Alzheimer's Talks
Stem Cells and Alzheimer's: A conversation with Dr. Frank LaFerla
November 26, 2012

George Vradenburg: Welcome to Alzheimer's Talks. Today's call is a discussion with Dr. Frank LaFerla of the University of California at Irvine about his cutting edge research with stem cells that will hopefully provide an increasing number of clues about innovative paths to research and treatment for Alzheimer's disease. He has recently reported data that shows neural stem cells can rescue memory and function in mice, thank God for mice, that have cognitive deficits.

My name is George Vradenburg. I'm Chairman and co-founder of USAgainstAlzheimer's. And I am passionately committed to finding solutions to this disease because of the loss of my beloved mother-in-law.

Thank you all for joining us today. This is one in a number of teleconference series by USAgainstAlzheimer's and sponsored by the Zickler Family Foundation. If you have a question for anyone during this call, please press star three on your phone. By pressing star three, you'll be placed in to the question queue. Have your question ready to share briefly with a member of our staff and they will try to get you on the air live with Dr. LaFerla as soon as possible when we open it up for questions.

I want to introduce at this time, Dr. Diane Bovenkamp. She is the Science Communications Specialist at the American Health Assistance Foundation. The American Health Assistance Foundation is a research funder that seeks to identify and support high-risk, high-impact innovative research on age-related generative diseases including Alzheimer's. They currently oversee more than 100 active research projects throughout the world. Dr. Bovenkamp will briefly let us know about how the American Health Assistance Foundation is involved in the exciting research findings that you're about to hear about. Diane?

Dr. Diane Bovenkamp: Thank you, George, and thank you everyone for tuning in today. It's my distinct pleasure to introduce Dr. Frank LaFerla, of the University of California, Irvine, where he is Chancellor's Professor and Chair of the Department of Neurobiology and Behavior in the School of Biological Sciences, as well as Director of Irvine's "MIND" Institute, known in its longer form as "the Institute for Memory Impairments and Neurological Disorders." Dr. LaFerla has been awarded two grants from my organization, AHAF. As a grant making organization, we are interested in identifying research that poses particularly innovative approaches and has a high potential to accelerate the field of research. Dr. LaFerla is a leader in a number of different fields, including his efforts to develop better ways of modeling Alzheimer's disease, particularly using mouse models, to ensure that treatment test results can better predict how people might respond in future clinical trials. His first AHAF research grant supported one of the other avenues of his research, that is, how disturbances to the calcium levels in

cells is linked to the deposit of beta-amyloid in the brain, a hallmark feature of Alzheimer's, and to the degeneration of nerve cells. His second AHAF grant is currently focused on discovering how stem cells could work as a treatment option for Alzheimer's, the topic of today's discussion. Without further ado, I'd like to welcome Dr. LaFerla and ask him to help us understand the promise of stem cells, and maybe their alternatives, in the race to beat Alzheimer's disease. Frank?

Dr. Frank LaFerla: Okay. Thank you very much Diane and thank you George. I really appreciate the opportunity to address this distinguished group and I just want to also convey my gratitude to AHAF for their funding of my research throughout my career and also a special shout out to CIRM, which is the California Institute for Regenerative Medicine, which has really been also major supporter of some of this research as well. I'm really happy and delighted to participate in this conference call and pleased to be part of USAgainstAlzheimer's. I understand that there been a lot of questions that have been submitted. Some of them have been transmitted to me and I will do my best to try to address them and integrate some of those questions during my talk as much as possible.

So I thought I would start off by giving a little bit of a background information about Alzheimer's disease including some of the latest statistics and then describe very briefly an overview of some of the most salient and critical biological features of Alzheimer's disease and including as Diane alluded to why we were able to use some of that information or how we view some of that information to try to develop animal models of Alzheimer's disease. And then the last part, I will try to focus on our latest research on stem cells and the promise that I think that offers.

Let me first say that I understand first hand what's it's like to experience dementia in one's family because my mother passed away at a relatively young age. She was 60 years of age and she died of dementia. She did not have Alzheimer's disease but rather had a brain tumor that led to dementia. And actually, this raises one of the most important questions that I get asked over and over again. There seems to be a little bit of confusion among people over what the difference is between Alzheimer's disease and dementia and it's kind of interesting. You'll meet some people who will say, "My love one has Alzheimer's. They don't have dementia." So I think the best way to think about dementia is as a broad umbrella term in much the same way that cancer is a broad umbrella term. If you tell someone that you have cancer and without telling that individual whether or not they have skin cancer or lung cancer or liver cancer. I think that's an incomplete diagnosis. In some sense, I think that same thing applies to dementia. Dementia is a broad umbrella term and as of today there are 3 criteria to defining someone as being demented. That individual should experience memory loss, should experience problems in another cognitive domain such as the ability to communicate and those changes must be so severe that they interfere with your ability to engage in a social setting or in an occupational setting. That's the official definition of dementia. Just like there are many different types of cancers, there are many different types of dementias. It turns out that Alzheimer's disease happens to be the most common type of dementia. I think it's important to really understand what type of dementia you have because that can determine the type of treatment that one would use. So you could imagine that if you had breast cancer, you will not want a drug that was used to treat testicular cancer because they would have different mechanisms of actions and the same thing is true among the dementias. Just because

