Alzheimer's Talks Edited Transcript

A brain-protecting protein with Dr. Bruce Yankner

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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 today. My name is George Vradenburg. The Co-Founder of USAgainstAlzheimer's and the Chairman of the Vradenburg Foundation. USAgainstAlzheimer's is an organization my wife and I founded with some close friends about 3 1/2 years ago committed to stopping this disease.

This afternoon's call, we are very pleased to have Doctor Bruce Yankner, who I will introduce in just a second. But Doctor Yankner's work has clearly stimulated a lot of interest, we have 350 people registered for this call today from 43 states as well as the District of Columbia and interestingly from the Netherlands, Germany and India. We have over 1,300 people who can't make it this afternoon but have asked affirmatively that they be provided information about the call and we will do so and they will have access to a transcript after the call. So a great deal of interest.

USAgainstAlzheimer's, just as a word of introduction for those who are not acquainted with us, is a disruptive and relentless movement committed to ending Alzheimer's, our goal is by 2020. We're driven by the suffering of millions of families around the world and in the United States, although our personal passion is driven by the loss of my mother-in-law, Bea Lerner, about 20 years ago. We work through six different affinity networks: WomenAgainstAlzheimer's, AfricanAmericanNetworkAgainstAlzheimer's, LatinosAgainstAlzheimer's, ResearchersAgainstAlzheimer's, ActivistsAgainstAlzheimer's and most recently last week we announced ClergyAgainstAlzheimer's representing multiple faiths of the clergy who this fall will be writing a book called Seasons for Caregivers, a book of meditations.

We've catalyzed change by collaborating with those who are ready, willing and able to join in this movement to reduce barriers and speed new innovative solutions to Alzheimer's and dementia to market. In addition to our networks, we work through two convened coalitions, Leaders Engaged on Alzheimer's Disease which is now a 68 Alzheimer's serving organization coalition by advocating a unified voice in a unified manner to the whole movement to policy makers here in Washington and in industry and in the scientific field. The second convened network is the Global CEO Initiative on Alzheimer's Disease which is now 15 organizations from Takeda in Japan to Roche in Switzerland and everyone in between, including banks and home care agencies, all of whom are bringing business to the

commitment to stop this terrible disease. And so you can see that we work in a collaborative passion to bring all the forces that are needed to find a solution to this problem - the great transcendent moral cause of our time - stopping Alzheimer's.

I want to thank you all today for joining us to learn about exciting new research from Doctor Bruce Yankner. He is a Professor of genetics and neurology at Harvard Medical School. He is also the Director of the Harvard Neurodegeneration Training Program and Co-Director of the Paul F. Glenn Laboratories for the Molecular Biology of Aging. He has studied extensively the molecular basis of brain aging and today we are very fortunate to have Doctor Yankner with us to discuss his work particularly his research into a novel protein called the REST protein, nicknamed the REST protein. It's been featured a great deal in the media and is a significant step forward to uncovering the mysteries of how to understand Alzheimer's and how it is that we can derive new potential pathways to stop this disease.

Just as a reminder for those who are not familiar with the call, if you have a question at any time during the call, please press star 3 on your phone. By pressing star 3 you'll be placed into the question queue, please have your question ready to share briefly with a member of our staff and then we will try to get you live with Dr. Yankner as soon as we open it up for questions.

Doctor Yankner, thank you very much for joining us today. Thank you for the research that you do that helps us to try and understand this damn disease and to end it. And we appreciate your willingness to spend some time with us today and to describe your research.

Dr. Yankner: Thank you George. I'd like to start by thanking USAgainstAlzheimer's and George Vradenburg for giving me the opportunity to talk to you today about our work and to participate in this important discussion.

I'll just start off by articulating the primary questions that motivated this direction of research and give you a brief history so you can see how we got to where we are today. I think this is actually a partial history of Alzheimer's disease research in the last 20 years.

So the primary questions are 'why is Alzheimer's disease a disorder of the elderly?' You never see it in your kids or in people in their 20's except in the case of very rare mutations. A second question is 'why some people live to be over a hundred with completely intact cognitive function, whereas others develop dementia decades earlier?' In addition, sometimes these two groups can show a similar degree of pathology, namely the amyloid plaques and neurofibrillary tangles, yet one person becomes demented whereas the other doesn't. Why is that? This is a central unanswered question.

