

MR. PITTS (7):

Standard cell culture technique includes cryopreservation (freezing of cells on a routine basis to maintain stocks of cells for purity, of identical nature as the originally isolated cells). Can you describe the basic cell culture techniques used at NIH to grow and maintain the "approved" cultures of human embryonic stem cell lines?

DR. ZERHOUNI:

The NIH supports the NIH Stem Cell Characterization Unit on its main campus in Bethesda, Maryland. All approved hESC lines are initially grown according to the suppliers' protocols, but the NIH Stem Cell Unit is currently adapting them to one simple protocol outlined below:

- 6-well plates (Falcon Cat #353046) are coated for 20 to 60 minutes at room temperature with 0.1% gelatin (Sigma Cat #G1890) in dH_2O.
- Mouse embryonic fibroblasts (CF1 strain), cultured in MEF medium, are mitotically inactivated by treatment with 10μg/ml mitomycin C (Roche Cat #107 409) for 2 to 3 hours at 37°C. Cells are washed three to four times with PBS, trypsinized (Invitrogen Cat #25300-054), and plated at a density of 0.75×10^5/ml with 2.5ml per well of a gelatin-coated 6-well dish. Alternatively, cells may be inactivated by exposure to 8000rads of X-irradiation and plated at the same density.
- Immediately before plating hESC, MEFs are rinsed once or twice with PBS. Cells are plated onto MEFs as small clumps in 2.5ml per well of hESC medium containing 4ng/ml bFGF (R&D Systems Cat #233-FB). Cells are fed every day until ready to passage which is determined by the size of colonies, the age of MEFs (should not be older than 2 weeks) or differentiation status of the cells.
- Colonies that appear to be differentiating are manually removed before passaging.

- To passage hESC, cells are washed once or twice with PBS and incubated with filter-sterilized 1mg/ml collagenase IV (Invitrogen Cat #17104-019) in DMEM/F12 for 10 to 30 minutes. Plates should be agitated every 10 minutes until colonies begin to detach. When moderate tapping of the plate causes the colonies to dislodge, they are collected and the wells washed with hESC medium to collect any remaining hESC. Alternatively, colonies may be removed using a cell scraper and collected.
- Colonies are allowed to sediment for 5 to 10 minutes. The supernatant, containing residual MEFs, is aspirated, and the colonies are washed with 5ml hESC medium and allowed to sediment again. This is repeated once more.
- After the final sedimentation, the colonies are resuspended in 1ml of hESC medium and triturated gently to break up the colonies to approximately 100-cell size. Generally, cell lines are passaged at a ratio of between 1:3 and 1:6 every four to seven days.

MR. PITTS (7a):

Does this include routine cryopreservation (freezing) of cell stocks to maintain the integrity of the cell lines, in case of contamination, mutation, or loss of cells that are in culture?

DR. ZERHOUNI:

Yes.

MR. PITTS (8):

You were asked why NIH did not fund Harvard researcher Dr. Denise Faustman who was the first to successfully treat diabetes in mouse models, and was FDA approved to begin a human clinical trial. You did not have information available at the hearing. Has NIH funded Dr. Faustman's diabetes research? If not, please explain why.

DR. ZERHOUNI:

Dr. Faustman is a diabetes researcher and Core Director at the Diabetes Endocrinology Research Center at the Massachusetts General Hospital in Boston. This Center is funded by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases. The Center facilitates research with the goal of developing new methods to treat, prevent, and ultimately cure Type 1 diabetes. The stated purpose of Dr. Faustman's Immunology Flow Cytometry Core is to provide cellular analyses in a cost-effective manner to the diabetes research community. Dr. Faustman cited this grant as a source of support for the mouse study you mention, results of which were published in 2003. Our records indicate that Dr. Faustman has not applied for NIH funding for any proposed clinical trials.

June 10, 2008

Amit N. Patel, M.D., M.S.
Director of Cardiac Cell Therapy
The Heart, Lung and Esophageal Surgery Institute
UPMC Presbyterian
McGowan Institute of Regenerative Medicine
200 Lothrop Street, Suite C 719
Pittsburgh, PA 15213

Dear Dr. Patel:

Thank you for appearing before the Subcommittee on Health on Thursday, May 8, 2008, at the hearing entitled "Stem Cell Science: The Foundation for Future Cures." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from a certain Member of the Committee. In preparing your answer to these questions, please address your response to the Member who has submitted the question and include the text of the Member's question along with your response.