they have certain commonalities such as maybe memory loss or other cognitive loss, doesn't mean that the mechanism of action is exactly the same.

Alzheimer's disease is the most common cause of dementia. We know it's an age related disorder of the brain that destroys the person's memory. And what's particularly interesting about Alzheimer's disease is that in the beginning stages of the disease, what happens is an individual loses their most recent memories. Those are the ones that fade away first. Memories that have been garnered for a long time remain until later stages of the disease. So one way in which this manifests is that an individual may forget the names of their grandchildren but they'll still remember the names of their brothers and sisters because their brothers and sisters they've known for all of their lives and they would have more recently met their grandchildren.

Besides destroying a person's memory, the disease also leads to many other changes it interferes with your ability to learn and to reason and make judgments, to communicate and what's the major problem for the families is that it also interferes with your ability to carry out daily activities of living. Individuals have a hard time, sometimes dressing themselves, bathing, brushing their teeth, eating and this as a result poses an inordinate burden on the caregivers. In addition, if that weren't bad enough, as the disease progresses some individuals also go on to experience psychiatric or behavioral issues. So they become anxious and depressed and all of this contributes to a lot of stress not only for that individual but also for the caregivers as well.

It turns out that Alzheimer's doesn't discriminate. It occurs in almost every society and many celebrities are not immune to this disease as well. And just recently, we found out that the country singer Glen Campbell has Alzheimer's disease. We know that the basketball coach from Tennessee, Pat Summitt has developed the disease at a relatively early age. But if we look at some of the most recent celebrities with the disease, we see that Perry Como, Charles Bronson, Ronald Reagan, Charles Heston, Norman Rockwell, Rita Hayworth, Burgess Meredith, Estelle Getty, Peter Ford. These are all some really high profile individuals that have suffered from this disease.

What is the difference between Alzheimer's disease and aging? And this also causes a lot of concern among people because individuals will think to themselves, "Oh I forgot to pay my house mortgage this month. Does that mean I have Alzheimer's disease?" And of course the answer is no. During normal aging, you're going to make a bad decision every once in a while. You're going to forget to pay a monthly bill every now and then. You may forget what day of the week it happens to be. You may forget what word you need to use in a sentence and of course you're going to lose things from time to time. That is all part of normal aging. That does not mean that you have Alzheimer's disease. People with Alzheimer's disease have difficulty making judgments a lot of the time. They don't have just problems just paying a bill and missing a payment every now and then. They have problems managing their monthly bills. They don't forget what day of the week it is, they lose track of the date or even the time of the year. They have trouble with conversations and they misplace things very often and are unable to find them. So you know, when people say that they go to the mall and they forget where they parked their car, I think that's normal and that just could be due to the fact that you're not paying attention, there is a lot of distractions now with cell phones. So if you go to the mall and you forget where you parked your car

that does not mean you have Alzheimer's disease. I think if you go to the mall and forget that you drove your car there, than that's the more worrisome sign there.

If you look at some of the early signs of Alzheimer's disease, they include things like finding it hard to remember things, asking the same questions over and over again, having trouble paying your bills or solving simple math problems or arithmetic problems, getting lost particularly in your own neighborhood, losing things or putting them in very odd places like for example maybe putting your pots and pans instead of putting them in your cupboards, putting them in your clothes closet. And then during the later stages of the disease, this manifest and then people forget how to brush their teeth, comb their hair, they're confused about time and they are confused about people that they meet and places. They forget the names of common things like a desk, a house or an apple, and one of the more problematic factors is that they tend to wander off from their homes.

