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Alzheimer's Talks Edited Transcript
Finding Drug Discovery Breakthroughs
with Dr. Howard Fillit

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The following transcript has been edited for content and clarity.

George Vradenburg: Welcome to Alzheimer's Talks. Thank you all for joining us this afternoon, at least this afternoon on the East Coast. Alzheimer's Talks is a monthly teleconference series presented by USAgainstAlzheimer's where we seek to bring to you leaders in the field who are working to stop Alzheimer's. We've brought you scientists, we've brought you investors, we brought you activists all so that we can be better informed about what is going on in the field and and what we can expect in the way of means of prevention or treatments for those with the disease, or at risk for the disease.

We have almost three hundred people registered today for this live call from 42 States and several countries such as Austria and Brazil, others will dial in or listen online. Additionally almost a thousand people couldn't join us at this particular time, but explicitly asked us for the materials discussing this call, which we will send in about a week and we will obviously also send a recap of this call to everyone who's registered for the call today.

I'm so happy that we have today Dr. Howard Fillit, he is a leader in the field and a professional but also very much a person who is moving forward the progress towards actually finding an innovative medicine that will help those with the disease or those at risk. He is a geriatrician, a neuroscientist, a leading expert in Alzheimer's disease, he's also the Founding Executive Director and Chief Science Officer of the Alzheimer's Drug Discovery Foundation, ADDF. The Alzheimer's Drug Discovery Foundation's mission is basically to take the discoveries that are being made in the academic and research laboratories around the world, to invest in the most promising of those, in order to accelerate the discovery of drugs that will actually prevent, treat, and cure Alzheimer's disease. ADDF has assessed more than a hundred suggested therapy ideas to prevent brain aging or dementia and has recently built a web-based portal http://www.cognitivevitality.org, to share evaluations of various prevention strategies with the public.

Howard, thank you for joining us today. Thank you for your work in this field, thank you for your leadership, and we look forward to your comments.

Dr. Howard Fillit: Well thank you very much George, I appreciate joining you on the call today.

We're very excited about what's going on in the field today and I know we want to talk about prevention as a beginning space and I have to say that having been in the field about 35 years it's really amazing how the concept of prevention has changed in our field so dramatically. There was some recent work

that even suggested that the risk of dementia has gone down among 60 year olds from people who were 60 years old 30 years ago and we think that part of the reason for that might be the changes in lifestyle that people are experiencing which was probably driven a great deal by efforts in heart disease to improve the quality of life of Americans and to create more people who are exercising and eating healthier diets and doing other forms of prevention that are not only affecting the heart but also the brain. And I think what we need to do is think about the brain as an end organ the same way that we think about the heart, we've certainly come to the understanding that in many ways, and this is based on a lot of evidence now including some randomized trials that have been conducted, that the things that you can do for your heart will also be good for your brain and the one intervention in terms of prevention that seems to be the most robust one is physical exercise.

I think from our Foundation's point of view, what we like to consider is not just the actual intervention but how the intervention might prevent dementia and Alzheimer's disease, and trying to bring scientific rigor to the field of exercise as a preventative and go beyond the various levels of evidence which are really delineated on our Cognitive Vitality website. We've known for many years that exercise has good effects on the brain in terms of cognitive function. About six or eight years ago, we helped Art Kramer design a study in which he brought 50, 75 year olds into his center and asked them to stretch and socialize three times a week for about 45 minutes. And then we funded Art to bring in another 50, 75 year olds and have those formally sedentary people to stretch and socialize and then go for a brisk 45-minute walk. And at the beginning of the study, we measured their brain volumes and their psychometric function, their cognitive function. And then at the end of six months we repeated those measurements. What Art found was that the people who didn't exercise, who didn't take that simple 45 minute walk three times a week, they had a progression of cerebral atrophy, particularly hippocampal atrophy, at about the same rate that we consider to be normal aging which is about .4% loss of volume per year and their standardized memory test declined along a similar rate. The people who exercised actually, and this is obviously a modest degree of exercise, actually had an increase in their hippocampal size and particularly areas that were relevant to memory and learning and their cognitive function improved. So here we basically had a randomized clinical trial of exercise and looked for biomarkers of that effort on the brain and showed very positively that this could affect the brain.