To facilitate the printing of the hearing record, your response to this question should be received no later than the close of business **Friday, June 27, 2008**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your responses should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Joseph R. Pitts, Member
Subcommittee on Health

The Honorable Joseph R. Pitts

1. You stated in your testimony, "The NIH has done a great job in terms of supporting cardiovascular cell based therapies by developing Cell Therapy Network, Heart Failure Network, and the Cardiac Surgery Network." Do these networks receive sufficient funding? How many heart trials using adult stem cells has the NIH funded, and how many patients have been treated in these networks?

2. You have collaborated with doctors around the world in initiating adult stem cell treatments, especially for cardiovascular diseases. Given that many of these clinical trials, even treatments, have been initiated in other countries before being done in the U.S., what would you say are the factors that should be improved in the U.S. so that more adult stem cell clinical trials and treatments can be done here? How would you describe the quality of medical care provided at the international programs with which you have collaborated?

3. Have you used knowledge from human embryonic stem cell research to develop your stem cell treatments for heart patients? Do you see human embryonic stem cell research being used to treat heart patients in the near or distant future?

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June 27, 2008

John D. Dingell
Chairman
US House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

Dear Mr. Dingell,

Please find the answers to the questions from the Honorable Joseph R. Pitts

1. The NIH has done a great job in setting up Networks related to cardiovascular disease. However, there has not been adequate funding to support the great science along with the large scale phase III clinical trials before cell therapies can be standard of care in the U.S. There are no patients that have been enrolled for stem cell therapy as part of the Networks to date. There are plans from the many centers involved to start patient enrollment later this year - 2008. There are a small number of patients (less than 10) that have been enrolled as part of other NIH sponsored cardiac trials in the U.S.

2. To increase the number of clinical trials in the U.S. for adult cell based therapies, there needs to be a stream-lined process for approvals of U.S. based data and funding along with maintaining ethical standards. However, in parallel there should be a process to evaluate clinical trial data from outside the U.S. which may be applicable to our patients. A truly integrated approach using a global perspective is warranted due to the rapid advancements in science based in the U.S. and clinical trials outside the U.S. The level and quality of care at programs I have collaborated are equivalent to the best hospitals based in the U.S., this has been validated by many standard metrics for outcomes related to cardiac surgery and overall cardiovascular care.

3. I have not used knowledge from embryonic stem cell research to develop any of the protocols I have been involved with for cardiac cell therapy. There may be knowledge to be gained in the future in science of developmental biology. However, there are no heart patients who have been treated with embryonic stem cells in the past, and it is highly unlike in the near or distant future based on the existing science base.

Sincerely,

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DOUGLAS T. RICE, RESPONSES TO QUESTIONS FROM HON. JOSEPH R. PITTS

June 19, 2008

U.S. House of Representatives
316 Ford House Office Building
Washington, D.C. 20515

Congressman John D. Dingell
Ref: The Honorable Joseph R. Pitts questions regarding testimony on May 8th, 2008

Question: Could you please tell us about your experience and difficulties in obtaining adult stem cell treatment for your heart condition? What were the costs involved? Was insurance coverage available? Was FDA approval available at that time?

Answer: As I testified at the hearing, I was given 3-4 months to live without a Heart Transplant, since I was diabetic, I was not eligible and did not want to have the Mechanical Heart transplant as I have seen the results and have never seen anyone get better. After verifying that no solution was available in the U.S., my ex-wife went on line looking for new technology and found that in Thailand, a company named Theravitae was doing Adult Stem Cell transplants that were successful. After meeting with my cardiologist, it was decided I had no other chance to live and the risk versus reward was worthwhile.

The costs were $40,000 plus airfare and you had to take someone with you, total cost was approximately $50,000. I had to borrow the money and move quickly to get there in time.

My insurance including the V.A. would not cover any of it, though there was nothing available in the U.S., luckily I had friends and family that wanted me around or I would be dead by now.