So early in the 1990's when I was just starting off in my research career as a young assistant professor, we were involved in research on the role of the amyloid-beta protein in Alzheimer's disease. Amyloid-beta is the major constituent of the plaques. We discovered that this protein can be toxic to neurons in the brain, and just about the same time it was found that there were genetic mutations in the gene for amyloid-beta which caused Alzheimer's disease in some families. This gave rise to the so called amyloid hypothesis which has been a dominant force in Alzheimer's disease research. About eight years later, I came to the realization that despite all the information we had about Alzheimer's disease genetics and

pathology, we really knew very little about the initiating factors that give rise to the sporadic late-onset form of Alzheimer's disease which affects more than 95% of the population. It occurred to me that this might be due to a gap in our understanding of basic mechanisms of brain aging that might predispose this disease. So at that time, we initiated a study of the genetic changes that occur in the brain as people age. We found that there was a signature of gene expression changes in the brain that characterized the progression from the 20's to the 30's to the 40's all the way up to people who lived into their 90's or 100's. This was also subsequently found by a number of other research groups. And it was very interesting because many of the genes that changes were known to be important for essential brain functions such as learning and memory, but there was no clue as to why these changes occurred in a normal aging brain in the absence of Alzheimer's or other neurological diseases.

More recently, about five years ago, new computer software tools became available which enabled us to look at changes in thousands of genes and implicate the proteins that might regulate these changes. It was actually this kind of approach, the basic computer informatics analysis that led us to the REST protein. The analysis predicted that REST could potentially mediate many of the gene expression changes that occurred in the aging brain. Now this was a little hard to believe at first because the REST protein did not have a known function in the adult brain. It had been shown to be very important in the development of the fetal brain and it may play a role in cancer, but these functions were supposed to be mostly turned off in the adult brain. So we embarked on a series of biochemical and genetic experiments in human and animal brains, which showed that as the human brain ages, the REST protein starts to come on again. And the cell type in which it is most highly expressed is the neuron, the brain cell that transmits electrical impulses. Furthermore, we observed that REST is expressed at a very high level in the brains of people who live into their 90's or 100's and are intact cognitively. But people who show mild cognitive impairment, an early stage of memory loss, show reduced levels of REST, and people who develop Alzheimer's disease have very low levels. What's more, we found that this reduction in REST protein also appears in other neurodegenerative disorders that are accompanied by dementia, namely one called Lewy body dementia and another called frontotemporal dementia, which are among the most prevalent causes of dementia in the aging human population.

So we then asked what does this mean? REST functions as a transcription factor, that's a fancy term meaning that it is a protein that turns genes off or on. In the case of REST, it turns them off. And it does this in association with a number of other proteins by leading those proteins to a particular gene and turning it off. By doing an extensive molecular genetic analysis, we found that in addition to the REST targets that had been previously defined in the fetal brain, in the adult brain we had evidence that REST was turning off genes that are involved in cell death and the pathology of Alzheimer's disease, namely genes that contribute to the generation of the amyloid plaques and neurofibrillary tangles. What's more, REST turned on genes that promote resistance of the neurons to stress and toxic insults. In other words, when the REST was there, you would predict that neurons would be more resistant to a variety of toxic insults, and would be more robust and resilient.

To test this hypothesis, we knocked out the REST gene in a mouse model and cultured neurons from the brains of these mice. We found that they were much more vulnerable to a variety of stresses than were normal neurons that express REST. Furthermore, if we let mice age without the REST gene, the mice had

normal numbers of neurons when they were young adults but gradually lost neurons as they aged, which appeared to die off in the parts of the brain that also are affected in Alzheimer's disease. It turns out that REST is somewhat conserved in evolution and in the the roundworm, C. elegans, there are proteins which are similar to REST.