So we know that there are a lot of risk factors for Alzheimer's disease. There are many and we could spend the whole conversation talking about this. Age is one of the most significant. It turns out that one out of every 20 people over the age of 65 suffers from Alzheimer's disease and that number doubles every 5 years thereafter. So we're talking about if we do the math together, 1 in 20 over 65, 1 in 10 over 70, 1 in 5 over 75 and essentially 1 out of every 2 to 3 people over the age of 80 to 85 suffers from Alzheimer's disease. So age is certainly one of the most important risk factors. We know that there are certain genes that run in families that can either cause the disease or increase your risk of developing this disease. Likewise if you have a family history of this disease in your family, that increases your chances of developing it as well. We know that head trauma is now a significant risk factor for this type of disease because it turns out that head trauma even in very young individuals starts to allow for the development of some Alzheimer's pathology and so football players for example. If you play football in the National Football League, you have a 19 fold higher chance of developing Alzheimer's disease versus someone who does not. Likewise, even high school football players who suffer from severe head trauma but then they go on to pass away for some unrelated reason like a car accident. When you look at these very young individuals and then look at their brains at autopsy, you could start to see very consistent Alzheimer's type pathology in their brain. In addition, we know one of the questioners asked me about down syndrome and it turns out that almost everyone born with down syndrome goes on to develop full blown Alzheimer's disease by the time they're in their late 50's and early 60's. The reason for that is that one of the Alzheimer's genes happens to be located on Chromosome 21. People with Down syndrome have 3 copies of Chromosome 21. Therefore, produce one and a half times more of this Alzheimer's protein and go on to develop an early onset form of the disease. We know that diet and other environmental factors can play a role. So for example, some diets are thought to be preventative. So diets that might include a cold-water fish that are rich in Omega 3 fatty acids such as the kinds of foods that you would eat for that include salmon, for example. A Mediterranean diet is thought to be beneficial and likewise, the flip side of that is there are certain types of diets that may exacerbate the disease. So people who are diabetic have a higher incidence of developing Alzheimer's disease. And as a matter of fact, some people now refer to Alzheimer's disease as the new type 3 diabetes. There are many other environmental factors. Smoking is one that may exacerbate the disease and we also know that stress can play an important role as well.

So these are some of the risk factors for Alzheimer's disease and when you factor all of that, it's not surprising that there are over 35 million people throughout the world that are suffering from Alzheimer's disease. And in the United States as of 2012, we know that there are 5.4 million Americans that are suffering from Alzheimer's disease and the statistics are just so staggering because it turns out that in the United States, there's a new case of Alzheimer's disease developing every 68 seconds. So essentially, almost every minute, someone in the United States is coming down with Alzheimer's disease. So this is going to really consume our national agenda over the next several decades in part because as I mentioned earlier, age is one of the most important risk factors and we know that the baby boomer population has already started to reach the time point when they are at the greatest risk for developing Alzheimer's disease. So we anticipate that there's going to be a tripling of the number of individuals with Alzheimer's disease by the middle of the century. All of this translates into essentially Alzheimer's is the 6th leading cause of death in the United States. And actually if you reconfigure it a little bit differently and put all the coronary heart disease on 1 category and cancer in its own category, then Alzheimer's actually drops to the 3rd leading cause of death in the United States. And we estimate that right now, and I think this is a very conservative estimate, that it costs about $210 billion a year, that's billion with a “b”, just to maintain this and the best estimates are that by the middle of this century, we're going to be spending over a trillion dollars a year to manage people with Alzheimer's disease. So we really need to do something to derail this or else it's going to consume our entire national budget just to deal with all of these Alzheimer's patients that are coming our way.

For me, one of the most alarming statistics that I have come across recently was the fact that according to the Alzheimer's Association, there are at least 800,000 Americans living with Alzheimer's disease and they live by themselves. And I think it's a terrifying disease to have to go through if you have loved ones but I couldn't imagine what it would be like to have to go through this horrible disease by yourself without someone looking after you. And I think this is part of the reason why we really need to put a lot of effort in to research because research is our only hope for finding a cure to this disease. As a matter of fact, as Diane pointed out, I'm the Director of the Institute for Memory Impairments and Neurological Disorders, UCI Mind and our motto here and our vision is to research ways to make memories last a lifetime. So that was sort of the 1st part of my talk. I wanted to just give you a basic overview of some of the latest statistics of Alzheimer's disease.

And now, I just want to talk very briefly about some of the changes that occur in the brains of people with Alzheimer's disease and some of these changes were actually described by Dr. Alzheimer himself at the turn of the last century. He was a German psychiatrist who was following a patient and at the time of her death, he analyzed her brain and he observed two unusual lesions in her brain. The first, he called plaques and these plaques look like brillo pads that accumulate in regions of the brain that are involved in learning and memory. And you can see them in normal individuals but Alzheimer's individuals will have them hundreds or a thousand times more abundantly than normal non-demented individuals. These plaques consist of a very small protein called beta amyloid and if you recall earlier when I mentioned about down syndrome, this gene beta amyloid comes from a larger protein called the beta-amyloid precursor protein and this is the gene that happens to be located on Chromosome 21 which

individuals with down syndrome have three copies of and that's why they develop that early-onset form of the disease.