FDA did not allow the use of the Adult Stem Cell in this type of treatment though they allowed the use of the ASC in Cancer and other illnesses. They would let you draw the blood to send to Israel but not the cath procedure to insert the stem cells. There are now successful trials being done in the U.S. using the Adult Stem Cells on the heart with tremendous success stories. Also, there is a new clinic using the same procedure as Theravitae in the Dominican Republic by an American doctor and has been very successful. He has recently saved the hands and feet of a young athlete that had lost all circulation there and after ASC treatment has saved them.

Question: To your knowledge, how many other patients have been treated for heart disease using adult stem cells by the doctors who treated you?

Answer: I believe that in Thailand, over 200 patients have been successfully treated for end stage heart disease and other heart related diseases. Me being one of them, also numerous other ones I have met and speak with. I have been in contact with other countries and most are using the Adult Stem Cell treatment to save many lives.

To cover some very valid issues about the Adult Stem Cell treatments that are being used in the U.S.

Almost a million people die every year in America from Heart Disease, there has been a valid treatment for years using ASC and yet Billions have been spent on researching the Embryonic Stem Cells (with no success) when those funds could have used for treatment rather than just research. Over 700,000 Cancer patients and other illnesses have been treated since 1959 and every day new success's are being tried and used.

Why, when a single celebrity dies does the news media cover it for weeks and months, yet when almost a million Americans die of a treatable disease, you never hear of them? I have tried to get on national media to tell the facts with no success, yet Embryonic are discussed all the time and they don't work at this time if ever. Why does Congress have hearings about it and the only thing really discussed is how well ESC is progressing, yet not one human treated! What will it take to convince anyone that with more treatment using existing Adult Stem Cells, Americans could live with treatment?

I was privileged to be there to introduce The Patients First Bill last year and yet it still hasn't passed. What is the real reason that a true success in medicine is set aside for something that doesn't work and even scientist say may never?

I travel as much as I can to educate Americans on the Adult Stem Cell and the difference with "Fact and Fiction" regarding Embryonic Stem Cells. And, believe me there is a lot of fiction going on about ESC.

Though I try, I am not financially strong enough to really make a difference, but I try as best as I can. But how can we let millions of people die every year when there is a possible treatment that works now? How do we face the families of the ones that could have been treated knowing that we are not doing all we can to help. How can you, as their representatives not stand up for them and fight for their right to live a better life. How do you sit in meetings and basically just talk about how great a job the funds you have allotted for research with ESC has not saved one life while the funds you did not fund for ASC could have saved millions? As an American, and one that was allowed to live, but had to go to another country using American technology to do so, I question the FDA's line of thinking and to be honest our government.

I hope and pray that this will help move the Adult Stem Cell Story into the news and the facts will speak for themselves.

Respectfully,
Douglas T. Rice
Adult Stem Cell Recipient

Response to questions asked by Honorable Representative Joseph R. Pitts
House subcommittee on Health; Hearing "Stem Cell Science: The Foundation for Cures"
Respectfully submitted by George Q. Daley, MD, PhD (answers in bold italics)

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1) Are you aware of any reports showing that embryonic stem cells can show tumor formation or overgrowth, even when reportedly first differentiated and then implanted into animals? If so, could you please supply the references?

There are numerous reports of differentiated derivatives of embryonic stem cells being injected into animal models without the formation of teratomas, and some that report teratomas. A non-comprehensive list of references is offered below. Scientists working with embryonic stem cells understand that teratomas may form if undifferentiated embryonic stem cells contaminate the differentiated cells that are transplanted into animal hosts or patients. Future efforts to develop therapeutic cell populations from embryonic stem cells—or from any cell source—must include pre-clinical testing to ensure that the safest cell product is delivered to patients. To date, most of the experiments in animals have focused on the therapeutic effects of transplanted cells, and have not been designed explicitly to exclude teratoma formation. Thus, in my opinion there is little predictive value in the current experience. More research needs to be done to understand the potential risks of teratoma formation for therapeutic populations of cells derived from embryonic stem cells. It is important to point out, that because iPS cells behave like embryonic stem cells, the same risks of teratoma formation pertain.

2) Do you think that scientists will use methods other than viruses to reprogram cells to become iPS cells? If so, how soon, and what methods might be used?