We then collaborated with a colleague here at Harvard who is an expert in worm genetics, Monica P. Colaiacovo. We obtained mutant worms, which had lost the function of their REST-equivalent genes. We found that these mutant worms were much more sensitive to oxidative stress and the amyloid-beta protein than normal worms. And when we introduced the human REST gene into the mutants, we were able to restore their resistance to these stresses. Interestingly the worm REST-like proteins were also expressed in neurons. So it was analogous to what we observed in mammalian systems, providing additional evidence that when the REST protein comes on during aging, it is most likely protecting the brain.

We then wanted to know how the REST protein was becoming re-expressed in the aging brain. Specifically, what are the molecular signals that are inducing it? This is an important question from a therapeutic standpoint if we want to eventually increase REST in patients with cognitive decline. We found that when neuronal cells in the brain are subject to various stresses, they communicate with each other using a set of signaling proteins called Wnts. The Wnts, in turn, activate other molecules that eventually turn on the REST gene to make more REST protein that can protect the cells. It was remarkable that a few cells could be stressed, and like a school of fish sensing a predator, all the cells would turn on REST in unison and become more resistant to the toxic stimulus.

Then we asked, what is it about the Alzheimer brain that's reducing the REST protein and interfering with its function? In normal cells, when the REST protein is turned on in response to stress, it's made in one part of the cell, the cytoplasm, and is then transported to another part of the cell, the nucleus where the DNA is situated. Once in the nucleus, REST interacts with specific genes and affects their expression. We saw something different in Alzheimer patients. In Alzheimer's disease, REST appeared to be diverted from its path to the nucleus and instead was routed to a compartment of the cell called the autophagosome, which is basically a cellular trash can that helps to clear out debris the cell wants to get rid of. REST was sent to autophagosomes together with other misfolded proteins. In Alzheimer's disease, we found the REST protein in autophagosomes together with the amyloid beta protein, which is a misfolded protein that accumulates abnormally in the disease. In another neurodegenerative disorder, frontotemporal dementia, we found REST in autophagosomes together with a modified form of a protein called tau that is misfolded in this disease. And in a third neurodegenerative disorder, Lewy body dementia, REST appeared in autophagosomes together with a different protein called alpha-synuclein, which is misfolded in this disease. These observations suggested that protein misfolding in a variety of different diseases of the aging brain may result in loss of REST function, potentially making neurons much less stress resistant.

An important question is whether changes in REST directly impact cognitive function in the aging population. To explore this, we collaborated with David Bennett who runs the Religious Orders Study. This is a longitudinal study of clergy who are evaluated extensively by memory and other neurological

tests every year while they're alive, and after they die their brains are donated to science. We asked whether REST levels in the brain had any relationship to memory test scores measured each year. We found that the level of REST in the brain was correlated closely with memory scores, particularly for a type we call episodic memory, which is autobiographical memory for events, places and time. Episodic memory typically declines very early in the course of Alzheimer's disease, and REST levels were closely correlated. We then performed an analysis, which to me was one of the most interesting in our study. It addressed a basic conundrum in Alzheimer's research, which is that some people can die with brains that from a pathology perspective look every bit like Alzheimer's disease yet these people never showed evidence of dementia. We carefully examined the brains of these people and compared them to the brains of people with the same pathology who did have dementia and a diagnosis of Alzheimer's disease The brains of the people with intact memory function had about three times more functional REST protein than people with dementia, despite similar pathology. This is intriguing, because it raises the possibility that some people are able to resist the deleterious effects of the plaques and tangles, and that REST might be part of the defense mechanism. If we could mimic this defense mechanism in a drug, we might be able to delay or prevent the memory loss of Alzheimer's disease. And finally in the last part of the study we investigated people who achieved extreme longevity, people who lived into their 90's or 100's. Interestingly these extreme agers had the highest REST levels, particularly in parts of the brain that are affected in Alzheimer's disease, whereas parts of the brain that are relatively resistant to Alzheimer's disease, such as the cerebellum, were unaffected. Since that time we've done additional studies, which are not yet published, that are consistent with the idea that REST might promote longevity. We are excited about that.

So I'll stop at this point and open the forum up to discussion.