The next step was to say okay in human beings, because this had also been shown in mice and rats on treadmills but in human beings, what would be the mechanism of the effect of exercise on the brain? And so Art then got some additional funding from us and from NIA (National Institute on Aging) and expanded the study and he actually got the older people on treadmills, measuring VO2 max which is the kind of thing that Lance Armstrong might have done or other Tour de France bikers in measuring their fitness, which is directly relevant to how fit somebody is based on how efficiently they actually use oxygen. And so there's a linear relationship between the VO2 max and exercise fitness and he looked at the relationship between VO2 max in these older people, their cognitive function, and other measures of biological relevance in the blood like BDNF. Now BDNF, or brain-derived neurotrophic factor, is one of the most powerful neuroprotective factors that we know of, it's made in the brain, it's made in the muscles, and it also plays a critical role in neuroplasticity and memory formation. And what Art found in this expanded study was again that there was a direct relationship between exercise and brain volume,

cognition, and BDNF levels in the blood. That's really interesting because now we have a couple of things, we have biological measures of the relationship between physical exercise and nueroprotection and neuronal plasticity. But what we also have is a clue to how to make new drugs for Alzheimer's disease that are nueroprotective because we know that BDNF is a powerful neuroprotective agent and we're seeing now in humans from these kind of studies, epidemiology, the randomized trial I just told you about exercise, and so on, that BDNF could have true efficacy in human beings.

Now we have been funding Frank Longo who's the Chairman of Neurology and Neuroscience at Stanford University since about 2002 to create neuroprotective small molecules that mimic, or in some way mimic, the effects of molecules and other protective agents like BDNF and also NGF or nerve growth factor which is another important neuroprotective trophin in the brain. And so following the studies of humans and exercise and the pointing to BDNF, we actually started early on to assist Frank and I'd like to tell this story about Frank and his work to give people an idea of how drug discovery goes. So Frank was very interested in developing small molecule drugs that can mimic the effects of neurotrophins in the brain, which are the most powerful neuroprotective agents and natural agents, natural products of the body. Certainly with previous biology demonstrating that BDNF and NGF are powerful neuroprotective agents, in fact, back I believe in the late 90's and in the early 2000's, there were even clinical trials of NGF in humans with Alzheimer's disease. The problem of course with NGF is it's a really big molecule, it's a biological, can't be delivered very effectively to the human brain and not only that but the problem from a biology point of view is that the NGF receptor has two roles, one is neuroprotection but the other is actually to send brain cells that are severely injured down a pathway we call apoptosis which means that the cell undergoes program cell death. So the challenge for Frank was to understand the NGF and BDNF receptors and dissect them so that he could have a small molecule which would only trigger the neuroprotective pathway of that receptor and not trigger the cell death signal that the receptor can also start in the cell under circumstances where the cell decides, well I'm too far gone and I've got to get out of here.

So the way Frank started his drug discovery program was on the computer and he bought a software library of about two million compounds and on the computer there was the structure of the NGF receptor, which was the first neuroprotective hormone that he started with. On the computer through something called computational modeling and computational chemistry was able to, over a period of months, match this library of two million compounds in his software library with the model on the computer of the NGF receptor and particularly find compounds that bound a region of the receptor on the cell surface that signaled the cell survival signaling downstream into the side of cell and did not trigger the cell death signaling. This was very high-risk work funded by ADDF in its earliest stages. Then what Frank did was he actually found 60 out of the two million, 60 compounds that he could purchase from chemistry companies that actually worked in the model and by getting the actual compounds in house, test them in cell culture in Vitro which would be the next step in the process and see if they work in Vitros. So basically the kind of thing he did was to culture neurons in cell culture in Vitro and then take for example beta-amyloid as a toxic signal to those cells and see if his NGF, at this time NGF compounds, could protect those neurons and cell culture from cell death and injury from the beta-amyloid and of course sure enough several of these compounds did and so what Frank did based on discussions with his

medicinal chemist was pick two for further development. So next steps, and we're talking several years later, now probably going into 2007 or so, he synthesized larger quantities of these molecules and began to test them in animals. And along the same time, what we said to Frank and discussed with Frank is that he was really moving along into a commercial space with the work and that solely relying on government grants to do this sort of work would not ultimately get him where he wanted to go and relying solely on foundations would not make it work either. So we helped Frank with money and some strategic assistance, and this was while Frank was still at the University of North Carolina, to spin out a biotech company called PharmatrophiX. And as I mentioned, to make a long story short now, Frank tested his lead molecules in animals, they worked there, he then got some money for IND-enabling work, through the company, did some safety and toxicology, about a year and a half ago got FDA approval for testing the drugs and molecule in humans and in doing a phase one safety and is now poised to do a phase two-a study of these neuro-protective small molecule compounds.