I am hopeful that scientists will learn to reprogram somatic cells without the use of viruses. Many laboratories worldwide are attempting a range of strategies. Personally, I believe some laboratory will succeed in achieving this important advance within the next year. The likely strategies that will succeed include: 1) introduction of genes with non-integrating viruses (e.g. Adenovirus); 2) engineering of reprogramming proteins with sequences that allow transfer across cell membranes (e.g., tat protein fusion to allow protein transduction); 3) identification of cell culture conditions and cell sources that favor reprogramming; 4) reprogramming with small molecule drugs, and many others.

3) You indicated in your testimony that it was extremely easy to produce an iPS line, showing the scar on your arm. Given your own statement, as well as statements from other laboratories including Dr. Rudolf Jaenisch at MIT, could you please explain what you mean when you said, "Reprogramming by nuclear transfer is faster than gene-based reprogramming," and why iPS reprogramming would not be easier, especially given the difficulty in obtaining eggs for nuclear transfer research?

Given that several laboratories worldwide have achieved direct gene-based reprogramming of somatic cells, the technique appears robust—that is, reproducible, technically straightforward, and readily practiced by scientists skilled in pluripotent cell culture and genetic manipulation of cells. Because the techniques for viral gene transfer are widely available in laboratories worldwide, I believe the technique can be easily adopted by many laboratories. Nevertheless, gene-based reprogramming is slow (taking weeks) and inefficient (fewer than 1 in a 1000 cells become a faithfully reprogrammed cell line), and significant improvements are needed to facilitate its use in medical research or clinical practice. The science of reprogramming stands to benefit from continued research into nuclear transfer. The mechanism by which the cytoplasm of the enucleated oocyte reprograms the somatic nucleus is different from the mechanism at work with virally transduced genes. Reprogramming of the somatic genome begins immediately following nuclear transfer into an oocyte, and major elements of the pluripotent state are reinstated quickly, in virtually all nuclei, within the first few days. Thus, even though there are few oocytes available for research, the study of nuclear transfer remains extremely valuable, because scientists hope to learn critical new information that will advance our basic knowledge of embryology and human development, and potentially enhance the efficiency of direct gene-based reprogramming.

4) As a leader in the ISSCR organization, you should be aware of how many stem cell lines are available worldwide. Could you please tell us how many human embryonic stem cell lines have been produced worldwide to date, and how many are available for research use? Likewise, how many human iPS cell lines have been produced worldwide to date, and how many are available for research use? Likewise, how many adult stem cell lines have been produced worldwide to date, and how many are available for research use? How many of all of these types of stem cells are available for U.S. Federal funding?

The ISSCR has launched an effort to compile a registry of existing human embryonic stem cell lines but this endeavor will take much of the next year, and the specific number of human embryonic stem cell lines available worldwide today is unknown. Media accounts that have explored this issue have concluded that several hundred have been developed. Because the iPS technology is new and its practice is growing, it is hard to estimate the number of lines available. From the publications to date, several dozen cell lines exist, although this estimate is certain to be out of date quickly. As for adult stem cell lines, the nature of adult stem cells in most cases precludes their culture as continuously propagated "lines" of cells. Most adult stem cells have a limited lifespan in the Petri dish, and stem cells for the skin, blood, gut, liver, muscle, lung, prostate, and several other tissues have been identified but never grown as "lines." Exceptions include neural stem cells and spermatagonial stem cells, which can be accommodated to cell culture and grown at least for several months, and various types of mesenchymal stem cells that can be grown for weeks but not indefinitely. It is difficult to define with any precision the number of neural, spermatagonial, and mesenchymal cultures exist as these are routinely generated by laboratories expert in these stem cell types. None of the hundreds of human embryonic stem cell lines derived after August 9th, 2001 (the date President Bush announced his policy) can be studied

using federal funds. Human iPS cell lines and adult stem cells of all sorts can be studied with federal grant dollars.

5) You have stated that you support the cloning of human embryos for research. Do you also support NIH funding for cloning (SCNT)? You have also expressed support for human-animal hybrid research. Do you also support NIH funding for human-animal hybrid research? What evidence is there that either human cloning or human-animal hybrid research will treat diseases in humans? When would you expect human clinical trials to begin with stem cells from cloned human embryos, and cells from human-animal hybrids?

