**Alzheimer's Talks Transcript**
**Stem Cells and Alzheimer's**
**with Dr. Larry Goldstein**
**November 18, 2015**

Note: This transcript has been edited for content and clarity

Welcome to Alzheimer's Talks, a monthly teleconference series presented by UsAgainstAlzheimer's where we seek to connect you with the leaders in research and policy working to stop Alzheimer's.

My name is George Vradenburg, Chairman of UsAgainstAlzheimer's, an entrepreneurial and disruptive organization, seeking to transform the fight against Alzheimer's to disrupt business as usual.

Thank you for joining us today to hear from Dr. Larry Goldstein about some really important research in the fascinating field of stem cells.

I want to give a special thank you to some individuals who have made this call, and indeed the entire Alzheimer's Talks series, possible. Thank you very much to the Zickler Family Foundation, Karen and Chris Segal, Tom Pheasant, and the Richard and Ruth Lavine Family Foundation. Their contributions, along with smaller contributions from many of you, have made this call possible and we are so grateful for your support and their support so that we can continue to bring you the latest in Alzheimer's research from leading scientists.

We have over 430 people registered today for the call from forty-six states and the District of Columbia, and an additional 700 people who couldn't join the call today but requested the recap materials. Additional individuals will call in and/or join the online stream.

If you have a question during the call, please press *3 on your phone. By pressing *3 you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff, or if you are listening to us online you can simply type your question in the box, and we will get to as many questions as possible after the opening presentation. Unfortunately, we will not be able to answer personal specific medical questions during this call.

Today, we are honored to have Dr. Larry Goldstein as our guest. Dr. Goldstein is Distinguished Professor in the Department of Cellular and Molecular Medicine at the University of California, San Diego and Director of the UC San Diego Stem Cell Program. He is also Director of the Sanford Stem Cell Clinical Center and Scientific Director of the Sanford Consortium for Regenerative Medicine.

He is a leading expert on stem cell research, particularly for Alzheimer's disease, and I am so glad that he's willing to join us this afternoon to separate myth from reality in the area of stem cells, and to speak a little more about his research and the search for a treatment. Thank you for joining us, Dr. Goldstein, and we look forward to hearing your comments.

**Dr. Goldstein:** Great. First of all, thank you, George, for inviting me. I want to thank everybody who is on this call; I know how busy people are, particularly if you are caring for somebody with Alzheimer's disease and I'm grateful that you took the time to listen to what I have to say. What I want to do is begin with a very brief background overview of what happens in Alzheimer's disease and then tell you about how we are, as a field, using stem cells to try to fight this terrible disorder.

To go back to the basics, let me remind you that the brain is made of cells, primarily cells called neurons. And it is the connections between these neurons that allow us to think, to move, to talk, to do all the things that we do in our daily lives.

The brain is an important center of connections between neuronal cells. What happens in Alzheimer's disease is, for reasons that we do not fully understand, these neurons in the brain lose their connections. And after the neurons lose their connections, that's when we start to see the symptoms of the disease and then, as a result of those lost connections, the brain cells die—once the cells are lost, they're gone. And at present we don't have a way to replace them, although there's hope that someday stem cell technology might do that.

So the sequence of events is neuronal connections are lost, symptoms develop, and then brain cells die. Now, I want you to remember that Alzheimer's disease is a very hard problem. If it had an easy fix, we would have it already. But in fact, it is one of the scientific and medical problems that is very difficult for a whole bunch of reasons. But the thing about stem cells that's important is that stem cell technology is potentially a disruptive technology in the fight against Alzheimer's disease because it gives us new ways to attack this problem.

Now, there are two major ways in which stem cells are being used to try to fight Alzheimer's disease. One way to use stem cells is to try to replace cells in the brain that are lost, or to repair damaged brain cells that have lost their connections. So that's one way, replacement or repair. And then the second way, to fight against Alzheimer's using stem cells, is to use stem cells that have the ability to make brain cells in the lab to reconstruct bits of brain in the lab that have Alzheimer's disease. So the idea is to develop so-called "disease in a dish" so that we can understand the disease by rebuilding the process of disease in a dish.

