USAgainstAlzheimer's NETWORK
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Transcript of Alzheimer's Talks
with Dr. Rudy Tanzi
April 16, 2012

George Vradenburg : Welcome to Alzheimer's Talks. A conversation about the role of genetics in Alzheimer's disease with Dr. Rudy Tanzi, director of the genetics and aging research unit at Massachusetts General Hospital and a professor of neurology at Harvard Medical School. Dr. Tanzi is one of our nation's foremost experts in genetics.

My name is George Vradenburg, I am the co-founder and chairman of USAgainstAlzheimer's, and a son-in-law of an Alzheimer's victim. I am also a co-convener with Alzheimer's Foundation of America of Leaders Engaged on Alzheimer's Disease with over 50 participating organizations from the Alzheimer's serving community.

Thank you all for joining us today. Three hundred and thirty-eight people are registered for this call from 38 states and the District of Columbia and more are expected to join us who did not register up front. This is the second call in a monthly series presented by UsAgainstAlzheimer's and today we are sponsored by Jill Lesser a board member of UsAgainstAlzheimer's network. Jill has a parent with the disease and is part of a burgeoning women's movement against Alzheimer's disease. Not surprising given the disparate impact of Alzheimer's on women, where women are two-thirds of the victims and over sixty percent of the caregivers.

Today we'll be discussing the role of genetics in Alzheimer's. We will hear about the role of genes, environmental factors and lifestyle play in creating risks for Alzheimer's disease, the impact of genetics on early and later on-set Alzheimer's, and what we should watch out for in the drug and therapy pipe-line based upon what we know about the genetic factors in Alzheimer's disease.

If you have a question at any time during this call, a question for Dr. Tanzi, please press star three on your phone. By pressing star three you'll be placed into the question queue. Please have your question ready to share briefly with a member of our staff and then they will try to get you live on the air with Dr. Tanzi when we open up the call for questions. Please appreciate that Dr. Tanzi cannot answer personal medical questions on this call.

Before Dr. Tanzi begins we're going to hear briefly from Tim Armour, President and Chief Executive Officer of the Cure Alzheimer's Fund. The Cure Alzheimer's Fund funds much of Dr. Tanzi's research and I would like to have Tim describe briefly what they are doing at the Cure Alzheimer's Fund to research a cure for Alzheimer's. Tim?

Tim Armour: Thanks, George. I want to commend you also for your leadership in this area both with UsAgainstAlzheimer's as well as leaders against Alzheimer's disease, the lead program,

you've really stepped out in front and made a huge difference in this campaign that we hope will be shorter rather than longer.

But thank you for the opportunity to say a little bit about Cure Alzheimer's Fund, which is a non-profit 501(c)3 foundation, whose mission is to fund research that will prevent, slow, or reverse Alzheimer's disease. It started with four founding families who recognized the same statistics that just about everyone on this call already knows. Most profoundly, that almost half the people 85 years and older have it. And it is the only one of the major diseases whose mortality rate is increasing. And of course, with millions of baby boomers about to enter the danger zone of 65 and older, it's a tremendously frightening phenomenon. But in short they recognize the tremendous suffering and economic burden on families enduring AD with no cure in sight and all that when the disease has been known for over a hundred years. And they had, as most people on this call do, a great impatience with the lack of progress. They and their friends, family, and others who joined them since 2004, wanted to help with fast, focused funding of high impact research that would make a difference by shortening the time to availability of effective therapies.

So, Cure Alzheimer's Fund really adopted four key approaches. One is strategic; we have a road map designed by our research consortium, of which Rudy Tanzi is the chair, with objectives and milestones - with the understanding that things on that road map are the things that we have to know more about to stop this disease. We work lean. It's important to know that all our expenses are paid for by our founders, so all donations go directly to research. No endowment, no holding tank. Fast - there's no bureaucracy, research proposals are approved by a panel of distinguished senior scientists in a matter of a few weeks. We move the money where it's needed fast. And finally, we go for the big play. We avoid funding incremental research. Our strategy is more like the football 40 yard path than the 3 yard dive into the line. We want to make big yardage fast.

So if you'd like to help Cure Alzheimer's Fund directly or just be included in our quarterly reports and research updates just press number two on your phone and we'll send contact information via e-mail. Last thing I'd like to know before turning it back to George is does it matter? We're a relatively small 501(c)3 non-profit, we contribute about 4 million a year, we've done roughly 20 million since our founding a few years ago. And we'll admit that this is a drop in the bucket to what's needed, and there are other Alzheimer's organizations contributing to the research as well. But all together the non-profit sector contributes less than 5% of the total. So is that important? Yes, it is. It is because an organization like ours can provide fast, focused, frugal ways to invest in very high impact big play research. We can turn modest amounts of money around very quickly and put it where it's most needed to leverage those proof of concept ideas into bigger amounts of money from the federal government and bigger foundations. And I'm sure Rudy will talk a little bit more in the course of his discussion about research and insights that have come through because of Cure Alzheimer's Fund's support. So I'll get on out of the way now and turn it back to George to introduce Rudy. But let me remind you again that if you'd like to know more about Cure Alzheimer's Fund please press number two on your phone and we'll e-mail you. Thank you. George back to you.