And the thing about this is, that it's a really different approach to treating Alzheimer's disease. It's really novel, it's really innovative, and I think it's really important because if you think of the ways that neurons get injured over the course of a lifetime, there are many ways that this happens and we know that aging itself is the leading risk factor for Alzheimer's disease and we think that, for example, molecules like beta-amyloid play a role but I think most of us think that it's certainly not the only misfolded protein in the brain and in the biology of Alzheimer's disease. But there are also many other forms of injury to brain cells that don't necessarily need a link to beta-amyloid for example oxidation, inflammation, Hypoxia. And if you think of a funnel basically, what you would like to have is an all encompassing neuroprotective agent that would enhance cell survival regardless of the kind of injury that the cell is susceptible to or suffering and so that's number one. Number two, Frank's work I think is revolutionary because it would be one of the first examples of a small molecule that mimics the effects of a neurotrophin which could really open up a whole new space of drugs and the way he's engineered these drugs through chemistry and so on to affect only a portion of the receptor is really quite revolutionary. So right now we've also continued to contribute to Frank's work and the work of PharmatrophiX and trying to raise additional funds for Frank to complete the funding necessary to conduct this phase two study.

Getting back to exercise, long loop around I know, but Frank's follow-on program has to do with developing BDNF small molecules that can hit the BDNF receptor and I'm very excited about that program, I'm maybe even more excited about that program because of its potential wider applicability than NGF, that's a little further behind. And I'll finish this story by saying that what we've learned from exercise and the potential role of BDNF and work like Frank's in the lab and understanding not just the biology but the process of drug discovery as one of my board members said to me one day, 'Howard you know I don't care what you tell me about exercise, I'm a couch potato, can't you give me a pill that would mimic the effects of exercise so I can remain a couch potato?' And we're hoping that Frank's work will deliver that pill and be able to not only prevent and treat Alzheimer's disease but enable couch potatoes to stay on a couch.

So George, that's one story that I'd like to tell and maybe you have comments about that one.

George Vradenburg: Well what it emphasizes is the length and patience and persistence that is required to take a basically new approach or presumably even a more conventional approach and derive something that will enter the brain, actually hit the target that you're trying to hit, and actually show effects and there is a process of trial, error and time which requires not just persistence on the scientist's part and the trial and error necessarily associated with that but also on the funders part whether they be foundations, government, or private sector investors.

Dr. Howard Fillit: Yeah, I think that's really true George. That people don't understand, even a lot of the biologists and academic researchers that we fund or that we're used to talking with who are so good at understanding the biology of disease and doing research on the biology of disease, we all don't realize how really, really different the science of drug discovery is compared to the biology.

Drug discovery is so much more based in chemistry and certain discipline to really get to the truth, which is ultimately the goal of all scientists and especially in disease-related fields like ours in Alzheimer's. You know every grant that's ever been written really says that at the end of the day, we hope that this science will ultimately lead to a new drug. But the only way to a new drug is really through drug discovery and that's really not biology that's really in chemistry, or in the case of vaccines it is the certain kind of biological research of taking biologicals into drugs not necessarily small molecules. But it's still the process of drug discovery which is so difficult and as the process moves forward from chemistry into animals and so on and the ramp up in costs is very dramatic and so risks become much greater for investors and funders and basically we don't really know in our heart of hearts where the next new drug for Alzheimer's disease will come from. I mean we have so many examples in disease states where there was rational drug discovery but so many examples where it was really serendipity that drove the discovery of new drugs. And I think that the rational approach has led us down the path of a focus on beta-amyloid as a key mover and I think we all hope that, that will turn out to be right but I suspect that hopefully one of these molecular antibodies will work. We're going to continue to need to develop new drugs for Alzheimer's disease for many, many, many decades just like we've had drugs for diabetes for almost a hundred years and hypertension for 80 years, but we're continuing to try to discover new drugs for those illnesses and for heart disease new classes of agents, because for example even though we think of Statins as miracle drugs, heart disease remains the leading cause of death in our country. So this is going to be a long-haul, incremental science, new classes of drugs being discovered for a very long time.

George Vradenburg: We have a number of questions here both online and those that have come in before the call. So I'm going to start with a series of questions, there's one online and there are a couple that came in beforehand and that is, aside from what you just described in terms of the extraordinary value of exercise, are there any existing products on the market, nutritional supplements or otherwise that can be helpful in either protection or disease affect and I'm thinking in part are there any generics now for Aricept and Namenda, there was a call last month where there was discussion of ashwagandha and cat's claws. I know you have in the past talked about DHA, Algal DHA. Are there things that are currently on the market, that you think there's evidence that they have any positive effects?

