Alzheimer's Talks Edited Transcript
A Major Breakthrough – Alzheimer's in a DIsh
with Dr. Rudy Tanzi

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The following transcript has been edited for content and clarity.

George Vradenburg: Welcome to Alzheimer's Talks and thank you all for joining. My name is George Vradenburg and I am the Chairman and Co-founder of USAgainstAlzheimer's. I'm so excited to have Rudy Tanzi today as our guest to discuss his groundbreaking new research, which has made headlines everywhere from the New York Times to Newsweek and really around the world. I'm also excited because Rudy Tanzi is one of the founding members of the Rock Stars of Science which is a group of musicians who are scientists, including Rudy and Dr. Francis Collins who leads the NIH but Rudy is a very, very talented song writer and musician. So he is a 'crossover artist' shall we say from the Hollywood speak.

For the purposes of today's call, Rudy has led the team that's been able to replicate Alzheimer's outside the brain, nicknamed cleverly 'Alzheimer's-in-a-dish'. Dr. Tanzi has plans already to quickly evaluate more than 6,000 existing drugs, a goal that would have been absolutely out of the question just a few months ago.

USAgainstAlzheimer's is a disruptive entrepreneurial organization committed to stopping Alzheimer's. Alzheimer's as you all know, everyone on this phone, is a grave and growing menace to each and every one of us, to our families, to our kids. An estimated 44 million people worldwide living, or should I say dying, with dementia - more than AIDS, cancer or chronic heart disease, more than a hundred million secondhand victims, the caregivers. In the coming decades, the numbers of those dying from Alzheimer's and those caring for them is expected to triple. We've committed to try and stop Alzheimer's by 2020. We mobilized and catalyzed change through collaboration with those ready, willing and able to join with us and tearing down the barriers impeding path of therapies, treatments, and ultimately cures. We co-convene 70 organizations in a coalition called Leaders Engaged on Alzheimer's Disease virtually every organization of the Alzheimer's serving community in the country, the unified voice of Alzheimer's, and we've also served as the convener of a major patient-power industry coalition called the Global CEO Initiative on Alzheimer's which has been quite active with Prime Minister Cameron in moving the G7 and the G8 to taking on Alzheimer's as a global cause.

We have over 2,500 people today either registered and on the call from 48 states plus D.C., Puerto Rico, several countries around the world including Canada, Italy, Switzerland, or signing up to receive the summary materials we generate because they couldn't make the call today. So we send them a copy of the recording, transcript, and key takeaways. We'll also e-mail that to everyone on the call today who's provided their e-mail address. So this call, Dr. Tanzi's work is proving to be very popular or at least very intriguing and mysterious and people definitely want to learn more about it.

Thank you so much for joining us today to learn more about Dr. Tanzi's exciting work. Remember if you have a question during the call please press star 3 on your phone. By pressing star 3 you'll be placed into a question

queue, please have your question ready to share briefly with a member of our staff. We'll try to get you on live with Dr. Tanzi as soon as we open it up for questions.

It's my pleasure to introduce you to Dr. Tanzi, one of the leading researchers in the country on Alzheimer's disease. He is the Vice Chair of Neurology at Massachusetts General Hospital in Boston and the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School. And we actually have an online streaming option, so if you're listening to us online you can type your question in the box and we'll try to get to as many questions as possible after this opening discussion with Dr. Rudy Tanzi of Mass General and Harvard.

Rudy thank you so much for joining us and we'd love to hear about your Alzheimer's-in-a-dish research.

Dr. Rudy Tanzi: Well you're very welcome George and thank you for having me and thanks to all of you on the phone who are listening as I sit in the comfort of my office and look out at the Boston Harbor today.

I want to tell you about the Alzheimer's-in-a-dish but I really want to put it in perspective of the history of Alzheimer's and where we're going and I'll probably be pretty emphatic about where I think we need to go next in terms of how to prevent and eradicate Alzheimer's disease.