Because of the Dickey-Wicker Amendment to the Health and Human Services Appropriations bill approved each year by the US Congress, the NIH is currently prohibited from funding human somatic cell nuclear transfer research, although such research would contribute to understanding basic mechanisms of human development, and would inform our understanding of the mechanisms of reprogramming, a frontier of human biomedical science. I would support allowing the current system of scientific peer review, whereby professionals skilled in the relevant biology evaluate research proposals, to determine the most meritorious topics of research to receive funding through the NIH.

Because of the scarcity of human oocytes for research, some scientists have performed nuclear transfer of human somatic cells into animal eggs in order to study how human nuclei might be reprogrammed. The cells created by this procedure are termed "cybrids" and not hybrids, which would entail the commingling of genomic DNA from two species, which does not occur in these experiments. There has been too little experience to date with interspecies nuclear transfer experiments to judge whether this research strategy will be successful. It is my belief that the merits of this research and whether it should be funded by the NIH are best left to the judgment of scientific experts in the context of the competitive peer review process.

Much of the value of somatic cell nuclear transfer research derives from basic insights into the mechanisms of nuclear reprogramming. Creating tissues that might be transplanted to treat human disease remains a hope but not a certainty. No human stem cell line has been successfully created to date using nuclear transfer, but several groups have reported the application of cells generated by nuclear transfer to the treatment of disease in mouse models (see appended references). Research into somatic cell nuclear transfer is important as basic science, even if tissues created by the process never are used in patients.

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WEYMAN JOHNSON, JR., RESPONSES TO QUESTIONS FROM HON. JOSEPH R. PITTS

June 23, 2008

Honorable Joseph Pitts
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Congressman Pitts,

Thank you for the opportunity to appear before the Subcommittee on Health on Thursday, May 8, 2008 at the hearing entitled ″Stem Cell Science: The Foundation for Future Cures.″

The field of stem cell research brings hope to millions of Americans who are affected by chronic diseases including more than 400,000 who are living with multiple sclerosis (MS). The National Multiple Sclerosis Society believes all promising avenues of research must be explored and remains committed to ensuring all types of stem cell research is pursued under strict ethical guidelines and in accordance with the law.

Enclosed in this correspondence is my response to the questions Chairman John Dingell sent to me on your behalf. I am happy to provide further detail if necessary.

The National MS Society stands by to serve as a resource to you and any Member of the Committee.

Sincerely,
Weyman Johnson, Jr., J.D.
Chairman of the Board

Enclosure

Cc:The Honorable John Dingell, Chairman
Committee on Energy and Commerce

The Honorable Joe Barton, Ranking Members
Committee on Energy and Commerce

The Honorable Frank Pallone, Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

1) Question: Is the National Multiple Sclerosis Society spending any research funds on ″somatic cell nuclear transfer″ or human embryonic stem cell research? If so, how much is being spent and what percentage of your research budget is allocated for these types of research?

Response: From the beginning, the National MS Society has funded research seeking clues to the cause, treatment and cure of MS, and to spark research efforts around the world. Although MS is not hereditary or contagious, it is believed to occur in genetically susceptible people who are exposed to an infectious agent, such as a virus or bacterium. These factors combine to cause the person's immune system to attack myelin insulation on nerve fibers.

The National MS Society is a driving force of MS research, and as such, our research efforts support studies in many different areas of scientific studies from immunology to genetics to understanding ways to repair the damage to myelin. The Society is expending nearly $45 million this year alone to propel MS research forward, including funding over 440 new and ongoing MS investigations in the U.S. and abroad, across all areas of research.

Today the most exciting area of research, and one that holds true promise for those individuals with MS, is in the area of repair and protection of the nervous system. The Society is currently not funding any projects using SCNT. Of the 440 projects which we are currently supporting, 80 (18%) are focused on repair using both human and animal cells. Of the 440 awards, 7 (1.6%) projects are using human

embryonic stem cells at an annual cost of $1.24 million (2.8% of our overall annual research budget).

2) Question: Has the National Multiple Sclerosis Society funded any adult stem cell research? If so, how much is being spent and what percentage of your research budget is allocated for these types of research?

Response: Some tissues and organs have little capacity for self-repair. One such organ is the brain; and nerve cells or neurons are known to be very restricted in their capacity to regenerate following damage or disease. The adult brain and spinal cord appear to have only a limited ability to produce new neurons. This is one reason why recovery is often limited when the nervous system is injured.