Dr. Howard Fillit: Right. Well you know we thought long and hard about that George and that's why we started the cognitivevitality.org site because almost every day now we read a front page story or a story in the newspaper about a study that demonstrates that one supplement or another or one strategy or another is a breakthrough for Alzheimer's disease prevention etc. And I think the problem with all these stories and the evidence is that both physicians who are advising patients and patients or laypeople, need a better understanding of the evidence and there are different levels of evidence. So for a lot of supplements, for example, there's a lot of what we call in Vitro evidence or test tube evidence so we take a supplement that's often a complex composition and mixture of a whole variety of extracts and we put them on cells and culture in an experiment and look at the effects and see effects and then publish those. And sometimes that might for example get into a press release from a University. Sometimes we'd see evidence in animals where supplements are injected into or given to animals and the animals get better and our Foundation has published some white papers on how we need to advance the rigor of animal experiments. We've cured mice with various forms of Alzheimer's disease over 400 times in the literature and who knows how many times people have tried and got negative results that aren't published. But you know none of those mouse experiments has translated into a new drug. So we need to understand if it's a mouse experiment or an animal experiment what is the rigor with which that experiment was done and was it randomized and so when we see in the newspapers something about a supplement, was the experiment done in animals? If it was done in humans, and we see this very rarely, were supplements tested in a randomized clinical trial of humans and what were the outcomes?

And then the other thing is we often, and perhaps most often, hear about supplements and these kinds of things as a result of observational epidemiological studies where the best we can come out with is associations between one factor and another. As far as epidemiology and we often see in the newspaper again press releases that red wine is associated with a decrease in Alzheimer's risk, and I would want to see all the evidence and evaluate all the evidence and if there was an association try to understand the biology and what it means and what is it in the red wine, is it resveratrol or something but at the end of the day these epidemiological associations are often not proven. The best example I can give, is I can prove that bread is bad for you and that you should not be eating bread and the reason is that 98% of all felonies that have ever been committed in the United States had been committed within 24 hours of eating bread. Now obviously that's a joke but it illustrates how associations that are even strong are not necessarily good evidence.

So the Cognitive Vitality website takes a lot of these supplements and evaluates the full range of evidence and gives some sort of opinion on efficacy and safety because for prevention, taking something over a long period of time, safety is critically important. Now within that context, DHA which George as you mentioned I often talk about, DHA has some really interesting evidence and besides exercise DHA was one of the only other strategies that the NIH Consensus Conference on Prevention actually gave some support too and the reason is that first of all there's a really rational mechanism of action. DHA plays a critical role in the brain. 97% of the omega3 fatty acid, and DHA is an omega3 fatty acid, 97% of the omega3 fatty acids in the brain are DHA and not the other kind, which is called EPA. And the DHA plays a critical role in neuronal transmission much as the insulation around a cup of wire enables rapid transmission of electricity. In the brain the myelin sheaths are primarily composed of fat and DHA plays

a critical role in the insulation around the axions, which are the connections between neurons and enables us as humans to have a very fast processing speed which enables us essentially to be human beings and think. So there have been a lot of studies and again I'll go through levels of evidence in Vitro study showing DHA is neuroprotective. Animal model experiments showing that DHA has beneficial effects on cognitive function in mice as we measure it, epidemiological studies which you know again this is on our website showing an association although not one hundred percent between DHA and certain kind of studies looking actually levels of DHA in the blood and looking at people who are actually deficient in DHA. So we don't make our own DHA, we have to get it from food primarily from fatty fish, so you would expect that people who don't eat much fatty fish certain people could get deficient in DHA. So some investigators looked at the actual levels in the blood of DHA, and you can measure this, and there was a correlation between the levels of DHA and cognitive function in older people and from a clinical practice point of view, what's interesting is that those people who were considered to be deficient in DHA had the lowest cognitive function and in some more recent studies when those people with the lowest level of DHA was supplemented, they have some improvement in their cognitive function.