The second lesion that he described are called tangles. Tangles actually occur mainly inside neurons and when you think of a tangle, think of your hair on your head when it starts to form a tangle. You know that that's very painful to get out and likewise when you have these tangles that accumulate inside a neuron, it can wreak a lot of havoc because it disrupts a lot of the transport systems within a cell and that starts to fall apart and the cell can no longer get rid of waste products nor can it transport nutrients from one part of the cell and eventually different components of that neuron start to degenerate. So today, as of 2012, a diagnosis of Alzheimer's is presumptive. It's not until the patient dies that we can say for certainty that the individual had Alzheimer's. When we do a brain autopsy, we do that by counting the number of plaques and tangles that they had.

So as Diane pointed out earlier, my lab was particularly interested in trying to make a mice model of Alzheimer's disease that harbored those two important neuropathological lesions, plaques and tangles. Now you might be thinking to yourself, why would you study a complex disease like Alzheimer's in mice and it turns out that there are several reasons. One is that mice breed pretty quickly and they age over a very short life span compared to humans of about 2 to 3 years. Their brains are organized comparably to humans. They're not identical. Someone asked about whether or not it would be better to study pigs because their anatomy is closer between a human and a pig than it is between a mouse and a human and that's certainly true. But it's a lot more expensive to do these kinds of studies in pigs than it would be to do in mice. It turns out that for example, in my lab here, we have close to 8,000 mice that we maintain because we've taken the approach that we should be as aggressive as possible in trying to study this disease. So even though it's relatively cheap to do this in mice compared to pigs or to humans, it's still quite expensive to do these kinds of studies in any type of animal including in mice. So for example, we have to pay a hotel bill to the university to store these mice every month. And depending on the month our hotel bill is anywhere from $20,000 to $35,000. So you could appreciate how expensive these kinds of research undertakings are. There's another important reason to do these kind of studies in mice and that is because many genes and proteins are actually conserved between humans and mice and that means then that you can take genes that we know cause Alzheimer's disease in people and put them into the mice and allow the mice to develop the kind of brain pathology that you would see in the human condition. And that means then you can study disease processes which are not possible to do in living humans, mainly because people don't like to give their brain up while they are still alive and also because you can now evaluate new treatments and try to determine the mechanism of action. So in 2003 we developed this model. It was at that time and I think it's still the only mouse model that has both plaques and tangles. In addition to developing those two important neuropathological lesions that are the signature feature of Alzheimer's disease, the mice also develop memory impairments as a function of age. And we can see that when we compare them to normal animals that the Alzheimer's mice perform much worse than normal age matched animals. As you can imagine, these animals were quite valuable and they have been in a very high demand. We have distributed them to over 150 investigators in over 30 countries now and there have been hundreds if not thousands of publications that have occurred from the utilization of these mice.

Another important feature of Alzheimer's disease is the tremendous loss of neurons that occurs in the brain. If any of you are in the Southern California area, you're welcome to contact me. We frequently provide tours of the Institute and one of the highlights is that we actually show you a human brain and many individuals really enjoy holding that brain. And it turns out that a control, normal, non-demented brain will weigh about 3 pounds. In contrast, an Alzheimer's brain will weigh about 1 and 1/2 to 2 pounds. So they're anywhere from 40% to 60% less than what a normal age brain could weigh. And so it really gives you an understanding of the kind of devastation that occurs in this disease.

My last point that I want to make before I get in to our topic about stem cells is to really emphasize how much Alzheimer's has been in the news recently and unfortunately a lot of that has been because many of these clinical trials have lead to disappointing results and that has certainly surprised some researchers because we thought that we understood the disease and that these drugs were acting on mechanisms that would lead to more positive clinical outcomes. And while much of that may be true, I think we now have a growing appreciation that when you intervene and when you provide these therapies is just as important and that if you wait until too late into the disease process, these potentially useful drugs might not be working. And a good way to think about this metaphorically is just think about when you have a little small brush fire, you're able to put that brush fire out with a bucket of water. However, imagine now that a whole entire building is consumed in flames. You can imagine that single bucket of water is not going to be very effective and so the same thing applies in terms of treating people with Alzheimer's disease. It's very critical to get them at their right stage.

So because of some of the problems that these drugs have been having and for other reasons that I won't get into today, we were interested in using stem cells to try to treat Alzheimer's disease. And there are several criteria that one would have to go through in order to justify this. First of all, you would have to show that a stem cell therapy could be competitive and that it has efficacy and it's effective compared to some of the available treatments. Well, that's actually pretty easy to achieve because many of the available treatments that are on the market today only provide very marginal and very short term benefits to individuals and they're really not disease modifying. I mentioned to you earlier that a lot of promising candidates have failed out of clinical trials. So that renders stem cells as still a viable option. Second thing we need to do is to show that the stem cells are efficacious and effective in improving memory in multiple animal models. We then need to determine what the mechanism is, how is it that stem cells are having a benefit in an Alzheimer's disease model compared to other approaches, and then eventually to introduce this into human clinical trials.