So let's evaluate where things are with each of those approaches thus far, because it's really very early in the use of stem cells in the fight against Alzheimer's disease. Now, as I mentioned, one very ardent hope for stem cells is to use them to build new neurons to replace those lost in disease. And I'll tell you, that while this is an important goal, and is something that we all dream of doing some day, it's really not yet ready. It's not yet a feasible approach with current technologies based on what we know thus far. So, replacement of lost neurons is an important goal, but we're not there yet.

Repair of lost neurons is not possible but repair of neurons that have lost their connections

may be a reasonable approach at present. One of the ideas that's being tested in a number of labs is based on the ability of stem cells to make, to be factories for, important brain molecules. And there's interest and evidence for the idea that replacement or a new supply of a factor called BDNF—brain derived neurotrophic factors. One idea is that stem cells might be used to make BDNF in the brains of people with the disease and that might support brain cells so they don't lose their connections to begin with, or they might regrow some of the lost connections. Now, this is a very important approach in animal versions of Alzheimer's disease, but it's just now getting to the point to where it can be tested in humans, but it has not yet been adequately tested in humans so we don't know if this approach will work or not, but it's an important approach to try. It's one of the current shots on goal that we want to see, to try to develop better therapies.

A second approach, as I mentioned, is the so-called disease in a dish approach, where what we do is, we use stem cells as factories in the lab, to make brain cells, and we have the ability to control the genetic constitution of the stem cells in the lab; that is, we can control the DNA of the stem cells using some trickery that is important new technology. And what this lets us do is to study the two different forms of Alzheimer's disease in the lab, to look for the cause of what's going wrong with the cells under the microscope where we can see what's happening.

So, just to remind you, there are two major different kinds of Alzheimer's Disease: there's a kind that is strictly hereditary, where it's passed from parent to child, and we know what some of the genetic changes are that cause that type of hereditary Alzheimer's Disease, which by the way is also early onset, it's a really terrible form of the disease that we need to solve; and then there's the more common form of Alzheimer's disease, ninety-five percent of people have the common form, called sporadic Alzheimer's disease, and what we know about that form is that it has important genetic factors but it's a combination of each individual's unique DNA and environment that that individual experiences during their life.

We have ways in the lab of making both the hereditary changes that cause aggressive early onset Alzheimer's disease and we in fact have the ability to make some of the genetic variants that predispose people to develop Alzheimer's disease in some environments that don't directly cause it on their own. So the important point is that we have the ability to control the DNA of the stem cells in the lab and so we can make stem cells that will develop the aggressive hereditary forms of the disease or that will develop the kinds of behavior that is, we think, typical of people who have the more common sporadic forms of the disease.

Now, you might think that making Alzheimer's in a dish is a frivolous goal, but the fact is, by making Alzheimer's in a dish, we can use powerful molecular tools to observe what happens in the disease and to get important clues to what we might do to solve the disease by developing drugs. And while you might think that, well, you know, one more drug, who needs it, the fact is that drugs, in some ways, may be the most straightforward and easy way to treat this disease, since it's easier to take a pill than it is to get brain surgery to have stem cells implanted. And by the way, we don't know which will really work better but we need, as I say, multiple shots on goal.

So there's a lot of work in my lab and others to develop Alzheimer's in a dish and then use that to test different drugs to see what kinds of drugs might reverse or alter the lost neuronal connections that happen in the disease, and what I can tell you at this time, is that we and others have some important possible leads that we're working very hard to develop into useful drugs in the coming years.

So the point, ultimately, is that we and others have been using stem cells in a variety of different ways, in a variety of different angles of attack on this problem of Alzheimer's disease, and we're trying both implantation of cells in animal versions of the disease and development of drugs in the lab. I'll conclude my remarks by saying I'm very hopeful, we have a lot of promising leads, but the point is, this is not an easy problem, but we have to fight on together to develop better therapies for this awful, terrible disorder.

So why don't I stop my remarks there, George, and we can begin to take questions.

**George Vradenburg:** Terrific, thank you very much. Just as a reminder to all of our listeners, press *3 if you'd like to ask a question; we'll put you in the question queue and get your question before Dr. Goldstein as soon as we can.