We generally consider the highest level of evidence, which I mentioned before, to be the randomized control trial and that's the problem with most supplements that they're not put through a randomized control trial where you give somebody a placebo and you give somebody the supplement and you actually see if it works on that basis. And it's unusual but if you buy it you'll see that the FDA allows the makers of DHA, the Algal DHA, in particular can have a label that says that it improves memory, which none of the other supplements really are allowed to have from a marketing purpose from FDA and it's just this one formulation of Algal DHA which is made from algae and not ground-up fish so has a better safety margin as well. What the randomized clinical trial showed was that in people who had basically normal aging, normal cognitive decline, that those people that took the 900 milligrams a day of Algal DHA actually had improvements in their memory compared to people who didn't take it. So DHA as a supplement actually had the full range of levels of evidence that we need to give it the strongest recommendation because it was put through a randomized trial. When it was given to people that already had Alzheimer's disease, it really didn't have an effect but again as we're seeing today, we need to be doing better clinical trials in patients with earlier illness and earlier populations and maybe measuring levels. So I'm not totally sure that in some populations, the people with Alzheimer's, it might not work especially those with earlier disease. But what I've tried to do with DHA is explain this issue of how we apply levels of evidence to DHA.

Now there are many other supplements that are important and particularly in people that are deficient and one that traditionally should be checked by every clinical practitioner in the field is B12 level. And that's because older people frequently develop an autoimmune disease of the gut called pernicious anemia in which they destroy the factor that enables us as human beings to absorb B12 into the blood and be stored in the liver. It's very hard to become B12 deficient from diet but if you have this disease called pernicious anemia, you can get B12 deficient. Now, in the old days, it was called pernicious anemia because people became so severely B12 deficient that they became anemic but now that we recognize the disease earlier we also recognize in older people that the first signs of B12 deficiency can

be dementia. And so whenever somebody comes into the office, we will measure B12 levels at the initial evaluation and if they're deficient in B12, certainly supplement them with injections of B12 as a supplement to actually improve their memory and I've seen that happen. It's not highly common but it certainly happens in the community.

We're also learning about vitamin D for example, that vitamin D is a hormone not just for your bones but also for your brain and there's some evidence, and we have a review of this on the Cognitive Vitality site as well, that there's a rational mechanism for vitamin D supplementation especially again in people who are deficient, that it can be beneficial for memory and there's a lot of research going on right now about vitamin D in the brain and vitamin D in epidemiological studies as a risk factor for cognitive decline in dementia and Alzheimer's disease.

George Vradenburg: Howard, we've got a number of questions I'm going to try and click through some questions and if you can keep your answers short and crisp so that we can get as many in as we can in the next 20 minutes or so.

Dr. Howard Fillit: I'll do that.

George Vradenburg: Ruth Becker on the line has asked us if you could quickly comment on your view of Dr. Dale Bredesen research on tailoring a set of supplements and other behavioral steps to particular people. Do you have a comment on his research?

Dr. Howard Fillit: Yeah, you know real briefly, I think what Dale's doing is practicing good medicine and he's packaging it in a way that makes sense and tailoring his program. It's really a program that distills out a lot of what I would consider good practice over the years and takes advantage of an individualized, personalized approach to optimizing cognitive function in older people taking in all the principles of good sleep and reducing stress and eating healthy diet and exercising and so on, taking some supplements, and evaluating each patient. That's what we should be doing in primary care for patients and that's what I've been doing for 35 years and I think Dale has very innovatively packaged, good medical practice into his study.

George Vradenburg: Great. So we have a number of questions that came in beforehand and one online from Catherine Ciafardoni. Basically what are the best candidates in the pipeline for potential disease modification or prevention and specifically any feelings that you might have regarding solanezumab's potential?

Dr. Howard Fillit: Well, answering the question about solanezumab. I want to be optimistic about it. I want to be optimistic that if we treat early, as they are doing in this new trial, that'll have a beneficial effect. I really want to be optimistic that we will have an approval in the next five years of the first disease-modifying drug and that it might be solanezumab. And I applaud Lilly for taking the risk that they're taking in conducting this trial because we know that one clinical trial in Alzheimer's disease in a phase 3 is $300-$400 million and so I think that what Lilly's doing by taking the results of their prior two different solanezumab phase 3 trials and analyzing them and seeing the signal in the data and then rather than deciding it's too risky or there wasn't enough signal and in those two studies they didn't

meet their primary endpoints, their primary outcomes, and most of the time in most disease states when two, $300 - $400 million studies fail to meet their primary endpoints the drug is dropped. But Lilly hasn't done that here and I applaud them and I am very hopeful that the design of this new trial which will be much improved than the previous trials because all people that enter the trial will get amyloid brain scans so we'll know they have Alzheimer's disease, we know that in the previous trial about 30% of people didn't have Alzheimer's disease which creates a terrible signal to analyze ratio they hadn't gotten their brain scans at entry to the trial. So it's going to be an improved trial in a more mild earlier population with presumably less disease and as a scientist I got to say, let's see the data and I want to be optimistic.