George Vradenburg: Thank you, Tim. If you have a question for Dr Tanzi during the call, just a reminder, please press star three on your phone. By pressing star three you will be placed into the question queue. Please have your question ready to share with one of our representatives and we

will try and get you on the air with Dr Tanzi when we open up for questions. Dr Tanzi, please, we look forward to your comments about the role of genetics as a risk factor in Alzheimer's disease.

Dr. Rudy Tanzi: Great. Well, thank you George and thanks for the invitation to do this and for all the great work you do in not only raising awareness for this disease but also to deal with the needed funding given the epidemic that this disease represents in this country right now. And thanks Tim for your comments and especially for the Cure Alzheimer's Fund, who make so much of our research possible and thanks to all of you on the phone for taking the time on this, at least in Boston, beautiful afternoon, to learn a bit about Alzheimer's and particularly about the genetics of this disease and what it has taught us and where it will hopefully bring us in terms of ways to end Alzheimer's in our lifetime.

As many of you may know, Alzheimer's is a dementia. Dementia is the umbrella term for all of cognitive deficit that leads to a catastrophic loss of memory, reasoning, etc. So, it's a type of dementia, but it's the most common form of dementia in the elderly. Right now, we have no effective treatments. We only have treatments like Aricept, Exelon and Reminyl, which try to preserve memory, try to preserve the ability to learn. But the brain is still going through that wasting process, that neuro-degenerative process to characterize the disease.

It's important to note that the pathology you see in Alzheimer's disease really occurs in everyone starting after the age of 40. There may be a few people who genetically, you know, escape it and they are very interesting, we actually study them. But for the most part, all of us start to get the characteristic plaques and tangles, which characterize the disease. The plaques outside the nerve cells are made up of something called beta amyloid, the tangles are inside the nerve cells.

Before I got any further, you need to know that all the genetics so far has taught us the following, and this is the first real important take home point: the excessive accumulation of the beta amyloid, what makes up the plaques, the excessive accumulation of beta amyloid in the brain is necessary to trigger this disease if you want to say it's dementia due to Alzheimer's, but the amyloid accumulation is not sufficient to cause the disease. The amyloid accumulation must then trigger the formation of the tangles. The tangles are accumulating inside the nerve cells and this is what kills the nerve cells. The third component is inflammation, once nerve cells start dying, as more amyloid accumulates, this leads to an inflammatory response in the brain. And while inflammation means well, that's the way the brain protects itself against bacteria and viruses, in this case the excess inflammation leads to a toxic loss of more nerve cells - so called friendly fire on the brain. So, that's basically the road map of pathogenesis in Alzheimer's. You accumulate amyloid, it triggers tangles as inflammation, and then eventually the slippery slope that leads to dementia.

Now, in terms of genetics, virtually every case of Alzheimer's disease involves genetics but the rule of thumb is that the earlier the age of on-set, the more powerful, the more robust, the genetic influence. So, the first genes that my lab found and others found in the 80's and 90's carry mutations in them which when inherited guarantee the disease. These genes, the first one we found was the amyloid pre-cursor protein. This is, as you might guess, the protein that gives rise to the amyloid. This is a normal protein that has many normal roles in the brain and in the body but

when it carries certain mutations, which are very rare, they guarantee Alzheimer's disease, usually under 60 years old.

The second two early on-set genes that we found in the 90's are called the presenilins - presenilin one and presenilin two based on pre-senility. Again, these two genes make normal proteins that play normal roles in the body, but when they carry any of over 200 different mutations they guarantee the disease. And for the presenilin one usually on-sets under 50, that's luckily only 1% of Alzheimer's. If it's presenilin two or APP, then the on-set is usually between 50 and 60. All told, these mutations, while rare, they only account for maybe 2% of Alzheimer's, have taught us the most about the disease because when the mutation guarantees the disease, there's no need for nature versus nurture or life style effect. The mutation simply guarantees the disease around 50, anywhere from 40 to 60, when inherited. Because of that we can create animal models with these genes. They are very powerful. We can put these gene mutations into mice create an Alzheimer's model in the mouse who doesn't normally get Alzheimer's disease and then this is a place where you can now try to understand the molecular mechanisms that underlie the disease and do testing of novel drugs and therapies.

So, what we learned from the first three genes that we found in the 80's and 90's, with the early on-set genes, all of them lead to the excessive accumulation of the beta amyloid in the brain, APP because it's the pre cursor of the amyloid, the presenilins because these genes make the enzyme that cuts APP to release the beta amyloid protein. So the beta amyloid protein is very small, it's called the peptide. It has to be excised, liberated, from the pre-cursor protein. So, if we picture a piece of rope and take a magic marker and make a little red segment in the middle of it, you would have to get a pair of scissors and cut twice to excise that little red painted piece of rope from the bigger rope. This is how a beta comes from APP. It's a normal process, it happens in the brain normally. You make a certain amount of it. But if you start to make too much of it, or if you make a form of it that's a little longer that usual and is more prone to clump up into amyloid then you start to accumulate more amyloid as you age and this is particularly true after 40 years old. As this material accumulates in the brain over decades at some point is triggering the tangles made up of different protein called tao, and then this eventually, this combination of amyloid outside the nerve cells, the nerve cells dying, leaving debris in the brain, gets the brain all fired up. There's inflammation and now it's friendly fire, which probably kills more nerve cells than the original amyloid in the tangles. So, you get this cascade process. But the genetics has taught us, that it starts with amyloid. But some of you who are really astute on this topic might say, wait a minute, if amyloid is so important and it's starting this disease, why am I reading every other month in the New York Times and Wall Street Journal that these drugs and therapies targeted on amyloid are failing? And I would like to tell you that it's not because amyloid is the wrong target, it's because so far the drugs and therapies that have been tried have not been optimal. And this is often the case when you are starting new drug discovery against a new protein target. The first wave often fails, even Aricept and Exelon. You may know that the first version of this was Tacrine or Cognex. It wasn't safe. It was causing liver problems. So, it was the first off the block but it failed in the end because of safety issues. So, the first wave is kind of a trial wave and the reason why the anti-amyloid drug so far failed, and I can get in to specifics if you wish to ask, is one of 3 reasons. One or more of three reasons, I should say. Either they didn't get into the brain. It's very difficult to get a drug into the brain. Only very small things get into the brain because the brain protects itself. It's amino privileged. Or if it did get into the brain, it wasn't very potent or very effective against its