Everyone on this call has an interest in this disease and most likely knows that this is the most common form of dementia in the elderly and that after age, the greatest risk factor is family history, and after that insults to the brain, physical insults like traumatic brain injury, neurovascular events like stroke or mini-strokes, to some extent even emotional trauma and cortisol that can kill neurons. If you're killing neurons in the brain, you can start to induce some of the pathology of Alzheimer's disease is what we're learning more and more.

Much of what we knew about this disease originally, in the early part of the last century, was that there are amyloid plaques outside of neurons, there are tangles that form inside the neurons, and there is inflammation. Those are the three boxes: plaques, tangles and inflammation and just to tell you upfront that I think what we're learning form genetics is - you can start in any one of those boxes and drive the rest of the pathology, it's a vicious cycle. Inflammation and white matter disease can lead to acute phase injury and amyloid and tangles. In other words, these pathologies lead to each other. In most cases of Alzheimer's we see amyloid first but you can have tangles first, for example from head bangs or playing terrible helmet-to-helmet concussion seasons of NFL Football. There are many ways to get tangles. I'm going to argue from the Alzheimer's-in-a-dish, that amyloid is the most common way over time that we get tangles and then the disease process begins. I'm going to argue that amyloid is the match that lights a fire called tangles because the tangles spread through the brain and that in response to that fire as neurons die is inflammation and this gets this vicious cycle in full gear and that's when a person who starting this pathology will slip off that slope and begin dementia.

Now most of what we learned originally about Alzheimer's disease in the 80's and 90's started with George Glenner at UCSD and he suggested then that Alzheimer's was an amyloidosis of the brain that amyloid accumulates in the brain and this causes the rest of the pathology. So this was the beginning of the amyloid hypothesis. And he didn't add a lot of plaque boxes, he said look I study amyloidosis, amyloid forms in the brain and tangles and inflammation is all coming from that, that was his hypothesis. And then I and others used his amyloid-beta protein sequence to find the gene, we call it the amyloid precursor protein, not a very imaginative name but it tells you what it is, it makes the amyloid. And then later in 1995 working with folks like Peter Hyslop and Jerry Schellenberg we found the other early onset familial genes called the presenilins and somewhere around that same time at Duke in 1993 Allen Roses and his colleagues found ApoE. Those are the

first four genes APP, PSEN1, and PSEN2. and ApoE. And what we learned from those genes what they had in common was that they lead to the excessive accumulation of beta-amyloid in the brain. That means the amyloid in plaques, also amyloid in small clumps called oligomers that can interfere with synaptic activity.

So as a result, most of Pharma and biotech and academia have focused on trying to stop the amyloid and they tried to either turn the amyloid production off or they tried to clear the amyloid from the brain and that's when we saw lots of therapies come and go, they fail and in some cases the amyloid therapies that failed just weren't great drugs, they weren't very potent like Flurizan or they weren't very safe like the gamma secretase inhibitor that Lilly had in trials. Others failed we think perhaps because it was too little too late. We've learned since then from imaging studies that amyloid is accumulating in the brain 15 to 20 years before symptoms. By the time a patient is even in the early stages of cognitive impairment, amyloid has begun to plateau. So if you're simply trying to treat a patient who has full-blown Alzheimer's disease as they were doing in trials, as we're still doing in trials, by hitting amyloid, I compare it to having a patient who just had a heart attack going to a cardiologist and the cardiologist says, here just take a Lipitor, just take a statin. You had to do cholesterol management 15 years before; I will argue that we need to do amyloid management 15 years before.