So in perusing the question list that I can see here, one of the questions that has come up over and over again is “when do we think we will be able to start human clinical trials?” So let me just say that because of the research funding that we got from CIRM and from AHAF, we've been able to do some of the background studies to try to determine first of all whether or not stem cells would even be useful for treating Alzheimer's disease. And it turns out that it can and because of some of the success that we have, we recently received a pretty large grant from CIRM to resolve some of the lingering issues that remained with the goal that we can get in file and investigational new drug application with the FDA within four years to try to begin human phase one clinical trials to evaluate the efficacy of this.

So let me first describe what stem cells are. Many of you probably know that stem cells are cells that are found in all organisms and the cells, what's unique about them is that they can divide and they can differentiate into many different cell types in the body including in the human body and they have the potential to self renew and to produce more stem cells. There's some controversy associated with one class of stem cells, which are embryonic stem cells because those are harvested from a human embryo that was discarded. For our studies, we have been using neural stem cells and there are several advantages I believe to using neural stem cells for our studies. Not the least of which is that there's no ethical debate because you're not required to destroy an embryo to obtain these neural stem cells. You could even get them from adults. You would be introducing neural cells into a neural tissue and these neural stem cells can differentiate into the three main cell types in the brain, neurons, oligodendrocytes or astrocytes. And because they are a little bit more differentiated in the pathway than say embryonic stem cells, the risk of developing a tumor is far greater reduced than it would be if you use an embryonic stem cell, for example.

So we had a very simple question that we set out to address and that is we wanted to know what would happen if we transplanted neural stem cells into old Alzheimer's mice, mice that had lots of plaques and lots of tangles and had difficulty performing some of the cognitive tasks that we gave them. So what we did was we transplanted mouse neural stem cells into the mouse brain and we put it onto both sides of the brain directly into the hippocampus which is ground zero for Alzheimer's disease. We waited a month, evaluated the mice on their behavior and saw that after one month, we had a marked improvement in the cognitive ability of our animals. That is that one-month after delivering the stem cells, the mice were now learning and remembering as well as normal mice that didn't have any Alzheimer's pathology. And so that was very exciting to us and we decided to sacrifice the animals to look at their brains, to figure out what was going on and this is why it's important to do scientific experiments because everything that we thought was happening did not end up happening that way. We initially thought first that the stem cells were going to reduce the number of plaques and tangles in the brains of these animals and it turns out it did not. The stem cells were improving the learning and memory in these animals but it was doing it not by reducing the number of plaques and tangles rather it was doing it through a different mechanism. And so we had to figure out what that mechanism was because when we counted the number of plaques and measured them using a lot of different criteria and the same thing for tangles, there was no difference between the Alzheimer's mice that got the vehicle and the Alzheimer's mice that got the neural stem cells. Rather to make a pretty long story short, it turns out that the stem cells were promoting new connections in the brain. So they were not becoming new neurons but they were allowing the existing neurons to put out more processes and to better connect to the existing neurons in the brain. Good way to think of this is that maybe think that these stem cells were in a way acting as fertilizer for the brain allowing the existing cells that were there if you were to establish a better root system as opposed to the animals that did not get that. So we were able to then figure out what that "fertilizer" was. It turns out it was an important neurotrophic factor or important factor for brain health called brain-derived neurotrophic factor, BDNF. And so we did some experiments where we were able to reduce the amount of BDNF inside these stem cells. And when we put the stem cells that have reduced BDNF levels into an Alzheimer's mouse, it didn't have the same robust effect that it had when we use a normal stem cell.