target. Or it might have gone into the brain and it was potent but it wasn't safe. In other words, it just caused toxic side effects that made the patient worse than it was worth.

For example, Lilly tried to block the gamma secretase. Gamma secretase is that enzyme I talked about made by the presenilins. So the presenilin genes make this gamma secretase and it makes the second clip that release the A beta from APP, so they say let's stop this enzyme. The problem is that enzyme is very necessary throughout the body and brain and you can't just hit it with a sledge hammer. So this people got sick and that drug failed. The alternative is to now make versions of that same type of drug different chemical classes where you would specifically just block the gamma secretase from making the amyloid beta protein, while letting the gamma secretase do its other jobs. So, the key in getting a safe drug is not only efficacy and potency but selectivity and specificity. You want the drug to only do what it is supposed to do and nothing more so that you don't cause side effects and that is happening now. In fact Cure Alzheimer's Fund is funding a class of this gamma secretase drugs which are looking very promising, so promising that the NIH has taken them up with their new translational medicine program and they are putting millions of dollars behind these gamma secretase drugs to get them into clinical trials and this was all made possible with just, you know, $300,000 as seed money from the Cure Alzheimer's Fund to get things going when it was still a high risk project. This is a type of funding we need these days. You know, ones in a high risk, potentially high big gain. Now the fourth gene is the APOE gene and this is involved with late-onset AD. And late-onset AD genetics is very different than earlier-onset. In late-onset what we see is the combination of various genes together and life style. So, it's not as simple in early on-set, you know, inherit gene mutation get disease, you don't need any other genes, don't need any lifestyle affects just get it. In late-onset, which is the vast majority of Alzheimer's cases, that occur after 60, that's 95% of the cases. There are multiple genes that work together and also effects of lifestyle. The number one late-onset genes is APOE or Apolipoprotein E. APOE comes in 3 different flavors APOE2, 3, or 4. APOE3 is the most common form. APOE2 is pretty rare but when inherited together with the 3. So, let's say, your mom gives you a 2 and your father gives you a 3 or vice versa, the 2-3 combination protects you from Alzheimer's but if you get a copy of 4 from a parent, you have a 4 fold increase risk of Alzheimer's, 4 fold. If you carry 2 4's, 2 APOE4, one from mom and one from dad, your risk for Alzheimer's increases about 12 fold but remember this is just increased risk. It doesn't guarantee the disease like the early on-set genes. The later, the age of on-set of the disease, the less influential the genetics. So, someone comes to me and they say, wow, you know my family: my mom had it, my uncle, you know, they go through it. First thing I ask is how old were they when they got it? because that's what really matters. Not so much how many people got it because they may be a family with longevity, they lived long enough to get the disease but what's more important is what age where they, because the earlier the age of on-set the stronger the influence of genetics, the less need for nurture over nature. So and again, as part of the Cure Alzheimer's Fund you heard about from Tim, they have funded in my lab a program called the Alzheimer's Genome Project, where the rationale is very simple. Most of what we know about Alzheimer's came from the genes. Before 1987, before we found the first gene, for 80 years after Alzheimer's described this disease in 1906, decades, we only knew the pathology of the disease and we had no idea what caused it. It wasn't until the genes came around that we can say, okay, here the proteins involved, here are the molecules involved. But those 4 genes I just told you about, the 3 early on-set ones and the late on-set one APOE only account for 30 to 50% of the genetic puzzle. 50 to 70% remains unknown and this is when Cure Alzheimer's Fund started the Alzheimer's Genome project or other similar projects around the world and this