One of the most exciting frontiers in medicine is the potential use of stem cells for treating diseases for which there are no cures. One strategy is by replacing cells using embryonic cells, and another strategy is using adult cells - either from a donor or by using the patient's own cells. It is important that both of these avenues are pursued.

Of the 440 projects which the National MS Society is currently supporting, 6 (1.4%) projects are using human adult stem cells at an annual cost of $2.0 million (4.4% of our overall annual research budget). With regards to the use of adult stem cells, it is important to clarify the two different approaches which are being studied: one is to repair the damage in MS, and the other is to use bone marrow adult stem cells in transplantation to reconstitute the immune system. To date, it is the latter research which has shown some promise as a treatment in some individuals with aggressive MS. MS investigators are currently studying whether bone marrow transplantation is an effective treatment in a group of closely matched people with MS. Since the immune system is misdirected in MS, the hope is that by transplanting these adult bone marrow stem cells, one can reconstitute a naive immune system that will not attack myelin and thereby, will correct itself.

The second use of stem cells is to repair the damage in MS. We know that the damage is occurring in the central nervous system, namely, the brain and the spinal cord and the optic nerves. So we need to figure out a way that repair, actually, occurs at the site of the injury. We can broadly divide the research efforts into two categories. One is, can we promote the cells that are already there, what we call the adult endogenous progenitor cells, to function more effectively, or is the challenge going to be do we have to provide the cells from outside? We know that during an attack of MS, the myelin is injured and; we also know that there is an element of repair. But how do we stimulate the repair in the body and what is the best source of cells to use? If we had ways of directing the function of these adult stem cells, then these are the cells that would, actually, be the ones used in the disease repair.

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June 19, 2008

The Honorable Joseph R. Pitts
U.S. House of Representatives
316 Ford House Office Building
Washington, DC 20515

Dear Congressman Pitts,

Below are my responses to the follow-up questions you posed following the May 8th Subcommittee on Health at the hearing entitled "*Stem Cell Science: The Foundation for Future Cures*."

1. **Question**: Do you support NJ's law that allows creating human cloned embryos, implanting them in a woman, and growing the cloned fetus so long as the clone is not allowed to be born? Do you support this process for possible treatments?
   Answer: We don't believe there is such a law. We would not support it if it did exist.

2. **Question**: Has NJ funded any human cloning (SCNT) experiments? If so, how much has been directed to human cloning experiments? How many cloned embryos have been created by SCNT, and how many embryonic stem cell lines from human cloned embryos have been created?
   Answer: NJ has not funded any cloning experiments. As far as we are aware no cloned human embryos have been created by SCNT, and no embryonic cell lines from human cloned embryos have been created.

3. **Question**: Has NJ funded the collection of women's eggs, and if so, how much money is offered to women to donate their eggs?
   Answer: NJ does not fund the collection of human eggs.

Sincerely,

Joseph R. Bertino, M.D.

JRB/des

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The Honorable Joseph R. Pitts
Committee on Energy and Commerce
316 Ford House Office Building
US House of Representatives
Washington DC 20515-6115

June 22, 2008

Dear Congressman Pitts:

Thank you for your interest in adipose-derived adult stem cells. Attached please find my answer to the questions you sent in follow-up to my testimony before the Subcommittee on Health on Thursday May 8, 2008 at the hearing entitled "Stem Cell Science: The Foundation for Future Cures".

Should you have any further questions, please do not hesitate to contact me.

With best wishes,

John K. Fraser PhD
Principal Scientist

1. Could you please list all of the human diseases, injuries, or conditions where human adipose-derived adult stem cells have been used in clinical trials, whether by your group or others?