So at this point, let me just summarize a couple of the key findings. We have found that the neural stem cells were able to rescue Alzheimer's related memory deficits even in aged animals that had pretty significant and advanced plaque and tangle pathology. It turns out that the stem cells were not impacting and reducing the amount of plaques or tangles that they had but rather they were promoting new connections in the aged brain. So we have now gone back and redone a lot of these studies with human neural stem cells. As you can imagine if we want to take this into the clinic, we can't use mouse neural stem cells but rather needed to identify human neural stem cells that we could transplant into the mouse brain and show that these human cells could improve memory and lead to the same kind of beneficial changes in the brain architecture. Now, this was a very complicated series of experiments to do because, you know, when we did this first studies, I think there were some of the best scientific studies that you can do because you're putting mouse cells into the mouse brain. But if we want to take this into the clinic, we first need to identify what human cells would be the best candidates to take forward. If you recall earlier in my talk, I said that there were 5.4 million Americans who were suffering from Alzheimer's disease, for economic reasons and biological reasons it will be impossible at this point to be able to grow up 5.4 million neural stem cells from each of these individuals. So we really need to find a couple human neural stem cell lines that can be targeted into different ethnic groups. Now to do that, we needed to first develop a way to suppress the immune system of the mouse because animals don't like when you put foreign cells into their body and even into their brain. So those studies took us about six to nine months time to figure it out and just the way science happens to work, it turns out that the best regimen ended up being the most expensive. Meaning that we have to use a combination of the antibodies that cost anywhere from $25,000 to $30,000 a month to be able to suppress the immune system in the mice so that they don't reject these human neural stem cells that we transplanted.

The bottom line is that we've identified a human neural stem cell line and because of this, CIRM has funded our disease team grant that will allow us to try to develop this and take this into the clinic within four years or so. The grant actually starts in January of 2013 and hopefully within a couple of years after that, we will be able to initiate our first human clinical trials. So we're looking somewhere down the road to about 2018 to 2020 before we can first undertake these studies.

Over the next 4 years, we have a lot of questions that we need to address. So for example, we need to know and we need to identify, does it matter if you put the best cell and let's say the best human cell comes from a male patient. Does that matter if you put it into a female patient? So is sex going to make a difference? Likewise, do some of the genetic risk factors make a difference having those in there? You can imagine that you would want to have a cell that has the least amount of genetic risk factors for Alzheimer's, rather than more, before you put them into the brain of a patient with this disease. So there's a lot of screening that still needs to be undertaken just to verify that. We need to know how many brain regions can we successfully transplant these cells into. Right now, we have been focused on one area which is the hippocampus which is a critical area involved in learning and memory but do we need to go out after other brain regions. That would be relatively easy to do. It won't be that complicated to do that but in our studies we focused only on the hippocampus because it was very easy to read out the behavior that's associated with improving hippocampal function. How many cells do we transplant? How long will these cells survive? Do you have to give the patient a booster dose every so

often and are there any adverse effects? Thus far, our cells have survived to six months in the mouse brain and we don't see any evidence of tumors. But what happens if we go out longer will that develop? So these are all some of the questions that we are going to be trying to address over the next four years including another question which is, can you maybe modify these stem cells genetically and maybe get them to degrade some of the beta-amyloid and will that lead to even longer lasting effect? And we've actually done some of those experiments right now. We modify the neural stem cells to express an enzyme that's capable of degrading the plaque protein and when we put them into the brains of our animals, we're able to see that we can markedly reduce the number of plaques that these animals harbor. So that kind of gives you an overview of where we are. I think it's very fortuitous that this year's Nobel Prize in Physiology and Medicine was awarded to Shinya Yamanaka for his pioneering work on figuring out how to reprogram cells, including just your regular skin cells and reset the clock so that they look like they are an embryonic stem cell. And that technology is referred to as induced pluripotent cells. And as I said, you can take these cells from any individual including an elderly individual just do a simple skin biopsy and you throw in a couple reprogramming factors and you can re-induce pluripotency which is what makes embryonic stem cells so unique is that they're pluripotent. Once you have these cells then they can differentiate into the appropriate cell type for the disease type that you're studying. In our case, we'd be interested in differentiating them into neurons so we can study how Alzheimer's impacts that process and then use them in high drug through put screening models to evaluate a lot of different new therapies for Alzheimer's disease. And potentially down the road, these cells could be reintroduced back into the patient's brain to try to repopulate their neurons or the connections between the neurons in their brain.

We are trying to establish a National IPS Stem Cell Bank here at UC Irvine because we have an Alzheimer's disease research center that's funded by the National Institute on Aging and we follow patients longitudinally. Sometimes as long as 20 years so we have a lot of clinical data that we will link to these IPS cells. And we just put in an application to the NIH to try to get one of these funded. As you can imagine, this is very expensive. It turns out that it costs on average about $10,000 to convert a person's cells into an IPS cell. About $1,000 to harvest the cell and about $9,000 to do all of the reprogramming. Now, that doesn't sound that expensive but when you start thinking of experiments that you want to do and if you think about doing this in 20 cells from 20 patients, that means you're talking about a budget of at least $200,000 just for the reprogramming and isolation of the cells plus the man power. You're talking on the order of about $300,000 to $350,000. That is significant because if you're studying 20 cells and you start breaking it down the middle, well let's say you're looking at 10 cells from normal individuals, 10 cells from people with Alzheimer's disease. If you break it down based on gender, five and five, you could see that you're really pushing the limit of what you can do with just 5 cells from a statistical point of view. Really need to be analyzing a lot more cells than that but unfortunately it's very cost prohibitive.