has now lead to over 100 different candidate genes that we're also looking through their DNA to find if they carry variations or rare mutations that also caused Alzheimer's diseases. And I should tell you, because I don't have time to go into all the details, but if you look at the 10 top genes, the 10 new ones. So, I told you about the original 4. If you look at the 10 newest ones that we all agree are true Alzheimer's genes of the 100 or so that we're looking at. Those 10, it will lead us back to amyloid, they again affect either the production of the amyloid in the brain or how it's cleared out of the brain and I forgot to add that APOE, even though it's known as a cholesterol gene in the brain, APOE is the key player to get the amyloid out. So, while the 3 early on-set genes are involved with making the amyloid beta protein. APOE is involved in clearing it out of the brain. As you might imagine that balance of production and clearance determines how much you accumulate. Many of the new genes are also affecting production and clearance of amyloid but they are also pointing us to the immune system of the brain. This is the fastest growing set of genes and that's not surprising because like I said that 3rd component after the amyloid and the tangles is inflammation, which is part of the brain's immune system. So, you're seeing an increasing number of genes involved with the brain's immune system and inflammation. When we put this all together, our goal is to learn from these genes, how to predict the disease so we need to do early prediction so we know who is at risk. This will require much better genetic privacy laws in this country than we currently have. Right now you are protected against discrimination from health insurance and employment based on your DNA sequence and your genes but you are not protected in terms of life insurance, long term care, long term disability. So we need more work there because eventually what's called the personalized medicine or pharmacol genetic approach will allow us to eradicate this disease. We use these genes to predict early who has the disease with reliable testing. We have to ask how these genes work together. And then if you are at higher risk, you might want to do early detection bio-markers, imaging that can detect that Alzheimer's is on the way even before there are any changes in cognition. So, pre-symptomatic changes. And most importantly, if you know you're at higher risk, if it looks like you're on your way to Alzheimer's, you want to be empowered with the therapy that would stop the disease before there are even symptoms and it's my guess that the information from these genes both the original 4 and the newest ones that would teach us how best to prevent this disease before it even strikes. So, that's the optimism for the future. Now, I haven't gone into specific therapies and things you may have read about in the papers in terms of how we are tackling Alzheimer's but if you have any questions in particular about stories you've read about Alzheimer's or genes and new findings or any new drugs, feel free to ask. But I'll stop there so we can get some questions asked. Thank you very much for your attention.

George Vradenburg: Thank you very much, Rudy. That was very enlightening and very frightening. The notion that in fact we are beginning to accumulate this beta amyloid in our brains at age 40 is a striking thought for those of us over 40. As you know, and as the folks on the call no doubt know, this is a particularly important time in the history of our challenge against Alzheimer's. Last week, a draft national plan on Alzheimer's was release by the Obama Administration that set as a National goal, the prevention and effective treatment of the disease by 2025. The Obama Administration reallocated $50 million of additional funds this year against this disease on top of the $450 million of resources available to the NIA, the National Institute of Aging for this disease and he has proposed $80 million in additional resources next year. The World Heath Organization just last week called Alzheimer's a public health priority for the globe. So this is a particularly opportune time for people to get involved because there is genuine, growing political will to

identify a path to stop this disease by 2025. I just ask anyone on the call. If you want to get involve in advocating against this disease, please press one. At the end of the call, we will have a little more of an update on policy developments.

First question I want to ask actually came in before the call from Gail. I've heard that daughters inherit more of their genes from their father. Is this true? And if so, do you find that daughters are more likely to have Alzheimer's if their father has the disease than their mother, or I might add vice versa?

Dr. Rudy Tanzi: Well, in fact every daughter has exactly 50% of their chromosome DNA from the mother and father. So, they don't inherit more of their DNA from fathers. It's only the case where a son may have slightly more DNA from the mother because the mother gave the son the X chromosome and the father gave the son the Y chromosome and Y is smaller than X. But other wise no that's not true. It is true that females get Alzheimer's more that males, even after you adjust for life span, but it doesn't matter so much about which parent transmitted the disease. There was one study from a colleague of mine from Germany that maybe when father's passed it on to daughters it was more likely to be passed on but that did not hold up and that was a study from over 15 years ago but that did not hold up in subsequent applications.

George Vradenburg: We have a question here from of all places, Bountiful, Utah from Susan. Susan, do you want to ask your question because it goes to the very question that Rudy was talking about of nature versus nurture.

Question: I... Can you hear me?

George Vradenburg: Yes, I can.

Question: Yeah, my question was just if you, if the gamma secretase inhibitor. Let say that drug was not successful and let say that the beta amyloid theory didn't pan out with all these drugs that we have in clinical trial thing and that did happen. Is there any kind of out of the box thinking with regard to research. I know that Mark Smith in California or not in California. He taught at Case Western Reserve University. He thought that beta amyloid was the result of the body protective mechanism, or something like that, and he didn't think that the beta amyloid was the cause of the disease. He thought it was a result of the disease and he was killed by a hit and run driver and so his research didn't continue. So, I just wonder what you thought about that.

Dr. Rudy Tanzi: Well, Mark was a very good friend of mine and it's terrible that he passed. He was a great scientist. Actually both things are true. All the genetics teaches us, I mean 4 different genes coming from 4 different angles, all have in common excessive accumulation of beta amyloid triggering this disease - even Down's syndrome patients with an extra copy of the APP gene make more beta amyloid and get the disease. Some people are born with a duplication - they have 3 APP genes rather than 2, they get the disease. There's no doubt from the genetics that amyloid triggers the disease but we are also like Mark Smith found that amyloid is made in the brain for good reason. We found it plays a role in protecting the brain as part of the brain's immune system. In fact, when the immune system of the brain is turned on, the amyloid beta protein is turned on and you accumulate more. It acts as an anti microbial peptide. Mark's idea was that the amyloid was

helping to seal off vessels that were hemorrhaging. That has not really held up in subsequent studies but it was the right idea but the wrong function and there are many who still against the amyloid idea but I don't think you can say that because those drugs failed, the amyloid is the wrong target. The genetics is just too strong. It's just the wrong drug but with that said, one scary notion is that once amyloid triggers tangles you may know that the tangles then spread. They can spread...

Question: Yeah. Yeah. They are doing the Neuron Mapping. Dr. Seeley in California is doing the Neuron mapping where he showing how it spreads

Dr. Rudy Tanzi: That's right.