George Vradenburg: Are there any other drugs in the pipeline that are intriguing you in terms of potential prospects?

Dr. Howard Fillit: Well there are actually many drugs in the pipeline that are intriguing and that we need to see the data. So for example, we've been we repurposing a whole bunch of drugs from diabetes and hypertension. There are hypertensives that have neuroprotective properties like the angiotensin receptor blockers, there are angiotensin receptors in the hippocampus that are neuroprotective, we've learned that from animal studies. So at the University of Toronto we're doing a study comparing angiotensin receptor blockers for the treatment of hypertension versus ACE inhibitors to see if we can get a neuroprotective effect. We are repurposing a Parkinson's disease drug for Alzheimer's. In diabetes at the Imperial College of London we're doing studies of repurposing liraglutide, which is a diabetes medication to improve insulin resistance in the brain and glucose energy metabolism in the mitochondria. We know that there is an energetic deficit in the brain of people with Alzheimer's disease and in aging and it links together the biology of aging with the treatment for Alzheimer's disease.

There's a study right now going on by Takeda and Zinfandel of pioglitazone in low doses, which is another diabetes drug that again can improve energy efficiency and protect neurons because when neurons lose their energy efficiency and metabolism they are at risk for degeneration. So a lot of repurposing going on. And then in terms of novel therapies, there is some renewed interest, we've been funding tau drugs for some time now, for probably over 10 years, but there's sort of a resurgence and interest in tau. Again as a misfolded protein that forms the toxic oligomers and seems to spread from neuron to neuron in the pathway that the disease spreads throughout the brain and now we have the p807 marker that can help us to do these clinical trials and I think an exciting new approach will be some tau monoclonal antibodies against the oligomers that will ask the question of whether if we prevent the spreading of a tau from neuron to neuron throughout the brain we can prevent the spread of the disease.

George Vradenburg: We got a couple of questions here on ApoE4. So Catherine Ciafardoni asked a couple of questions online. I'm going to pool these questions and then call on Frank Presto to ask his question, but Catherine's question is the likelihood of actually knocking out ApoE4 in high-risk individuals? What are your feelings regarding the use of hormone replacement therapy for ApoE4 menopausal women? And Frank from South Park, Pennsylvania I'm going to ask you to go ahead and ask your question and we can sort this family of ApoE4 questions for Dr. Fillit.

Question: Yes, yes this is Frank Presto. My wife died of Alzheimer's disease and she had it for 5 years, she was originally diagnosed in December of 2008. The reason why I'm calling is my wife was diagnosed as having the gene I think they mentioned it as ApoE4 and she was going through a clinical trial with a medication that they were testing, I believe it was called Bapineuzumab, and they deleted the trial because it wasn't working. The reason I'm calling is, seeing that this was in her genes, is there any way that my children can get tested early to see if they have it in their genes and maybe they could have some medication that could maybe stop the gene from forming as bad as it did for my wife. Like I said she had it for five years and passed away.

Dr. Howard Fillit: Yeah. Thank you for that question.

Let me tell you some background for the audience. There's three kinds of ApoE: ApoE2, ApoE3 and ApoE4. About 75%/80% of people have the three and that's what we would consider the normal risk. People with two are protected against Alzheimer's disease. About 20% of the population has at least one 4 from a mother or father and about 5% of the population has two 4's, so they get one from the mother and the father. The people that have a double 4 have about a 15 to 20 times risk of getting Alzheimer's disease and they get it about 10 years earlier so instead of 75, 65. Now we've known this and it's been highly reproducible for over 20 years so we know the biology, we have the test, we know the epidemiology, and we don't have any drugs and it's been over 20 years.

And again another example of why drug discovery is so important and underfunded. Now we started a portfolio of ApoE therapeutics about six or seven years ago and I think we probably as an organization have funded the largest portfolio in the world of ApoE therapeutics playing every which way so far to fix that ApoE4 and the most exciting thing that we're funding right now is really a kind of genes therapy and what's being done is that in people that have double 4's, and this is being done at Harvard and done at Cornell in two separate studies that we're funding, that there's a way to take either the ApoE2 DNA or ApoE3 DNA and put it into what's called a virus that's a very, very safe virus that's approved by the FDA and inject that virus into the brain. Right now this is all pre-clinical, in monkeys and so on. And give people that have ApoE4, which is a bad protein we think, an ApoE2 gene that's produced by the virus in the brain, in the glia of the brain, to make the good kind of ApoE4 as a therapeutic. There are other ways, there have been attempts to use small molecules, that would be pills, to fix the ApoE4 problem. But right now we just need a lot more funding to get these ApoE drugs into the clinic.