George Vradenburg: Well, I got to tell you I'm fascinated by this. Part of what fascinates me, aside from the actual results that you're getting, is how in the heck you can see all these processes? Are you using imaging, what is it that enables you to detect these changes and levels and where in the brain they're occurring? I'm just curious as to the tools that you used to get after these very complicated, very sophisticated, and very clearly described processes that you've discussed.

Dr. Yankner: We used several complimentary methods. To localize where the protein was located in the brain we used antibodies against the REST protein that are visualized using fluorescent tags. We added the antibodies to brain sections or to cells in culture and we image it on a high-resolution microscope that enables us to see down to the single cell level. What's more, we can see within the cell to determine whether REST is in the nucleus or in other parts of the cell. To biochemically assess the protein we can isolate the nucleus from the neurons in the brain using a machine called a fluorescent activated cell sorter and detect the REST protein and genes with which it interacts. Finally, we can take samples of brain tissue or cells grown in the laboratory and measure the levels of REST using biochemical methods.

George Vradenburg: The intriguing notion is that somehow in an Alzheimer's affected brain, there's a diversion of the work of the REST protein, and as you say sent to the trashcan of the brain rather than to

protect against the encroachment of beta-amyloid or tau. So do you have a hypothesis about what is happening there that causes that diversion to occur?

Dr. Yankner: Our leading hypothesis is that when proteins such as amyloid beta build up and start to misfold, they activate the autophagy waste disposal pathway. There is evidence of this in many neurodegenerative diseases, including Alzheimer's, frontotemporal dementia, Huntington's and Parkinson's disease. We hypothesize that REST interacts with what is called a cargo protein that is activated when autophagy is turned on, and the cargo protein keeps REST from getting to the nucleus and instead shuttles it to the autophagosome.

Now the second part of our working model is that some people can overcome this diversion of REST from its normal destination whereas other people can't, and that might depend on the absolute levels of REST protein that they make. If you have enough REST protein, the diversion of some of it gets to autophagosomes may not be a problem, but if your levels are borderline you may not get enough to the nucleus for REST to function properly. One possibility is that there is a genetic component to how much REST people make.

There are likely to be multiple factors that influence this, but the ultimate outcome may be depend on the absolute amounts of REST and its associated proteins that get into the nucleus. This may influence how resilient that neuron might be in the face of toxic insults.

George Vradenburg: Oh I think there's a question that's come in that actually now asks the immediately next relevant question. So, Karen would you like to ask your question of Doctor Yankner?

Question: Yes, my question is, do we know of any intervention whether it's nutrition or targeted drug or whatever that would boost the levels of this REST protein so that all of us could have this resilience?

Dr. Yankner: This is an important question. In our paper we show that there is a drug which is used in the human population, lithium, that for 50 years has been the primary treatment for manic-depressive illness, bipolar disease. Lithium boosts REST levels by activating a molecular signaling pathway that also appears to be increased in the aging human brain.

We also found that a drug made by Chiron, which acts through the same pathway, has a similar effect on REST levels. These findings suggest that increasing REST levels is possible using known drugs.

The issue with lithium is toxicity, especially in the elderly population. Notably it causes tremors and toxicity to the kidneys. So the blood levels have to be very carefully monitored by a physician Lithium should not be used at this time for Alzheimer's disease. But lithium may be a prototype for drugs that might act the same way but with less toxicity.

As for nutritional supplements, we don't have any data on this topic. One relevant point is that what REST does is it turns genes off, and it does that by coordinating a number of processes one of which is called DNA methylation in which the chemical structure of the DNA is changed. B vitamins, particularly folic acid and vitamins B6 and B12, are involved in this process and they also prevent build up of homocysteine, which is a byproduct of this pathway. When the pathway is not functioning efficiently

homocysteine accumulates and that has been thought to be a risk factor for heart disease and possibly Alzheimer's as well. So it is possible that the B vitamins might augment REST function, but this remains to be demonstrated. There was a recent study done in the UK, which suggested that people who were given vitamin B12 and folic acid supplements had a reduced rate of brain shrinkage with age. There's normally some brain shrinkage that occurs with age.

George Vradenburg: Thank you very much, Karen. That's a great question that stimulated a great response.

Our next question. Carolyn Redmon, would you like to please ask your question of Doctor Yankner?