I've got just a couple to kick off. You said that we're just now getting to test in humans this BDNF approach to repairing neuronal cells. Are stem cell therapies using that approach now being tested in Phase I or Phase II or are they still in preclinical animal model stage?

**Dr. Goldstein:** So the question is, whether BDNF production from stem cells is in human trials yet, and the answer is that to my knowledge it is not yet in Phase I human trials, but it's getting closer.

**George Vradenburg:** This is just me as a layman, because I am a layman, I'm not a scientist, but there are, just to my understanding, a lot of different sources for stem cells, and a lot of different properties of stem cells depending upon their sourcing. So I'm curious as to how the stem cells are derived that are, you think, the kinds of stem cells from the kinds of sources that are going to be most useful in these potential therapies.

**Dr. Goldstein:** Sure. So, just to summarize a very long list, there are dozens of kinds of stem cells available in humans that we might use to try to develop therapies for Alzheimer's Disease. There are stem cells from blood, there are stem cells from fat, there are stem cells from brains. The type that's being used to develop the so-called disease in a dish version of the fight uses stem cells derived from a method that's called reprogramming. So, the idea, George, is that we could take some of your skin cells, and your skin cells have your unique DNA, and using some fancy genetic tricks in the lab, we can turn your skin cells into a kind of stem cell called a brain or a neuronal stem cell, and from that we can make the various types of brain cells and study how your unique DNA drives the behavior of your cells. So it would be as if we had parts of George's brain in a dish. It's a remarkable concept. And then we could test to see how your particular genetic variation led to behaviors, biochemical behaviors typical of Alzheimer's Disease, and we could, in principle, at some point, test candidate drugs on your cells to see how your brain cells, in principle, would respond. So that's a mouthful but

that's what we're trying to do.

**George Vradenburg:** That was very clear. So what about the types of stem cell sources and properties of the stem cells being potentially used for this repair approach, BDNF?

**Dr. Goldstein:** Those cells are primarily derived either from fetal sources of neural stem cells, or from embryonic sources of stem cells, and that's being done because those cells have the greatest degree of plasticity and we think have the best behavior. It's very tough, it's very difficult, to get stem cells from the brains of adult people, which is why these other sources are being used and being tested.

**George Vradenburg:** I recently ran across a company that was pitching mesenchymal stem cells. Would you comment on what mesenchymal stem cells are and how they might be used, if at all?

**Dr. Goldstein:** Yes, mesenchymal stem cell is a kind of stem cell that has been argued by some scientists to be derived from either bone marrow or from fat. And these are stem cells that are thought to be capable of producing bone and tendon and cartilage, connective tissues, and are being tested by some investigators to see if they would provide important missing factors to brains that are losing their connections. But there's a problem with the mesenchymal stem cell approach in principle. One problem is that some investigators have argued that they're not truly stem cells, and second, they're not truly capable of making brain cells. There are some papers in the scientific literature that say that mesenchymal stem cells can make brain cells, but most of us who work in the field think that there are defects in most of those papers thus far. And so, there are companies and there are individual scientists who think that the mesenchymal stem cell approach will be beneficial for this disease, but I have to tell you that my personal opinion, based on my reading of the scientific literature and our own experiments, is that this is not going to be the best possible approach.

**George Vradenburg:** There are anecdotal reports, and people have told me, that they have gone to Mexico to get a stem cell therapy that's available there but not available in the United States. Are you aware of those reports of that availability there and would you just comment on what you think of it?

**Dr. Goldstein:** Sure, this is an important question, George, and it's related to the question of so-called stem cell tourism. And to be honest, the field has a problem. And the problem is that the hope, the enormous hope, from the scientific promise of this area, has led clinics around the world to market therapies for Alzheimer's disease using stem cells that are not yet proven to work. And so these reports from Mexico, and other countries, I don't want to single out any one country, but these reports of miraculous recoveries using stem cells, is in many cases, we think, what we would sometimes refer to as unproven. So, the problem we have is that if you go to a clinic and you get treated, you're one of maybe 10,000 people that will be treated at that clinic.