But anyway, I think that's going to be a major future for the field of Alzheimer's disease and so I think with that, I will stop and address any questions that anyone had. And again, I just like to thank everyone for participating in this program. I think it's fantastic and I hope I've given and conveyed successfully

some of the efforts that we're undertaking here at UC Irvine to try to research ways to make memories last a lifetime.

George Vradenburg: Thank you very, very much Frank. That was really quite fascinating and very clear. I have one quick question and we have some on the line and since we only have about 12 or 13 minutes, I will try and keep this one simple.

You mentioned that the way that the stem cells get into the candidate brain is through transplantation directly into the hippocampus. Does that mean that in fact at least in the current approach to administering a treatment that one will have to have sort of open skull surgery of some sort?

Dr. Frank LaFerla: Yes. But as scary as that sounds, it turns out if you talk to neurologists and neurosurgeons, they will tell you that elderly people survive brain surgery in some senses much better than they do appendectomies for example. One other thing that we're trying to work on here as well is to try to study other cell types, other stem cell types like hematopoietic stem cells and other ones that could be delivered either through nasal routes or direct injections into the patient's blood stream. But we're much further behind in that work than we are with this. So I think that right now, we have to think about this as the most direct approach is going to be transplanting these cells and delivering them into the patient's brain.

George Vradenburg: I'd like to ask Michael Ellenbogen from Jamison, Pennsylvania. Michael, you have a question which I think is intriguing. Would you please pose it to Dr. LaFerla?

Question: Sure. Thank you very much for speaking here. You're fantastic and you're speaking here is so clear. What I was really wondering is I've heard that I guess in today's technology after using supercomputers, they have been using many different animals as models loaded into the computer and therefore they're able to do diagnosis and research using the computers. Is it possible to load your information in to some supercomputer and to see this supercomputer come out with the results of your research? This way it could expedite the time frame and come up with much more faster conclusions than you would be able to do as a scientist or waiting for your models to show your diagnosis.

Dr. Frank LaFerla: Yeah. That's a really great question Michael. I think the most successful computer modeling occurs when you have the most accurate predictions of what's actually going on in biological mechanisms so that you can predict from your super computer different scenarios. I don't think we're at that point yet in Alzheimer's disease that we can really predict that. We're just now at the tip of the iceberg in terms of understanding the genetics of this disease and the pathological contributions. I think maybe in 20 years, that would be a great avenue of research but I think for right now, at least based on my limit of thinking, I think we are not quite there yet but I think it's a fascinating question and it really shows how technology is evolving and eventually we will get to that point.

George Vradenburg: Next question is from Gaylynn Mann of Bethesda, Maryland. Gaylynn, please ask your question.

Question: Hi. Thank you so much for taking my question. I am wondering if this stem cell transplantation is financially viable to be a widespread treatment for Alzheimer's and also if the stem cells are plentiful enough to be a widespread treatment or if this is going to be something that, you know, could be used to treat a very small few who may have the resources to access that? Thank you.

Dr. Frank LaFerla: Yeah. I think that's an outstanding question. So let me answer some aspects of that. So we know that the number of stem cells is not going to be a problem and we know that the company for example that we've been working with that has these human neural stem cells can produce them in high enough yield to be able to treat a large number of these individuals. I can't comment on the economic aspect of it although I suspect that if you can take a patient who is disabled and now allow them to do very simple task for themselves, you know, I think we need to address what is our real goal in the therapies that we address? We're not hoping that these patients could go back to doing calculus problems but if we can get a patient who can now dress themselves, eat by themselves, brush their teeth, go out, come home without getting lost, do simple tasks. I think that will be, you know, very achievable and something that the stem cells could help achieve here as well.

I think the main question of what you're asking though is in a sense, is everyone going to be a suitable candidate for stem cell therapy and I don't know the answer to that. I would bet that the answer is probably no, that only a fraction of individuals may be a suitable candidate and I don't think that's necessarily because of economic reasons but might be more based on biological reasons but that doesn't obviously preclude economics from playing a role here. I think, let's assume that only 20% of people are eligible for this kind of therapy, when you talk about the numbers of Alzheimer's, you know, 20% of 5.4 million is still well over a million people that could benefit from this kind of therapy here. So it could be quite useful in that regards. So I hope I addressed your question.

George Vradenburg: Our next question is from Susan Ildefonso from Bountiful, Utah. I love the name of your town.

Question: Thank you. Thank you. Thanks for taking my question. Can you hear me?