Question: Yes, is there a test or some means to determine if the REST protein has been turned on?

Dr. Yankner: That's an important question and we're actively working to address it. It would be great if there were a blood test that could tell us whether the REST protein has been turned on or is in the early stages of getting turned off to let us know if this is a person in which an intervention should be started.

REST is expressed outside the brain in almost every cell. But we do not yet know whether the expression in those cells mirrors what is happening in the brain. We are about to begin a study in which we are collaborating with a group that is doing brain imaging of people at very early stages of cognitive decline and is also obtaining blood samples from those individuals. And we're going to ask exactly your question. Do REST levels in blood cells parallel what's happening in the brain? Of course we can't assay the REST in the brain because those people are alive. But the functional imaging can provide a sense of what is happening structurally to the brain, and neuropsychological testing on the patients can give you a sense of how good there memory is. The goal will be to determine if there is a correlation between these three measures – REST, structural changes in the brain and memory.

George Vradenburg: Is that the A4 Study or is it ADNI?

Dr. Yankner: It is part of the A4 study that's being led by Reisa Sperling.

George Vradenburg: She was our most previous guest on this Alzheimer's talks and she's going to do another one this Fall.

Can you tell how far in advance of symptomatic presentation of Alzheimer's or other forms of dementia the REST protein is turned off? That is, if you were able to find the signal that says that the REST protein was being turned off. How far in advance of symptoms might that be?

Dr. Yankner: The data that we published recently shows that people who have mild cognitive impairment, which antedates Alzheimer's disease, have reduced REST levels. So we suspect that REST levels fall quite early in the course of cognitive decline, but we can't say how early at this point. Now, if we are lucky and can assay it in blood, then we would be in a position to assess that because the A4 study will look at normal aging individuals enabling us to follow individuals this over a longer time span.

George Vradenburg: We have our next question here from Marilyn, Marilyn Diina from New York. Marilyn, could you ask your question please.

Question: Thank you for taking my call. My question is this, how is this discovery going to benefit the sons and daughters, the grandchildren, the great-grandchildren of patients with Alzheimer's currently, in terms of how soon can we expect this research to benefit us? I'm worried about myself, I'm worried about my brother and sister, my grandchildren, my great-grandchildren I don't have yet. I'm worried about how to prevent this from happening to us. Maybe that sounds selfish but I don't want my kids to have to see what I'm witnessing with my mother.

Dr. Yankner: No I don't think that's selfish. I think it's a societal question and one that every person should be worrying about.

By way of background, the RAND Corporation completed a study last year on the cost of different diseases in the United States and surprisingly Alzheimer's disease came out number one, exceeding the costs of cancer or heart disease. It's predicted by the year 2050 that Alzheimer's will cost about 1.3 trillion dollars a year in the US, and might contribute to the bankruptcy of Medicare if nothing is done about it by that time. And it will entail enormous suffering, because the incidence is predicted to triple by that time. So this is a concern that every single intelligent person in the Western world should have at the top of their mind.

Unfortunately, I can't give you a good answer to that but I can say this, that sometimes progress is surprisingly rapid in medicine. Before this talk, George and I were discussing the incredible progress that was made in AIDS. When I was a medical trainee, it was thought to be incurable and intractable, but within 10 years it became a chronic disease with many HIV positive people living a normal lifespan. So the time it takes to affect a disease is hard to predict. However, I'm very encouraged. I think new ideas about Alzheimer's disease are emerging from many different areas of research. This is an incredible time for biomedical research, a renaissance of sorts. New genomic tools are becoming broadly available to many laboratories enabling rapid progress and important discoveries. But it is also one of the most difficult times because of the constriction in federal funding of research. So I think your question is a very important one and to tell you the truth, I think the best approach to accomplishing this goal is to actively lobby your congressman or senator about the importance of providing more Federal support to the NIH.

George Vradenburg: Dr. Yankner, we're going to sign you up as an advocate.