We know that people sometimes spontaneously get better when they have disease. Disease course is very variable in people. And if it just happens that you're the one person out of

10,000 who got a little bit better the day after you were treated, you might think that it was the treatment in Mexico that did it, but the fact is, you were only one out of 10,000. And when we think about using stem cell approaches to disease, we want to develop therapies that will help *all* people with Alzheimer's Disease, not just the occasional lucky person who randomly happens to get better after a treatment in Mexico. It's the problem with what we call anecdotal reports, to use the same word that you did, they're one out of 10,000. You don't hear about the other 9,999 who didn't get better. You just hear about the one person who happened to get better temporarily just due to the variable course of disease. So, these kinds of approaches are unproven and the clinics are, I think in most cases, selling snake oil, unproven therapies.

**George Vradenburg:** We've been talking about the application of stem cell technologies in research and therapy for Alzheimer's. Are these approaches being tried in related dementias other than Alzheimer's dementia?

**Dr. Goldstein:** The question is: what about the other kinds of dementia? And the answer is that stem cells are being used to try to understand all different types of dementia using different types of approaches with stem cells and they are also being used for other neurodegenerative diseases such as Parkinson's disease, ALS, and Huntington's disease, and for each one of these diseases, stem cells are being used in different ways to try to understand and to treat that disease. It's part of the concept of using a powerful technology to generate multiple different shots on goal and we're actually hopeful that if there were successes for other types of disease, it might help us in the fight against Alzheimer's disease, which I personally think is the toughest of the problems.

**George Vradenburg:** We do have a question online, specifically about whether there are applications learned through stem cell research with MS that can be transferred to Alzheimer's?

**Dr. Goldstein:** So, the answer, as far as I know, is that there are some important stem cell therapies developing for MS, that are approaching clinical trials, and there are some approaches using so-called adult stem cells in MS that are being potentially helpful. I think the best answer is that what we learn about any one disease is going to be helpful for Alzheimer's disease. But it is important to remember that MS is a very different type of disease from Alzheimer's disease. MS appears to happen when the immune system, that protects us from foreign invaders such as bacteria and viruses, when the immune system, in MS, seems to become defective and begins to attack brain cells. As far as we know, in Alzheimer's disease, it is not the case that the immune system is attacking the brain cells. So there are very different causes based on what we know thus far between MS and Alzheimer's disease, and so therapies for one are probably not going to be directly applicable to the other. But you never know; somebody might get lucky and discover something that's beneficial for both. But I think that in general the approaches to these two problems are very different and they have very different causes.

**George Vradenburg:** We have a question here from a listener named Sharon. Sharon, would you please put your question to Dr. Goldstein?

**Caller:** Yes, I'd like to know if you're using stem cells that have been taken from people who have been definitively diagnosed as having Alzheimer's.

**Dr. Goldstein:** The question is, are we deriving stem cells or making stem cells from people who have definite diagnosis of Alzheimer's disease. The answer is yes. What we're doing is, in order to understand the so-called sporadic form of the disease, the common form that's caused by the interaction of the genes with the environment, we're working with the Alzheimer's Disease Research Center, ADRC, at UC San Diego. And what we're doing with the Alzheimer's Center is, we take skin cells from people who have definitive diagnoses of Alzheimer's disease, as well as skin cells from so-called controls, people who don't develop disease, and we make stem cells from both and then we make brain cells from people, effectively, or we make brain cells that carry the DNA of people who had a definite diagnosis of disease, and we're studying those cells in the dish to see how those cells interact with their environment and for the testing of drugs. It's early, for us and others in the game; this is all very new, as we said, disruptive technology, but we're very hopeful that we'll get the kinds of clues that will give us additional shots on goal with the development of drugs and other therapies.

**George Vradenburg:** Here's an interesting question that's come in online. Is the sex of the stem cell considered during development? I've never thought of stem cells having sex but . . . Is the sex of the stem cell considered during development? Given the differential impact of hormones on the brains of women and men, could stem cells used for repair act differently depending on where they come from?

**Dr. Goldstein:** The question is, will stem cells that are male differ from stem cells that are female. And I think that the answer is that we really don't know yet. That's a very important and very perceptive question. One hope is that by studying the interactions of brain cells that are male or female in the dish, with different hormonal influences, we might begin to tease apart why women seem to be developing the disease more often than men. But it's early in the game and those approaches are just now starting up. But it's an important angle of attack that will have to be pursued in coming years.