If we go through some of the amyloid therapies, some of the immunotherapies, Bapineuzumab didn't do very well, Gammagard, but Solanezumab from Lilly, Crenezumab from Roche, in both cases in the mild cases of Alzheimer's there was some benefit suggesting that maybe they could be used more in a preventative way and there's a trial going on called A4 for Solanezumab and I supposed you may see the same for Crenezumab. My own thought about this, and this is my own opinion, is that if we're going to have a statin for Alzheimer's where let's say at 40 years old you do imaging for amyloid, which is FDA approved, it's not covered by insurance but you can get it done, and you see excess amyloid in your brain, then you say well I need to start managing my amyloid just like if you have a cholesterol test and you see too much cholesterol. My guess is that if you need to take a therapy for 40 years, the way some people would take a statin to decrease risk of heart disease, I'm guessing is probably going to be a safe small molecule. I just can't predict whether the body could handle 40 years of an antibody, an immunotherapy. So I've always been a fan more of little white pills than biological therapies and there you have three to think about. You have gamma secretase modulators, this means drugs that stop the production of A-beta by hitting gamma secretase but you don't stop gamma secretase from doing its job that caused all the side effects in the Lilly trial. You modulate gamma secretase only against APP and I'm working on drugs like that with Steve Wagner. The Cure Alzheimer's Fund, a very forward-thinking foundation, has funded our gamma secretase modulator work. One of those molecules is from the original stock that's going into phase 1 and we're hoping that another one that we think is quite potent and hopefully safe, will be going into phase 1, hopefully next year. So that's one way, there are also many companies Merck, Eisai, and Novatis, AZ, Roche working on beta secretase inhibitors. That's the first enzyme that clips to make A-beta. Now there I'm a little more concerned because they're not modulating beta secretase just to stop it against the amyloid precursor protein, again they're hitting, just like Lilly hit gamma secretase inhibitor with a sledgehammer to stop the whole thing with a drug. Beta secretase inhibitors stop beta secretase activity and then inhibit the enzyme itself and beta secretase does have other substrates and it does have other things that has to clip and so time will tell whether beta secretase inhibitors will be safe to take for 40 years because when you think amyloid you're going to need a drug you will start early on 15 years before symptoms knowing you need to take it presumably because of amyloid imaging or because of other biomarkers and you need to take that for the long haul.

So the third one, and now I'll state my conflict of interest, I started a company in my lab in 1997 called Prana Biotechnology and this is a drug called PBT2 that basically prevents amyloid from aggregating and clears amyloid by interfering with the copper and zinc binding to the amyloid beta protein. We learned in a paper we published in Science 20 years ago that amyloid formation requires copper and zinc and if you can chaperone the copper and zinc away from the amyloid and get it into distribution elsewhere in cells in the brain that amyloid will be cleared from the brain. This was shown in most studies and there was a trial in 2008 in humans that showed less amyloid in the CSF after treatment. A more recent trial tried to look at a small group of patients for the ability to lower amyloid in the brain by looking at imaging of plaques and amyloid and there, it's funny, the drug actually lowered the amyloid in patients in one year but, and what I have to think is a very fluky result, the placebo group also had lower amyloid. These are Alzheimer's patients who in one year lost amyloid which is something you just don't really see very often, kind of fluky bad luck, so the drug did not meet it's endpoints because even though it lowered amyloid in the patients in the placebo group they also lost amyloid, which is unusual. But it's a small trial and I still continue to be interested in the presenilin as a potential statin. So we have this idea of maybe not giving up on amyloid but trying these drugs that could be statins and I emphasize the gamma secretase modulators, beta secretase inhibitors, PBT2 and you'll also have the immunotherapies that are in trials.

Now when you think about testing these drugs you have to think about prevention trials. Prevention trials can take five years, they can be extremely expensive by the time a pharma company is done with a prevention trial your patent life might be over. So not a lot of companies want to do this and then you get the other concern - well wait a minute I might spend a billion or two billion dollars on a 5-year prevention trial. How do I know amyloid is really the target? How do I know amyloid causes the disease? Yeah you have genetic data where those first four genes have in common excess accumulation of amyloid but where are the real data? And this is where 'Alzheimer's-in-a-dish' comes in.