Just for the audience's information, the levels of Alzheimer's research investment by NIH have been historically at around 450 million dollars and last year or this current fiscal year is now 550 and next year we anticipate it will be 650. Now, compare those numbers to what we spend annually for cancer, at close to six billion dollars a year, or HIV/AIDS, which is close to three billion dollars a year, and you see that the differential in terms of investment in brain disease generally or with respect to Alzheimer's and dementia more specifically is way out of kilter. So that, if you measure it in terms of the impact on society, numbers of people with the disease or at risk for the disease, or the cost to society we don't have our priorities straight. We haven't been able to adjust our priorities to the aging population and to

the chronic diseases of aging but we work on that. And Dr. Yankner, we're going to get you on the next plane down here.

We have question here from Laura Murphy, which I think is an excellent question. Laura?

Question: Thank you doctor for doing this very important research.

Dr. Yankner: You're welcome.

Question: My question is, is there a link between the ApoE4 genotype and decreased levels of this protein in the brain?

Dr. Yankner: That's an interesting question and we're working on that as well. We don't have a definitive answer at this time. But we are using a new technology called genome engineering that enables you to edit the DNA code. We have to change the ApoE4 gene, which is the risk gene for Alzheimer's disease, to the non-risk variant the ApoE3-gene and we're doing that in neural stem cells from human patients, cells that can give rise to any cell type in the brain. And we're going to see the consequence of that genetic change in multiple biological areas relevant to the disease.

George Vradenburg: This is somewhat more general question along the same line from Connie Nolan from Kentucky. Connie?

Question: Thanks for taking my call doctor. And it's a very general question because when I was listening to your explanation of the REST protein, you talked about so many different things but what jumped out at me was that there possibly is a genetic component. I along with thousands of others have had parents die of this horrible disease so we're just clinging to every word that you say. I'm wondering what we can do?

Dr. Yankner: I think there are things that you can do right now, based on the knowledge we have from epidemiologic studies that look at large numbers of people and determine populations that are more prone or less prone to getting the disease. There are several studies which suggest that the Mediterranean diet may lower the risk of Alzheimer's disease compared to a typical western diet which is higher in saturated fat and processed sugar. I think a reasonable approach is to try to emulate the Mediterranean diet which is high in fruits and vegetables, low in saturated fat, and high in omega-3 fatty acids, which are present in fish and certain plant based foods such as walnuts, flax seeds, and so forth and especially to keep refined sugar at a minimum. The second intervention supported by a number of studies is regular exercise. And I think there's also evidence for a third arm to this lifestyle approach which is mental health. I think those three interventions: diet, exercise and mental health are something any person can undertake at this point and they are all supported by scientific evidence.

George Vradenburg: There was a recent study released at the International Conference of Alzheimer's Researchers called the FINGER study, coming out of Scandinavia, in which there was a systemic look at a combination of five behavioral interventions over a course of several years and there was a marked decreased in the incidence of Alzheimer's in those people who, as Dr. Yankner suggested, pursued a low-fat, low-sugar diet, who exercised, who through social interactions and cognitive training were mentally

active and who otherwise, engaged systematically in reducing their cardiovascular risk factors, hypertension, anxiety and stress. And so there is a series of things that you can do, that anyone can do as Dr. Yankner's pointed out today, at virtually any age will be helpful in reducing your risk for cognitive decline.

Just a reminder again, if you have a question during the call, please press star 3 on your phone. By pressing star 3, you'll be placed in the question queue and you'll get on the phone with Dr. Yankner.

Karen, you wanted a follow-up question about vitamins?

Question: Yes. Thank you so much George and thank you so much Dr. Yankner. Your work has given me great hope because up until this point, I've seen a lot of work that's focusing on the amyloid and tau protein hypothesis and it's almost as if the drug companies are married to this and when things don't work out they go back and say we just have to start earlier. But this seems to be something that's outside that box and that is very hopeful. I had a question, you mentioned lithium and the problem was with the toxicity but there is a lithium orotate, I believe and lithium aspartate that you don't even have to check blood levels but I don't know if it's effective as lithium and I don't know if you've done any work with that.

Dr. Yankner: That's a good question. We have not looked at lithium orotate. I am aware that there are a number of different lithium salts that might have differing toxicities due to blood concentrations and other factors. But we have not looked at this issue in terms of their ability to activate REST so I can't comment, but I think it is an interesting possibility.