Now as far as the blood test, the answer is absolutely yes. For people who want to know, it's a very simple prescription. You should be able to just ask your doctor and through your local quest or left corp or whatever there is a company out in California called Athena Neuroscience, and there are some others out there, that do the ApoE4 DNA testing based on the blood and it may cost some money if your insurance doesn't cover it but the answer is absolutely yes it's a very relatively simple blood test that can be done in any doctor's office and sent out to the laboratory.

George Vradenburg: But I take it, in fact, you should be concerned if there are two variants of ApoE4 in the child. But if in fact, he had his child tested and he had a double E4 variant, what else would he do now? What would he do differently?

Dr. Howard Fillit: And by the way if you only have one, you are still at five times greater risk so it's not even good to have one ApoE4. But as far as what you can do, I think that's an important question. We actually did a study looking at what people said they would do, and of course one thing is that they would live their lives a little differently. I think they were much more focused on prevention, what we know about prevention, they did more of their wills, especially older people that found out they have ApoE4, quite frankly and I'm not being self-serving here, but I think the most important thing that people who want to know - and a lot of people don't want to know, like I don't want to know myself, but the gentleman on the line does because his wife was affected and if my wife were and I thought my children would be affected I might be similar to the gentleman. But I'm in this anyway discovering drugs every day for Alzheimer's so it's probably not going to change my behavior but quite honestly I think the most powerful thing that people with ApoE4 can do is help us do the research, help us disseminate the message and fund ADDF, we have the largest portfolio of ApoE drugs and access to clinical trials in development and pre-clinical studies, because that's how we're going to fix it. Like I said, we've known about ApoE4, biology and risk for over 20 years and we're really not that close to developing drugs.

I just want to say that I really appreciate the question about estrogen. I actually opened up the field of estrogen in dementia and Alzheimer's disease back in 1980 when I started the Alzheimer's clinic at the Rockefeller University and the first clinical trial we did for various reasons was testing estradiol in postmenopausal women with Alzheimer's disease and we did see an effect in that. That kind of study is still going on, particularly in menopausal women, and the lady is right that estrogen has some effects on levels of ApoE but it's not clear to us even now what direction we should be moving the ApoE in terms of levels. So it's a good question and I think that we would love to manipulate it. There's another way that we're funding that right now is through Gary Landreth and a company that he has spun out from Case Western Reserve in Cleveland, using a cancer drug called Bexarotene. Because one of the theories is that it raises levels of Apoe4 and so we're funding a study using a novel technology to actually look at that in human beings sort of a phase one study and there's also another clinical study that just wrapping up of Bexarotene for Alzheimer's disease and one of the outcomes there would be Apoe4. So there's a lot of interest but we don't have the answers yet.

George Vradenburg: People ought to be reminded who are on the line that the Alzheimer's Drug Discovery Foundation is a foundation and contributions to it are tax deductible and they will go to the kinds of research that Dr. Fillit is describing.

There is a question from Bert Greenberg online. I'm going to give you a percentage range here that you can answer this, Howard. What chance do we have to get adequate federal funding for basic research on Alzheimer's?

Dr. Howard Fillit: Basic research? Well you know, Alzheimer's is historically underfunded, it's a relatively new disease. The National Institute on Aging wasn't founded until 1976, at that time the government was spending about $600,000 on aging research, mostly caregiver work, at a time when the country was already spending billions of dollars on cancer and heart disease. The amyloid gene wasn't discovered until 1984, so really recent history. We've come a long way, but we have a long catch up to funding Alzheimer's research. We're currently spending about $500 million a year, maybe $550 on Alzheimer's

research. We're spending billions and billions of dollars on heart disease, on diabetes, on cancer and AIDS. We're spending about $3200 per patient annually with AIDS on research. We're spending about $150 per patient per year on research for Alzheimer's disease, almost a 24-fold difference in the per patient amounts, at the same time the deaths from Alzheimer's disease are exponentially increasing and deaths from breast cancer and other forms of cancer and heart disease and AIDS are declining. We discovered that there are 500,000 deaths a year probably from Alzheimer's, that Alzheimer's is the most expensive disease in this country and out of that 550 million that we're spending on basic research and on research in general and neurodegeneration at the government level, a very small percentage of that is actually going to developing new drugs. A lot of pharmaceutical companies are getting out of the space because it's too risky. So again as George said, the need for funding is incredible, a hundred percent of every dollar that's donated to us goes solely to drug discovery research. We don't fund any basic research, we're only trying to translate the basic research that's funded by the government into new drugs. That's all we do and a hundred percent of every dollar is going to that. But we need more partnerships, George has been fantastic throughout the world in encouraging partnerships between organizations because no one foundation, no one government, no one pharmaceutical company can do this alone.