Adipose-derived adult stem cells have been (or are being) used in the following human diseases, injuries, or conditions:

Disease, Injury, or Condition	**Citation**
Acute myocardial ischemia (heart attack)	Ongoing clinical trial sponsored by Cytori Therapeutics Inc. http://clinicaltrials.gov/ct2/show/NCT00442806
Chronic myocardial ischemia (chronic angina)	Ongoing clinical trial sponsored by Cytori Therapeutics Inc. http://clinicaltrials.gov/ct2/show/NCT00426868
Radiation therapy-induced skin wounds	Rigotti *et al*, Plast Reconst Surgery 119: 1409-1422, 2007
Graft versus Host Disease	Fang *et al*, Bone Marrow Transpl 38: 389-390, 2006 Fang *et al*, Transpl Proc 39: 1710-1713, 2007 Fang *et al*, Pediatr Transplantation 11: 814-817, 2007
Pure red cell aplasia resulting from transplant graft rejection	Fang *et al*, Am J Hematol 82: 772-773, 2007
Rectovaginal fistula associated with Crohn's Disease (inflammatory bowel disease)	Garcia-Olmo *et al*, Dis Colon Rectum 48: 1416-1423, 2005
Tracheomediastinal fistula secondary to radiation therapy for lymphoma	Alvarez *et al*, Thorax 63: 374-376, 2008
Bone repair	Lendeckel *et al*, J Cranio-Max Surg 32: 370-373, 2004
Breast reconstruction following partial or total mastectomy	Kitamura *et al*, Breast Cancer Res Treat 106 (Suppl): Abstract 4071, 2007
Breast augmentation	Yoshimura *et al*, Aesth Plast Surg 32: 48-55, 2008

2. Could you please list all of the human diseases, injuries, or conditions where human adipose-derived adult stem cells have been proposed for use, based on basic science and preclinical studies?

Use of Adipose-derived adult stem cells has been proposed for the following human diseases, injuries, or conditions:

Disease, Injury, or Condition	**Citation**
Parkinson's Disease	McCoy *et al,* Exp Neurol 210: 14-29, 2008
Degenerative Disc Disease	Lu *et al,* BBRC 359: 991-996, 2007 Li *et al,* Conn Tiss Res 46: 75-82, 2005
Periodontal Disease	Tobita *et al,* Tiss Eng 2007 (ePub ahead of publication)
Pulmonary emphysema	Shigemura *et al,* Am J Transplantation 6: 2592-2600, 2006 Shigemura *et al,* Am J Respir Crit Care Med 174: 1199-1205, 2006
Muscle injury	Mizuno *et al,* Plast Reconst Surg 109: 199-209, 2001 Bacou *et al,* Cell Transpl 13: 103-111, 2004
Tendon Repair	Kryger *et al,* J Hand Surg 32A: 597-605, 2007
Hepatitis and Liver Cirrhosis	Banas *et al,* Hepatol 46: 219-228, 2007 Talens-Visconti *et al,* Toxicol in vitro 21: 324-329, 2007
Prevention of transplant rejection	Wan *et al,* Hepatobiliary Pancreat Dis Int 7: 29-33, 2008
Bone repair	Cowan *et al,* Nature Biotech 22: 560-567, 2004 Halvorsen *et al,* Tiss Eng 7: 729-741, 2001
Diabetes	Timper *et al,* BBRC 341: 1135-1140, 2006
Hemorrhagic Stroke	Kim *et al,* Brain Res 1183: 43-50, 2007
Ischemic Stroke	Kang *et al,* Exp Neurol 183: 355-366, 2003
Urinary Incontinence	Rodriguez *et al,* Proc Natl Acad Sci (USA) 103: 12167-12172, 2006 Jack *et al,* J Urol 174: 2041-2045, 2005
Kidney Damage	Bi *et al,* J Am Soc Nephrol 18: 2486-2496, 2007
Spinal Cord Injury	Kang *et al,* Stem Cells Dev 15: 583-594, 2006
Cornea Repair	Arnalich-Montiel *et al,* Stem Cells (ePub

	ahead of publication; Dec 6, 2007)
Vocal Cord Repair	Lee *et al*, Cells Tiss Organs 184: 198-204, 2006
Heart Failure	Planat-Bernard *et al*, Circ res 94: 223-229, 2004
Peripheral ischemia	Rehman *et al*, Circ 109-r52-r58, 2004
Wound healing	Nambu *et al*, Wound Rep Reg 15: 505-510, 2007
Cancer therapy	Kucerova *et al*, Cancer Res 67: 6304-6313, 2007
Inflammatory Bowel Disease	Ando *et al*, Inflamm Bowel Dis 2008 (ePub ahead of publication)
Muscular Dystrophy	Rodriguez *et al*, J Exp Med 201: 1397-1405, 2005

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