**George Vradenburg:** Thank you to Liliana Losada for that really interesting question.

We have a question here from Carla Danesi from East Rochester, New York. Carla, please ask your question.

**Caller:** Yes, hi, George, best regards to you. You are my hero; you know that. This is Carla Danesi, I'm an Alzheimer's independent research advocate and a caregiver for my mom, been sick for twenty years. Dr. Goldstein, I just wanted to ask you. I've been following very closely a drug compound called J147, and Dr. Dave Schubert, you might be aware of him, at the Salk Institute, had published a manuscript entitled "Alzheimer's drug discovery tailored to stimulate human neurogenesis," and in that, he talks about what you've brought up, about the drug compounds. This particular compound, J147, has been shown to have some benefit as far as helping in terms of stem cell replication, in that, being that it is neuroprotective. And

what he's saying basically is otherwise new cells will die, and neurogenic, what he's saying, it will help expand introduced cells or stimulate an endogenous stem cell population. So in other words, it seems very promising and it might help the cells actually take effect and hold. What are your thoughts on that?

**Dr. Goldstein:** Carla, that's a very interesting question and gets into a very important line of investigation. So, as background, I'll remind people that there *are* stem cells in the brain of adults that make some new brain cells throughout adult life. And the idea is that this compound, J147, might help the stem cells that ordinarily live in your brain, and could potentially help new stem cells that are transplanted into the brain of people with Alzheimer's Disease. Again, it's very early in the game. This compound looks very promising in mice that have animal versions of Alzheimer's disease. But it's important to remember that humans are not just big mice; we don't respond to drugs that work in mice the same way that the mice do, and so it's going to take very careful clinical testing to see whether this drug will work in humans the way it works in mice. So it's an important lead. It's another one of what I call shots on goal. We're not always sure which of these shots will work but we have to test them all carefully to find out what's going to be the best approach in the fight against this disease.

**George Vradenburg:** You mentioned before that the sourcing of the stem cells that are being on the verge of testing in humans, not yet being tested in humans, on the repair strategy, use a fetal or embryonic stem cell. There's a question here online about whether there's a stigma against using fetal or embryonic stem cells, whether that might inhibit that line of attack.

**Dr. Goldstein:** It's an excellent question and it would be naive of me to say that there's no problem. The fact is, there are people in the United States who have ethical and moral objections to the use of stem cells from fetal or embryonic sources. But I'll just remind everybody that these cells are only used when there's been a prior decision that's unrelated to the question of whether they're going to be donated to science, to either terminate a pregnancy or to donate frozen embryos. That is, in these cases, no matter what the decision is about the research, those potential lives are terminated and some people think that's unethical. My argument is that it's a little bit more like the case of an auto accident where we don't necessarily like auto accidents that kill people and give us a source of cells postmortem to study, but it would be a waste to lose cells that could potentially help us to develop therapies for people who have the disorder. It actually doesn't take very many so-called embryonic or fetal sources of cells to develop cells for these potential therapies, but I don't want to downplay the fact that people do disagree. I personally think it's ethical when the cells have been donated under stringent ethical standards and that it would be a mistake not to use all reasonable attacks on this terrible disease that kills millions of people every year.

**George Vradenburg:** A couple of online questions from Laura, related, slightly different. What are your thoughts on gene editing such as using the tool Crispr to edit an APOE-4 gene to be an APOE-3, especially in a person who has a very high risk with two copies of APOE-4? And you mentioned you are using stem cells to emulate disease in a dish; have you tested gene editing such as changing APOE-4 to APOE-3 in the disease in the dish?

**Dr. Goldstein:** Well, that's a very perceptive technological question so let me cue everybody

in on the call. So, there's a very important new method that's been developed called gene editing using a method called Crispr. We, and others in the field, use Crispr routinely in the lab to edit the DNA of stem cells to study what goes wrong. So in answer to the second question that you posed, do we use Crispr gene editing to study Alzheimer's disease? The answer is yes, it's very important technology and we use it on a daily basis. The first question of whether it would be possible to edit the genes of a person who has Alzheimer's disease using Crispr. I never want to rule anything out as being possible at some point in the next few decades but the fact of the matter is that the brain of a person is composed of billions of different cells and so you run into what's called the delivery problem, where getting the Crispr gene editing machine into every different cell of the brain that's being affected in Alzheimer's disease is a really difficult technological goal. I won't say it's not possible some day to figure that out, but at present, we really don't know a good way of delivering the editing machinery to every cell in the brain that's affected. But we do use it quite routinely in our labs.