George Vradenburg: So I have just one more question and Carla Danesi has her mom, who's been a survivor for 20 years. Carla we just have a few minutes left, could you just give us a minute or two about what you've done with your mom and we'll get a comment from Dr. Fillit and then we'll close up the call.

Question: Oh thank you so much George, my deepest respect to you as always. You know what I've done with my mom for the past 20 years, diet, exercise always the Mediterranean diet, similar to that low fat, low carb, low sugar, low sodium. I've also done the Axona shake every evening with vitamins, every vitamin you can think of A, C, B, D, E. I have also done 2 tablespoons of Brazilian nut powder everyday adding to the shake, which helps with her lucidity. She's been able to eat and swallow her own food due to that. I have also done extensive research on my own and every day she goes to a medical day program prior to that, she went to a social day program. I keep her exercising, I keep her social, I keep her going, I keep her on a routine, I keep her walking, I fight no surrender and I have never given up and she's doing extremely well. Her Alzheimer's doctor is the head in Rochester, Anton Porsteinsson he says she's a survivor - 20 years.

George Vradenburg: Carla that is terrific. That is a lesson, thank God we've got you on the line and thank God we're going to put you in all of our notes so that everyone can hear that in detail when we distribute the transcript to this call. Howard, what's your reaction to that comprehensive approach that Carla's taken with her mom?

Dr. Howard Fillit: Well, it's very hard to generalize from one patient. I think if your mom has been stable for 20 years quite frankly, and I don't mean this in a negative way at all, it's very unlikely that she actually has Alzheimer's. But I think what you're illustrating is a very, very important point. The goal at this point is not to find the cure. Average life expectancy for women in the United States is 80 and I think it's fair that we'd say that the average age of on-set of Alzheimer's in women is probably about 76 or 78. So if through things like prevention and perhaps Carla the things you're doing and the other things we'd

talked about today, we can delay the onset of Alzheimer's disease by just 5 years, we would reduce the number of cases by 50% and we would move those people to an age where they hopefully, and we're all going to die, will die peacefully in the middle of the night from a heart attack rather than suffering 7 to 10 to 15 years of the nightmare of Alzheimer's disease. And I think that the preventative measures like Carla's described, that we've talked about today, exercise, diet, all these things that we learned about, and drugs because we're going to need medications. Preventative measures can help move the needle to delaying the onset of Alzheimer's, but it's not going to prevent it inevitably and we're going to need drugs, the equivalent of Lipitor for Alzheimer's disease, and I think that's the most critical need. We know what to do in prevention but we are going to need drugs so that people like Carla's mother and my father and so many other millions of people in this country will not get Alzheimer's disease and have to suffer the nightmare of Alzheimer's disease in old age.

George Vradenburg: Thank you Howard and that's a good note to end on.

As I said before I think Howard's work is some of the best in the field because it is so tangible and it takes the academic work and tries to really move it into products and into protocols and into practice that will really have an impact on the people we care about. So reminder, he has his Cognitive Vitality website. ADDF, you could look it up online, and in fact this is a terrific organization and I would urge to consider if you've got a year-end gift, other than USAgainstAlzheimer's, which of course everyone ought to contribute to, contribute to ADDF.

A lot of questions we couldn't get to today. Thanks so much to the intensity of interest and with Dr. Howard Fillit I am quite hopeful and increasingly confident that we'll have something on the market by 2020 and that we'll see continuing improvements thereafter in the kind of innovative medicines that we need.

As I said earlier, in about a week you'll have a copy of this recording and a transcript on our website for you to share with friends. Our next call is Friday, January 16th from 1:00 to 2:00 PM with Dr. Bruce Miller who's Director of the University of California San Francisco's Memory and Aging Center. He's a behavioral neurologist who studied frontotemporal lobe dementia and he's been working with the NFL on brain health. I hope that you'll be able to join us for that next Alzheimer's talks.

Thank you for joining us today and have a great afternoon and Howard thank you so very much for joining us today.

Dr. Howard Fillit: Thank you George.

George Vradenburg: Bye-bye.