Question: Based on how... Yeah.

Dr. Rudy Tanzi: Yes, that's right. So, we may need to think about stopping the amyloid accumulation very early so that's again, why early prediction, early detection is so important. We also will need a drug that can stop the tangles from spreading, maybe an antibody. And in fact Cure Alzheimer's Fund is funding a lab in Pennsylvania for doing that. Making an antibody that stops the tangles from spreading. So, I think we do have to think out of the box. I think if you hit amyloid the right way and you do it early enough, you will have the equivalent of a statin for Alzheimer's, the same way we hit cholesterol. You don't want to turn cholesterol off but you need to dial it down to a safe level to lower your incidence and risk for heart disease. The same thing here with amyloid, you don't want it to turn it off. I agree with Mark Smith. You don't want to turn it off. You need some but you want to turn it down but I think all the genetics and everything we know says that amyloid is one way to trigger this... is the way to trigger Alzheimer's disease. Now, you can get tangles without amyloid but it's not Alzheimer's then it's frontal temporal lobe dementia. So, for it to be Alzheimer's as originally described, the amyloid comes first, triggers the tangles then the inflammation. So, if you want it to nip it in the bud, you would hit the amyloid.

Question: Do you think that if we find...

George Vradenburg: Susan. Thank you very much. We have a number of people in the queue. So, I think I'd like to go on to the next questions. I hate to interrupt and cut you off but there are number of people that have questions. Our next question is from Nancy Olsen. Nancy, would you please pose your question to Dr Tanzi.

Question: I'm wondering if, I'm confused about the rule of mild cognitive impairment in relationship to Alzheimer's disease and genetics. Is mild cognitive impairment a doorway into Alzheimer's?

Dr. Rudy Tanzi: Yes. Mild cognitive impairment is another way of saying the very early stage of Alzheimer's disease, that almost, you know, just beyond what is called the prodromal stage. We needed a term for a disease that wasn't quite disease yet. So, people like Ron Peterson and John Morris started these terms that can define a state of cognition where you're not, you know, you can still go to work. You can still function. You don't really have disease yet but you're going down hill. It turns out that you know, if you have, if you're diagnosed with MCI (or mild cognitive

impairment) over about a 6 to 7 or maybe 8-year period. It's over a 90 % chance that then you will proceed to Alzheimer's disease. So, I would look at it as an early form of Alzheimer's and in terms of genetic involvement for MCI, it's going to follow the same rule as how genes either cause or predispose to Alzheimer's disease.

Question: Okay. Thank you.

Dr. Rudy Tanzi: You're welcome.

George Vradenburg: Thank you very much, Nancy. Our next question is from Chris Carter from the society for Women's Health Research. Chris, would you please pose your question to Dr Tanzi?

Question: My question. Hi, Rudy.

Dr. Tanzi: Hi, Chris.

Question: Nice to hear from you and this has just been again and always so informative. My question is this. In terms of the ApoE story. I understand that the e4/e4 combination when you inherit that allele from both mother and the father is the most sort of deleterious situation and confers a risk of about 12 fold over the normal allele but my question is this, are pharmaceutical companies looking at only this combination or are they also looking at the e2/e3 combination which you mentioned is essentially a protective combination against the development of the disease. So, is pharma actually looking in that direction as well as in the direction of, you know, the worst-case scenario?

Dr. Tanzi: I don't have evidence that pharma is doing much of that. I know, but in the academic sector, there is a quite of bit of research on the difference between an e2/e3 versus an e4/e4 and one other thing we know is that if you're 2/3, you clear amyloid from the brain much more readily than in an e3/e4 or especially an e4/e4. So, if you looked at the risk alleles for ApoE, the protective allele e2 seems to actually give you more clearance than usual of the amyloid from the brain. The common allele 3 is neutral and if you have this 4 allele and one or two copies. One copy, you clear less well and two copies even less than that. Now when you get older, it also appears that ApoE can play a role in the rate of aggregation of A beta. Where 4 makes it aggregate more, 3 still actually makes it aggregate if you have a lot of it but again 2 comes out clean. 2 actually prevents the aggregations. So, Apo E is involved with both the clearance and the aggregation rate of amyloid in the brain and unfortunately, I don't know of a lot of pharma work in this area of trying to take advantage of ApoE for drug discovery. It may just be kept quiet but a lot, most of this is going on in the academic sector. And again this is another reason why we need federal funding, foundations because some of the most important seed work is not happening in pharma and you really need to get it going in the academic labs.

Question: Thank you so much.

George Vradenburg: Thank you very much for your question. I'd like to turn to Sherwin Lehrer of the Boston Biomedical Research Institute has a questions relating to over the counter medications. Sherwin?

Question: Yes. Thank you. Sorry for the background noise. It's the Lexington Patriot Day Parade. But any case, I have a question about, are there certain over the counter medications like curcumin and green tea extract which are not very soluble in the blood stream and I wonder if there are any studies or any way to make them more soluble and still get through the blood brain barrier to do it's job?