**George Vradenburg:** Is there not some gene editing that occurs really at the very outset of life, a gene editing in the womb where if in fact you could identify E-4 there, you could edit it to E-3? You wouldn't have to do every cell, you'd just have to do the initial, the burst, what's that called? Excuse me for being so stupid!

**Dr. Goldstein:** No, it's not stupid, it's a good question. There is debate currently about whether gene editing during early embryonic life should be something that we pursue as a field. And I think the answer to that is that, at present, the ethics of doing this kind of gene editing early in embryonic life, is being debated. And it's being debated for a couple of different reasons. Both of the reasons ultimately come down to the question of, can we control the Crispr editing completely precisely? So the thing to remember is that there are billions of so-called bases, or letters, in the genetic alphabet in our cells. And using Crispr, we're trying to edit just one out of those billions of letters in that alphabet. We know that in the lab at least the Crispr editing is not perfect. There are some off-target effects. So there's an ethical issue about whether the risk of editing is too high in the developing embryo to warrant attempting to edit out one of these genes that predisposes but does not guarantee the development of Alzheimer's disease. So it's another important new general approach, but there are some grave concerns about the safety of the approach and that's being debated right now.

**George Vradenburg:** You know, we have people on this call that I would not characterize as laypersons. Here is a question that came in both online and the same person, Maria Pereira, from Hunter College, asked it beforehand. Stem cell therapy seems to be associated with problems such as inducing local immune responses and inflammation, disrupting local tissue homeostasis, and increasing the risk of tumor formation. Have you considered the advantages of using stem cell secretome for treatment instead of the cells themselves?

**Dr. Goldstein:** Okay. So that's a very technologically advanced question.

**George Vradenburg:** These laypersons who call in to Alzheimer's Talks are pretty smart!

**Dr. Goldstein:** I'm impressed by the level of information that your membership has. So, the

question is whether it would be better to use the products made by the stem cells directly, as opposed to using the stem cells following implantation. And the answer is, we don't yet know. The point of medical therapy development is, we do test different ways of doing things. So there's a great deal of interest in using the products of stem cells directly, such as BDNF, to treat Alzheimer's Disease, and there are groups working on gene therapy approaches to doing that, and then there are approaches, as I've just said, that are being developed in animals for possible testing in humans, using the stem cells directly to secrete, that is, to produce the factors that might support neural connections. I think again it's early in the game; we have to ultimately test a variety of different approaches and no amount of speculation will tell us what's going to work the best. We do have to get in there and do human clinical trials to find out and to test which therapies work better than others.

**George Vradenburg:** I've got a couple of practical questions that came in before the call, and online. You mentioned the potential on the repair approach to using stem cell therapy, not yet in human trials but still in preclinical work. And you mentioned during the course of that discussion that the route to administration of that therapy would be brain surgery. Is that right? Did I hear that right or is there a possibility of delivering that therapy, if it is successful in human trials, in a way other than implantation in the brain through brain surgery?

**Dr. Goldstein:** Thus far, the approach that does look the most straightforward for using products of stem cells to support brain cell connections is in fact brain surgery, either to put the stem cells in, so that they can produce factors, or to use the so-called gene therapy approach, where viruses are used to carry the genetic factors that produce products such as BDNF. These are introduced into the brain usually by brain surgery. There's something called the blood-brain barrier which makes it hard to get materials from the blood stream into the brain, and that's why we think that to get stem cells to act directly in the brain, they have to be implanted via brain surgery.

**George Vradenburg:** There are efforts now underway to explore nasal administration of things that otherwise have difficulty in getting into the brain through the periphery. Would that conceivably be an alternative mode of administration?