Dr. Frank LaFerla: Yes.

George Vradenburg: Yes, we can.

Question: Yeah. My question is will the blood brain barrier be a problem when you're introducing these stem cells? And then also, if you are able to cure the disease with stem cells, do you think that will lead to a cure for other neurodegenerative diseases like Friedreich's Ataxia? I have a niece and a nephew that have that and it's, you know, they talk about Alzheimer's disease and FA together a lot. And so I'm wondering, do you think that it will help to find a cure for some of those diseases also?

Dr. Frank LaFerla: Yeah. Great questions. Yes, I think they will be because I think what we're finding out is that these stem cells are not working through replacing the cells that died but actually by allowing the existing cells to promote new connections.

We've done very similar studies in a different disease with one of our collaborators here at UC Irvine, Dr. Leslie Thompson looking at models of Huntington's disease, which is a devastating brain disorder, and it turns out that the mechanism of action is quite similar to what we have seen in our Alzheimer's disease models. So I do think that the potential here will be quite useful and applicable to multiple neurological diseases.

The key question is, what's going to be the best cell type to use? Would it be neural stem cells or should we take those neural stem cells and either differentiate them a little bit further along into a specific subclass of neurons or to other glial cells or maybe even go backwards and take more the de-differentiated cells like embryonic stem cells. I think all of that needs to be resolved but I think it can be useful for a wide variety of other neurological disorders.

George Vradenburg: Let me ask one final question and then I think we have to sign off or close and that is you raised an intriguing question, the way you characterized what was happening in the brain with the introduction of these stem cells was that the existing stem cells were able to gain new energy and create new connections. Is there a possibility that these stem cells can actually work to reverse or at least mitigate the actual effects of normal aging through the same mechanism?

Dr. Frank LaFerla: So that's a great question, George. A lot of people do believe that one of the problems with aging is that your stem cells lose their ability to differentiate and to self-renew. So there's a lot of work being conductive right now to use stem cells to try to reverse gray hair and skin wrinkling and all that kind of stuff. So it wouldn't surprise me if it could be used to try to rejuvenate the brain down the road. I think right now, we need to focus on Alzheimer's disease. Since that's such an easy read out relative to what, you know, brain aging would be.

George Vradenburg: Well again I want to thank you for your time today.

There are actually a number of researchers that have joined this call and I just want to in 10 seconds describe an initiative, of which Dr. LaFerla is a part, called ResearchersAgainstAAlzheimer's, which is now over 300 researchers who have committed themselves to advocate for increased resource being paid and devoted to research on Alzheimer's and related dementia. And if you are a researcher and would like to join this effort and/or at least learn more about it, please press one now and someone from our staff will get in touch with you to provide more information about this initiative.

Finally just in concluding, as a sort of quick policy update. There is by the end of the year has to be a determination by Congress whether or not to address the so-called physical cliff. One of whose consequences is a very sharp reduction, if it is not addressed, is funding for both defense and non-defense programs. The consequence of that so called sequester taking effect would be a drop of over 8% in the NIH budget, over $2.4 billion in a $30 billion budget. The consequence to any number of research programs would be quite devastating because most of, or many of, the NIH programs are multiple year so the number of new grants that could be stymied as a result of the taking effect of the sequester would be quite substantial and those of us in the Alzheimer's community have been quite active in urging Congress not to allow that sequester to go into effect and not to allow the dramatic reduction in NIH funding that would occur as a result of the sequester taking effect.

So if you are all interested in supporting the efforts that all of us are making in that regard, please go to USAgainstAlzheimers.org and sign-on to our efforts to try and prevent that sequester from taking effect. Also while you're there, you might sign the Stop Alzheimer's Petition. This is an effort to get a million people to sign onto a petition that would be presented to Congress early next year to try and persuade them to pay more attention to the Alzheimer's issue and to provide greater funding for research to fight against it.

I want to thank you all for participating in Alzheimer's Talks. We're grateful for the support of the Zickler Family Foundation that made this call possible. Alzheimer's Talks is a monthly series where we discuss a wide range of topics. I hope you'll participate in these calls and share information with friends and colleagues. And again to our friends at the American Health Assistance Foundation for introducing Dr. LaFerla today and to you Dr. LaFerla, thank you so very much for participating today, and even more importantly thank you for the research that you're doing to try and save the lives of those who have this disease or those who are at risk of this disease in the future. We deeply appreciate your work.

Dr. Frank LaFerla: Thank you very much.

Dr. Diane Bovenkamp: Thank you.

George Vradenburg: And stay tuned for information about our next call in January. We will be sending that out in the coming weeks. Take care all. Thank you.

Dr. Frank LaFerla: Bye.