Speaker : Yes. So, you correctly state that curcumin although, you know, if you use it in cells in a petri dish, you can lower the amyloid beta protein production. Curcumin doesn't really get into the brain. We are working in collaboration with Bill Klunk at the University of Pittsburgh as part of a Cure Alzheimer's Funds sponsored project to make drugs that look like curcumin but allows them to get in to the brain. So, these are curcumin like compounds that can get into the brain and we are testing them for the ability to lower amyloid beta proteins and the goal is to come up with one that can lower amyloid beta protein as well as curcumin but get in to the brain and safely try to control amyloid beta protein levels and we're making progress there. We actually have some compounds that do it but of course it's a long way from that to getting them safely into a clinical trial. As far as green tea goes, a colleague of mine, an ex-trainee of mine actually, Tae-Wan Kim at Columbia has been doing something similar with the active ingredient in green tea that acts as an anti oxidant which is also very helpful in curbing some of the inflammation and the damage from inflammation in the brain and he is making compounds that mimic the green tea chemicals that again would be able to get into the brain. He's now at the point of testing those in animal models. We'll be testing our curcumin-like compounds in animal models pretty soon as well and that's just the tip of the iceberg. There are many other folks who are doing similar studies.

George Vradenburg: Thank you, Sherwin for your question. Our next question is from JS Hurley who has another question relating to diet and to statins. Mr or Mrs Hurley please ask your question.

Question: Yes. Thank you very much. I'm particular interested in lower carbohydrate diets as they relate to insulin and as they relate to the fact that most older people in America have anywhere from 55 to 60 to 70% of their calories from carbohydrate foods and what is the effect of lowering that to a probably 10% of your in-take. It would reduce the insulin level and also be closer to a diet that have been done in some studies.

Dr. Tanzi: Well, it's an interesting idea, I mean, I think the first thing to state is, you know, just simple caloric restriction in what we know, I mean, of course carbs are high calories and so are fats and it's often the question is it high fat or high carbs that matter for disease. In Alzheimer's disease, if you put a mouse on a low calorie diet, just caloric restriction and this is the mouse that, you know, we have given them the Alzheimer's gene mutations so they are getting Alzheimer's, you have about as strong an effect on lowering the amyloid, the Alzheimer's pathology with a caloric restriction protocol as you would with most drugs that have been tested. Also, exercise does the same thing. If you just give the mouse a running wheel and a big cage, you can get reduction. And we've done these experiments were you give them a big cage, running wheels and you also put them on caloric restriction and you get a tremendous synergistic effect of lowering pathology. Now, the mechanism behind that is it through insulin? Could be, it could be through insulin signaling because we know from aging research, you know, work from people like Cynthia

Kenyon that the insulin signaling path ways are directly related to life span and health span in lower organisms. So, it's a good bet that insulin is involved in that process but we don't fully understand the entire molecular pathway yet.

Question: And I guess my other question was with the statins that have been so widely prescribed for the last 20 years. Is there any possibility that may have contributed demyelinating some of the nerve fibers in the brain?

Dr. Tanzi: You know, it's an interesting question, I don't know of evidence that statins would increase risk for Alzheimer's. If anything, there have been studies that say that statins can protect against Alzheimer's because high cholesterol diets can increase amyloid beta protein production and so there have been numerous studies coming out one after another when they say, we see protections from statins or they say we see no effect. I haven't seen a study that says that statins make it worse but, you know, in terms of myelination, it is something to consider that one of the class of drugs that is really hot right now is beta secretase inhibitors. Beta secretes is the enzyme that makes that first clip to release the A Beta from the APP. The second clip is gamma secretase. Well, beta secretase is necessary to make myelin in the brain. So, I'm very worried about the safety, just like we... the field forged ahead with gamma secretase inhibitors only to put the breaks on them when it wasn't safe. I think with beta secretase, we need the same caution because in this case beta secretase will directly affect myelination. So, I'd be more concerned there.

Question: Thank you very much

George Vradenburg: Thank you for your question. Before this call, I had told Rudy that I thought that the questioners would be very intelligent, but not expert, and I clearly misread the audience today. These are extraordinarily insightful questions.

Dr. Tanzi: They're fantastic questions.

George Vradenburg: Our next question is from Amy Duffield from Cary, Illinois. You had a related question actually.

Question: Yes, I did. It had to do with insulin. I was wondering how much has been found out about how insulin affects beta amyloid processing and if any work has been done researching the mutations of the glucokinase gene with respect to Alzheimer's?

Dr. Tanzi: Right. So, it's unclear, I mean, you know, about this trial where insulin was being spritzed in the nose and it was a small trial, I think it was 100 people or so as a preliminary trial but there was some, you know, there were enough promising result to say it would be worth doing a larger trial. I think the jury is out in terms of how insulin would work. On one hand, insulin could just increase, could just effect the glucose utilization. When synapse activity is down in the brain, and this is what really if you're ask what correlates with the degree of dementia in Alzheimer's it's loss of synapses. So, if you were to somehow spike up the activity of the synapses that are there then you'll create a more aware patient. I received I don't know how many e-mails and letters of folks who say when I give my father with Alzheimer's ice cream or candy, he seems to be normal for about 5 or 10 minutes. He comes back around. So, I don't know how much of the insulin effect

is due to simply a higher spike of energy or whether the insulin is doing something specific to amyloid. Now back in 2000, my lab published a paper in science showing that the insulin degrading enzyme, so you might have guessed that's the gene that makes the enzyme that breaks down insulin, that it carried mutations leading to Alzheimer's disease, very rare one's, and that same gene can carry mutations leading to diabetes as you might imagine. So, we have actually gone through all of our, we've tested every gene in the genome with these various genome chips. So we went through and just did what is called a hypothesis testing set around insulin to ask if any other insulin related genes show association and we didn't find any. So, we came up empty on the insulin related genes beyond insulin degrading enzyme but I think, you know, tracking how insulin affects this disease is very important. I don't know if it's necessary going to affect it at the level of amyloid beta protein. My guess is it's more along the way of synaptic activity in glucose utilization but again, this is a guess and we will have to see as more data come out.