George Vradenburg: All right. Joyce Stoops, question from Richardson, Texas.

Question: Hello. I was just trying to figure out how do you spell REST?

Dr. Yankner: It spelled the way it sounds, REST.

Question: Okay. Thank you very much. That's all. I've been writing it. I just want to make sure I was writing it correctly. Thank you.

George Vradenburg: Dr. Yankner, what does REST stand for or is it just a nickname you've given to this protein?

Dr. Yankner: It is an acronym that stands for RE1-Silencing Transcription Factor. It is meant to indicate that this protein silences genes that have a specific code or arrangement of DNA called the RE1 motif.

George Vradenburg: Okay. Thank you.

Dr. Yankner: You're welcome.

George Vradenburg: We have a call here from a woman named Trish. She shares my last name so I think it's wise for me to call on her, Trish Vradenburg.

Question: Thank you, Mr. Vradenburg. When you talked about things you can do like exercise and diet, we know that Alzheimer's is in your system though it doesn't present itself for twenty years. Is this something you can do if it's already in your system to stop or reverse or do you have to have caught it before it started?

Dr. Yankner: I think the consensus view is that the earlier you start intervening the better. I don't think there's a good answer yet to how long before disease onset it is possible to effectively intervene. The study George referred to, looked at people at a somewhat earlier stage when they may have some cognitive impairment but not enough to be classified as Alzheimer's disease.

Question: So basically it couldn't hurt.

Dr. Yankner: It can't hurt. None of these things can hurt because it is established that the first two interventions, diet and exercise are at the very least good for your heart.

Question: Okay. Thank you.

Dr. Yankner: You're welcome.

George Vradenburg: We're next going to go to Margaret Howard from Nevada. Margaret, would you pose your question please?

Question: Yes, doctor. I'm wondering if you can speak about the possibility that Alzheimer's and sleep apnea may be related? I know that there is a study that's new, I think that is going on at NYU about the possibility of these two being related. I'm wondering if you know anything about that? Has it been going on or is this something brand new?

Dr. Yankner: I'm not aware of an association between Alzheimer's and sleep apnea. There is an association between sleep apnea and a number of other medical issues: cardiovascular for example, but I'm not aware of a clear association with Alzheimer's disease which doesn't mean there isn't one. So unfortunately, I can't comment on that.

George Vradenburg: Which makes all of your other comments much more credible.

Nanette McCoy from North Carolina. Nanette, could you ask your question please?

Question: Yes, sir. Nice to meet you. I appreciate your work. I just lost a mother in January, to end stage Alzheimer's as a registered nurse...

Dr. Yankner: I'm sorry to hear that.

Question: ...it destroyed my life. Seven years into it. But I was using anti-inflammatories like turmeric and also incorporated coconut oil into her diet and I saw a change in her cognitive level. What is your opinion on Dr. Perlmutter's diet, the Grain Brain, and diabetes linked to Alzheimer's and use of supplements like alpha-lipoic acid in lion's mane. I know the B-12, the vitamins, the B-vitamins also helped when I gave them to her but coconut oil...

Dr. Yankner: So I'll start with the most well established association of those you mentioned which is between type 2 diabetes and Alzheimer's disease. It used to be thought that the two were distinct and any overlap was due to the fact that the two conditions are prevalent in the aging population. But now it's thought that there really is a predisposition to Alzheimer's disease from type 2 diabetes as well as cardiovascular risk factors such as hypertension.