**Dr. Goldstein:** I think the answer is yes, conceivably. One of the problems we as scientists sometimes have is that there's a universe of different possibilities that we could try, and so we try to prioritize where each of us thinks our effort is best spent. So I'm not smart enough to think that I should be the only one who says what routes of administration should be tested. I'm personally using the approaches that I think will be best, but I do think it's important for a variety of approaches to be tested and to leave no stone unturned in the fight against this terrible disorder. So, yes, conceivably. Do I think it's the most likely to work? No, I don't think it's the most likely, but I do think somebody should test it.

**George Vradenburg:** This is a question from Elaine Hanson from Sedona who suggests that the costs to the patient of, for example, brain surgery, to get a treatment, would be significant and thus exacerbating the inequity of who gets the treatment and who doesn't, that the cost to the patient needs to be taken into account.

**Dr. Goldstein:** I think that Elaine is right. There's no question that the cost of therapy—particularly with a disease that affects so many people—the cost of the therapy is ultimately important. But I'll remind everybody that there are two factors that are important when thinking about cost. One is, sometimes a therapy is very costly when it's first applied, and then as there are improvements in that therapy over time, and as it comes into more general use, the costs drop. And it is important to remember that while the costs of therapy could be high, the cost of Alzheimer's disease is very high. Alzheimer's disease is more than 200 or 300 billion dollars a year in the United States, and the cost that many families experience for care and support of an Alzheimer's patient is $30, $40, $50,000 a year to care for a person in many cases. So, therapy could be expensive, but caring for a person can also be very expensive, so that's one answer.

The second answer is that sometimes an expensive therapy may be too expensive to deliver to everybody who has the disease, but we learn, from the expensive therapy, a cheaper way to deliver that therapeutic benefit. So an expensive therapy can sometimes teach us what's the best way of intervening in the course of disease, and that could lead to a less expensive variety. So there's no question that ultimately in the fight against disease, we have to find cost-effective therapies, and developing therapies that are extremely expensive ultimately have to lead, in the long run, to therapies that are less expensive to be generally applicable.

**George Vradenburg:** That's a very good analysis of a more general problem.

There are a couple of comments here that I think are a little speculative right now, but nevertheless important. A question that came in before the call from Patti Bondor: Will saved stem cells of a grandparent's grandchild be able to be used to help the grandparent? And online, from Joann Orovitz, is there a chance that stem cells of a sibling or relative would be better to use on a patient?

**Dr. Goldstein:** Wow, so those are two very important questions from Patty and Joanne. I think the question that's being asked is, would cells from a relative of a person with Alzheimer's disease be helpful in understanding or treating the person who has the disease. And I think that the best answer is, maybe. You know, at present, we are trying very hard to understand how each individual's genetics leads to their development of disease. It's a very important angle of attack on the problem and it might turn out that using the cells of relatives will help us understand how genetics leads to disease, and so, again, I'd say, it's early in the game, we're exploring how to best use stem cells that have different DNA variation patterns, to understand disease and to develop drugs, and so it's premature for me to say yes or no to a question like that.

**George Vradenburg:** We've got a question here from Dan Dietz from Texas. Dan, would you like to ask your question?

**Caller**: Yes, Dr. Goldstein, I am doing research in storing blood by zapping a bag of blood to extend the life of it, and it came to mind that if I'm using electrical stimulation and there's stem cells actually flowing in blood, has electrical stimulation been applied to any research in unison with chemicals, the actual drugs that they are using now to see if there's any increase

or decrease?

**Dr. Goldstein:** So if I understand Dan's question correctly, the idea being asked about is whether electrical stimulation of cells from the blood or cells from other sources might be used in combination with drug treatments. I think the answer is, someday, in the future, it may be that electrical stimulation of the brain could be part of a therapy, but that based on what we know now, it may be very hard to deliver electrical stimulation to the brain. We certainly can deliver electrical stimulation to cells in a dish, and that's part of understanding how the cells interact with each other. I'll remind people that part of how brain cells connect to each other and talk to each other is through electrochemical signals and so stimulating cells in a network with electricity may give us clues to how the cells fail in Alzheimer's disease, because we can observe changes in their response patterns to electrical simulation. But again, that's one that's early in the game and we're just beginning to explore under laboratory conditions.

**George Vradenburg:** I've got a question based upon my own history. The question is the extent to which the research has been, and is being advanced, as a result of California's bond issue, which invested three billion dollars plus in stem cell research technology and infrastructure. What role has that funding played in your work or, in your estimation, the work in the field?