Question: Okay. Thank you.

Dr. Tanzi: Sure.

George Vradenburg: Thank you for your question, Amy. Next question is from Rosie Goering in California. Rosie, could you ask your question please.

Question: If there are any studies out there now available for someone who is still well like me. I'm 60, almost 69. I have a history of 5 starting with my grand father, my mother, my mother's sister and now my sister and a cousin with Alzheimer's or who have already passed away in most cases and so of course I'm very concerned and I have tried to do some looking on my own on the internet and so forth and phone calls. Is there any study? I mean, I would be really willing to be somewhat of an experiment with new drugs but I haven't been able to find anything like that.

Dr. Tanzi: Yeah. Again, as I mentioned earlier it would depend on the age at which those in your family got the disease.

Question: It's all beginning in their early 70's. My mother had it about 10 years, died at 86. My grand father died the youngest at 71.

Dr. Tanzi: So that, you know, that looks like, you know, it's more of a modest to moderate genetic effect. Many of the studies that could use family members who are well from families where there is clustering of the disease as you describe are looking for those where the disease strikes very early. Because the genetics there is more robust and you can be more sure that as specific person is either not going to get the disease because they lucked out on that 50/50 chance or they are going to get the disease. In the 70's and 80's because you have multiple risk factors combined together, the only study that would be potentially applicable are those where they are looking for folks who are already complaining of forgetfulness. Not even MCI but just what we called benign forgetfulness where someone is getting forgetful but it's not enough to even say mild cognitive impairment and then you would track that person to see if they convert to MCI into AD. But if you're perfectly well and you're in a family with on-set at that age, I don't know of a whole lot of studies that would be able to make use of your situation but I do admire the fact that you are willing to step up and if something does come up, I'd be happy to try and let you know.

Question: You just mentioned something about lifestyle under for adult late on-set. Could you expand just a little bit on that?

Dr. Tanzi: Well, the risk factors with life style, head bangs, any trauma to the brain, mini strokes. So, you might imagine, if you have risk factors like cardiovascular disease, diabetes, metabolic diseases that increase risk for strokes. These will create end results that can turn on the brain's immune system and make amyloid. Head bangs will also increase amyloid production in some cases a severe head bang like these athletic concussions or a blast injury in the war can allow you to bypass the amyloid and go directly to tangles because the brain get so shaken up that the nerve endings get frayed and you form tangles immediately. So, the way we think about it is in Alzheimer's it's decades and decades of amyloid accumulation that slowly triggers the tangles and traumatic brain injury can cause the amyloid to increase but you can also have a severe case in fact we have a paper in press in one of the science journals where we look at soldiers from Afghanistan and Iraq where with blast injury, they instantly get tangles because the brain, you know, it's like jelly inside of the skull gets shaken up so much that the synapses get frayed and you make tangles and you get to dementia immediately. This happens with boxers and some football players as well. So, the thing is to protect your brain. You know, you don't want insults to your brain, the way to help your brain and keep it healthy is again like anything else, diet and exercise. Even moderate exercise everyday, even just walking and a low calorie diet, not in so much based on what you're eating but just eat less of it is the probably the best advise. And stay intellectually engaged just doing this phone call, getting new information, making new synapses will protect the synapses you have.

Question: Thank you very much.

George Vradenburg: Thank you very much Rosie. Jamie Tyrone from California. Jamie, would you ask your question please?

Question: What an honor it is to be speaking with you Dr Tanzi. Thank you so much. My question is in relationship to genetic knowledge with APO 4 alleles and whether this information is helpful and whether or not you feel that genetic counseling is necessary before one finds out their ApoE status?

Dr. Tanzi: Yes. I mean, I wouldn't recommend one, you know, go after their ApoE status for Alzheimer's simply because Apo E4 is not sufficient in its self to predict risk. So, you can carry one or two copies of e4 but we're still trying to determine, I mean actively determine, what are the other gene variants that either exacerbate the risk of Apo E4 or mitigate the risk and when we find genes in our genome screens like the Alzheimer's genome project, we find both protective genes and risk conferring genes. When I say genes, I mean gene variants, all the genes are fine. It's just the variants of the gene that matter. So, it really depends not just on your Apo E status but what did you inherit together with your E4 that you might have inherited other variants that mitigate that risk and so we have people in the 80's and you know, with 2 e4's who are fine.

Question: Right.

Dr. Tanzi: So, my fear is that you might get a genotype back of 2 e4's but you know, you don't know what the rest of the deck is and you might worry needlessly...

Quesiton: Well and thank you so much about that you have this opinion regarding this because I do have 2 copies of Apo 4 allele and I found out about it with not really full disclosure I felt from an informed consent process.

Dr. Tanzi: I know many with the same story of accidentally finding out that they have two e4's and saying, oh my God what do I do and you know...

Question: Well, yes and I have actually been diagnosed with PTSD from it, but on the other hand the good thing about it is that I am a lab rat and that's positive thing that has come from it and so, you know, I question in my mind about you know whether this is good information or not. But the stress behind it has quite unbearable to say the least but…

Dr. Tanzi: Yeah.