Coconut oil is interesting. There are anecdotal reports of Alzheimer's patients who have been given coconut oil with dramatic improvement in cognitive function. From what I've read I can't ascertain how long lasting those improvements were and how well documented in terms of objective testing. One has to be very careful about this; sometimes people tend to see what they want to see, which is why rigorous clinical trial are performed with the investigators blinded and in a large enough population to get meaningful results. There is a clinical trial of coconut oil in Alzheimer's disease, which has recently been started, and there should be some results in about a year's time but there's no data yet. It's believed that coconut oil might act in an interesting way in the setting of Alzheimer's. The main fat in coconut is what's called a medium-chain triglycerides. And these get broken down in the body to what's called the ketone bodies. It is believed that the utilization of glucose is not very good in an Alzheimer's brain because it's a little bit like a diabetic cell in that it's resistant to insulin – the hope is that ketone bodies derived from coconut oil might bypass this block. But this has not yet been established and the caveat about coconut oil is it is very high in saturated fat and might pose a cardiovascular risk factor. Turmeric is interesting too. Tumeric is a commonly used ingredient in Indian food. It is a potent anti-inflammatory and anti-oxidant agent, which has been shown in Alzheimer's mouse models to reduce both pathology and improve cognitive function. However, I'm not aware of any studies in humans yet that have validated this intervention for Alzheimer's disease. At least for turmeric we know from a whole continent using it in food that it's pretty safe.

George Vradenburg: All right. I think we have time for one more question here and I'm going to ask John Speigel of New Jersey. John could you ask your question?

Question: Hello. Thank you for taking my call. I'm actually a biology undergraduate. I'm planning to pursue a PhD in neurobiology so I've been thinking of your results in a mechanistic basis, trying to understand it that way and I was wondering - so when you found out that the levels of the REST protein increased with aging presumably that's in response to some factors biochemical or biological that accumulate over time aging signals. So I was wondering if you investigated whether the different levels of REST in different aged individuals comes from different responsiveness to some of these signals and whether it might be possible to metaphorically reduce the signal, to try and promote increased expression of REST.

Dr. Yankner: One signal that we have identified is related to what we call the Wnt signaling pathway. Wnts refer to a set of related growth and differentiation factors that are released by cells. They have many different effects. In the brain they appear to up regulate REST, and we have evidence that the same cells in the aging brain that have more REST also have activated the response molecules involved in the Wnt pathway. An interesting possibility is the one you mentioned, which is that some people may be more sensitive to these signals than others leading to higher REST levels under stress related

conditions. And in fact we believe this is the case that there's a host of genes that impact the REST response, the REST network if you will. Some of this variation may be genetic and some environmental, and may come together to influence greater or lesser effectiveness of the REST pathway, potentially influencing predisposition to Alzheimer's disease.

George Vradenburg: Thank you very much Doctor Yankner for joining us today and for answering so many questions about this really very important and, as I said earlier, well described and clearly described research.

And thank you all for participating in this Alzheimer's Talks. In about a week we will have a copy of this recording and transcript on our website for you to share with your friends. If you did not register for this call and just called in but would like a copy of the transcript then go to our website in a week or otherwise at the end of this call simply by staying on the line, you can leave your e-mail address so we can send it to you. If you did register for the call, you'll be sent a copy of the transcript.

I hope you'll join us for the next Alzheimer's Talks, that conversation will be on Tuesday, August 12 at 1:00 pm Eastern with Doctor Sandra Bond Chapman. She is the Founder and Chief Director of the Center for Brain Health at the University of Texas at Dallas and the author of Make Your Brain Smarter. She is doing fascinating work with victims of TBI and other brain injury in finding ways to increase their cognitive brain power and I think she will have a most interesting presentation staving off and slowing cognitive declines generally and help from injury and disease is really her critical focus and she is doing some path-breaking work down in Dallas and obviously with implications for us all.

As always, please stay on the line if you would like to leave us a message with a question or comment. We are particularly interested in what you would like to discuss on future calls, so reminder just stay on this line after we hang up and just leave us a message if you'd like to get in touch with us, ask us any questions.

And for those of you who want to follow Doctor Yankner's advice and get in touch with your Congress people, sign up to USAgainstAlzheimer's if you haven't already because you'll be getting an e-mail every couple of weeks with very precise Congressmen, Congresswomen and Senators to e-mail, to actually affect things that are going on, on the hill. Although Congress is about to go on vacation for five weeks and so there will be nothing happening in Washington but it will pick up again in September. So please sign up for e-mail reminders on how you can easily get in touch with your member of Congress or other members of the Administration.

Thank you all for joining us today and have a good afternoon and finally Doctor Yankner thank you again for your research most importantly but also for spending time with us today. Take care.

Dr. Yankner: Thank you for your interest.

George Vradenburg: Bye-bye.