**Dr. Goldstein:** So the question is, how has California's landmark stem cell bond legislation, which has directed three billion in funding to stem cell research in California, how has that funding affected the development of therapies for Alzheimer's disease and in my own research? The answer is that three billion is being used for research on all possible diseases, so each disease gets a fraction of the research but there is research in labs throughout the state on Alzheimer's disease using the California funding, and my own lab has been very generously benefitted by funding from Prop 71 to help us develop our disease models in a dish. In fact, I think it's fair to say that without funding from California state bond legislation, we would not be as far along as we are, in the development of the disease models in a dish and the drug leads that we think we have; they've been very dependent on the California bond legislation and so, I think it's been a very positive development.

**George Vradenburg:** Here's somewhat of a personal question, but nonetheless, what the heck. This is from Laura, online: my understanding is that you worked with Craig Venter and he has one copy of the risk gene APOE-4. What would you tell someone like Craig Venter that has a higher risk of Alzheimer's disease, of what he should do with his lifestyle in ways to delay or prevent the disease?

**Dr. Goldstein:** Okay, that's a tough question. So, I think I'll boil it down to, how would you counsel anybody who has genetic variants that predispose to disease about their lifestyle. And I think that it's early in the game still, and our understanding of how lifestyle affects the likelihood with which we'll develop Alzheimer's disease. To date, the best known environmental factor that predisposes to Alzheimer's disease is head injury. And so, avoiding head injuries is probably a good thing if you carry an E-4 variant, but I would say it's good for anybody with any kind of genetic composition to wear helmets during bike riding and horseback riding to avoid head injury. In terms of the details of lifestyle, I think the best we

could say is the factors that are consistent with a healthy lifestyle in general, not being overweight, not developing diabetes, remaining active both mentally and physically, are the best way we know now to combat disease, although we're still not entirely sure which lifestyle factors are the most important for developing disease.

**George Vradenburg:** Also vascular health and not smoking.

**Dr. Goldstein:** Exactly.

**George Vradenburg:** Well, I think you've been extraordinarily informative and clear in all of this discussion, Dr. Goldstein.

**Dr. Goldstein:** Thank you

**George Vradenburg:** A real education and a very promising area but we're, as you repeatedly emphasized, we're still on the verge of discovering what are the possibilities here, at least for therapies, although it sounds like induced pluripotent stem cell research tools are at least being applied and are proving somewhat useful.

So thank you very much for your time today, and thank you everyone for your questions, a lot of which were way above my head, but it simply demonstrates the talent in our listener base for which we're deeply appreciative. Dr. Goldstein, we thank you for what you do every single day.

Thanks to all who have contributed to this phone call, and certainly thanks to all who've contributed a donation, which we solicit when we send out an invitation, because those contributions have enabled us to be able to continue this call series.

There still are some questions we couldn't get to today. We always seem to have some left, so we apologize to a number of you for not being able to get you on the line.

Due to the holidays, we will not be having an Alzheimer's Talks in December. I hope you have a safe and wonderful time with your loved ones and look forward to having you join us in January.

If you have not already joined UsAgainstAlzheimer's, please go to www.UsAgainstAlzheimers.org and sign up. We will send you important updates every week, and simple ways that you can take actions that really are affecting policy here in Washington and affecting the way industry is approaching drug development. We know we can stop this disease, but we can't get there without your help. It's now a critical time here in Washington, when in the next two to three weeks, the amount of money to be allocated for Alzheimer's research at NIH is being determined, and that will be, we believe, resolved by December 11. The prospect of significant increases in Alzheimer's research investments is on the table; we have some cautious optimism but there is a range of possible increases. So weighing in, right at this point in time, on all of our action emails, asking you to weigh in with Congress, are very important.

Thank you to everyone on the phone or online for participating in this Alzheimer's Talks. In about a week we will have a copy of the recording and a transcript on our website for you to share with your friends. As always, please stay on the line if you would like to leave us a message with a question or comment. We are particularly interested in what you would like to discuss on future calls.

Thank you for joining us today. Have a good afternoon and again, Dr. Goldstein, thank you for joining us.