Question: It has motivated me to be involved in research and actually tomorrow it will be official I start my own non for profit. So, this is a good thing from that aspect but it has been very stressful.

Dr. Tanzi: Well, yeah, I know others with a similar story. They may have gone somewhere where they do Apo E because it's also a risk factor for heart disease right? E4 is also a cardiovascular risk factor. So there are many fake plug places and just go ahead and quickly do an Apo E test instantly for heart disease but then you find out you have two e4's you go to the web, and you say wait a minute what's this Alzheimer's thing going on? And the thing is, look we have E4's, double E4's, who are quite old and fine. So, it is not guaranteed like those early on-set genes but I tell you what, if I had 2 E4's, I would probably be exercising more than the next person, keeping my calories down, doing whatever I could in terms of trying to stave off this disease more than the next person. Now, is that worth, you know, because you can just do that, is it worth knowing your E4 status? I don't know, I would say if there was a safe drug that you could take, you know, then I would say, even if E4 is not the whole story. It's a part of that story, just knowing you have an E4 get on this drug. My own situation, I have a heart disease in my family, right? So, I'm taking a statin just prophylactically because it's a safe drug I can take and I watch my diet and exercise and if we could do the same for Alzheimer's and then I'd say find your E4 status. For now though, I think your questions is really illustrating one of the biggest issues in the genetics of Alzheimer's and I really thank you for it and I wish you the best of luck.

Question: Well, thanks.

George Vradenburg: Thank you very much, Jamie. Last question today before we finish up with just a quick sort of program note so to speak. Phil Choban. Phil, would you please ask your question?

Question: Yes, Good afternoon. Hello, George. This is Phil in Cleveland and I'm back by the way too. So, okay. Doctor, my wife was actually diagnosed at age 44. So, she was early on-set and she's part of the Dian, I should say the Dian study also. I'm just wondering with the genes and everything, do

you feel in the future is there going to be something in the research line that may be able to alter the genetic aspect of this particular disease?

Dr. Tanzi: So, with the early on set genes, you know, the majority of mutations for early on-set Alzheimer's whether it's on the APP, the presenilins one or presenilins two. Most of them increase the longer form of the amyloid beta protein, what's called the A Beta 42 versus the more normal, more common form of it in the brain is A Beta 40. A Beta 42 makes the amyloid aggregate more and it's tougher to get out of the brain. So, that's what most of those mutations do. So, the gamma secretase drugs, the gamma secretase modulators that we're working on, others are working on, that selectively block gamma secretase from clipping APP. The question is, will they work when you have a mutation an early-on set mutation in APP or an early on-set mutation in the presenilins because remember the presenilins are the active form of the gamma secretase. The presenilins genes make the active part of the gamma secretase enzyme. So, if you have mutations and presenilins with APP for early-on set. Will this gamma secretase modulator still work? And I'm happy to tell you that although are drugs are still, you know, a year or two off from getting to clinic that we recently found out that our gamma secretase modulators still work when the early on set mutations are there and it was a pleasure for me to deliver that information to some of the families I know who have these mutations because it says well, while the mutations unavoidable, you know, you're going to be making more of this A Beta 42 more readily getting the disease, here's a drug that will still work even if you have that mutation, so that really was a great day that we got that information and I'm hoping that drug can be used early enough in life with folks who have that mutation should it work so that we can prevent the disease from striking even in those with this hard hitting early on-set mutations like your wife.

Question: Great. Thank you.

George Vradenburg: Thank you very much Phil. Dr Tanzi, thank you very much.

Just a couple of closing remarks. If any of you who are on the phone want to help us fight to find a cure for Alzheimer's, please press one on your phone to let us know that you'd be willing to help and we'll be in touch with you. We need your involvement. This is a critical moment in the fight for a cure for Alzheimer's.

Tomorrow is the last meeting of the Advisory Council to Secretary Sebelius making our recommendations of what should be in a national plan. Secretary Sebelius will receive those recommendations together with a draft plan which has been prepared by an inter-agency working group of 22 different government agencies and departments. That will be presented to her in the coming weeks and she is expected to promulgate the first national strategic plan against Alzheimer's between May 10th and May 14th.

On May 14th and 15th, the NIH is convening a global Alzheimer's research summit at NIH to begin to identify the gaps in our national and indeed international portfolio for research against Alzheimer's and to begin to prioritize where we ought to apply additional resources going forward. So even as the Obama administration has set a bold plan of stopping the disease by 2025, even as the research community is beginning to develop the global research plan, we need to fight to assure the congress provides the funds that Obama has requested and in coming years builds

rapidly the resources needed to fight this disease and to get a means of prevention and effective treatment by 2025. So, again, if in fact you are willing to join us in this battle, please press one on your phone and let us know that you want to get involved and we will be in touch.

Again, thank you for participating in Alzheimer's Talks and again we are grateful for the support of Jill Lesser a board member of our organization that made this call possible. This is the 2nd call in a monthly series where we will discuss all types of topics from genetics to international coordination to gender differences in the disease. I hope you will participate in these calls and share the information with friends and colleagues. Please stay on the line if you would like to record a message for us or have any other ideas for what we ought to cover in future calls for Alzheimer's talks. Thank you for joining us today. Thank you Dr Tanzi for what has been a very enlightening and insightful conversation and good luck in your research. We're all counting on you.