For years people were using petri dishes and growing different types of nerve cells whether they be from mice or humans and trying to recapitulate, trying to recreate Alzheimer's disease in that dish. And they would put in, for example, stem cells from a patient and turn those into neurons, grow them in the dish. Maybe they could see some amyloid-beta protein floating around. They certainly weren't seeing full-blown pathology. So the question remained, was George Glenner right in 1984 when he said amyloid causes tangles. And I have an old little mini cassette tape from an answering machine that I kept to this day where I used to be friends with George Glenner, he's passed away since, and he had a very gruff voice, he smoked Marlboro cigarettes, kind of like the Marlboro man, and he left this message and he said, "Rudy it's about the amyloid and don't give up on the amyloid, the amyloid causes the disease don't give up on it". And you know I didn't and this is where we get to 'Alzheimer's-in-a-dish'. Does amyloid cause tangles? Now the earlier models didn't work and a very talented postdoc who's now a junior faculty member in my unit. He actually was originally a post-doc who trained with my wife Dora Kovacs, who's a cell biologist, came up with a very simple idea he said: You know the brain is not made of liquid, the brain is made of gel. Your brain is like jello, you're lucky your skull is there to keep it from quivering. So let's make a substance that looks like the same as jello, a gel with the consistency of the brain and have that in a dish and let's take human stem cells, put in the familial Alzheimer's mutations that we know make amyloid. Now in this case we're using lentivirus, we're using virus. We're only putting in those genes to make amyloid, we're not looking at how those genes work. We're using those genes as tools to make lots of amyloid from these human stem cells that we're going to turn into human neurons and grow them in a three-dimensional matrix of gel, it's that simple.

And sure enough when we did that in six weeks we saw full-blown plaques, just like you see in the brain, growing in 3-D. We saw a little clumps amyloid, the oligomers, and their affecting synapses. And you wait a little longer and we see the tangles. So I quickly got back to the Cure Alzheimer's Fund, who funded this work. They love to take chances on high risk, potentially high benefit work. And I said 'we did it'. I remember meeting with the Cure Alzheimer's Board and saying we have amyloid in a dish, we have plaques, we have tangles, and guess what if you stop the plaques, so if you use a beta secretase blocker or a gamma secretase blocker as a proof of concept drug and you block the plaques from forming in the dish, you don't get the tangles. So proof of concept - tangles follow plaques. And these are real tangles you can do electron microscopy on them, there's paired helical filaments, it looks like the stuff you get out of the brain. So the landmark results from this were basically first time Alzheimer's pathology from amyloid to tangles was recapitulated in a dish. But more importantly the first in 30 years proof of concept that George Glenner was correct, amyloid is sufficient to cause the tangles. Even the amyloid hypothesis as it was rephrased later in the 90's and then the early 2000's had all these asterisks. Well the amyloid has to first cause inflammation and cause this and that and that, the big black box of events and finally when the neurons about to die, now it's like the signature of the dying neurons is the tangle. Well not in this system. In this system you have neurons, you have no microglia, you don't have inflammation, you have a few astrocytes, you're basically getting directly tangles from amyloid.

What we also showed is that you can let all the amyloid you want form in the dish but if you block with this drug known as a GSK inhibitor, you can have amyloid and not get the tangles. So we're able to detach the tangles from the amyloid. So we showed that if you stop the amyloid, you stop the tangles and in some cases you can let the amyloid go and still stop the tangles downstream by blocking this enzyme GSK-3 beta. So that's the Alzheimer's-in-a-dish story and what it means is that we now have a real model for the disease. Now let me note that the animal model, the mouse model for Alzheimer's where you put the same familial genes there they make amyloid, mice make amyloid, but in response to the amyloid you get some inflammation, you get some cell death so the animals get some cognitive problems later in life, but you don't get tangles from that disease, you don't get tangles in that model. The reason is that you need a special form of the protein that makes the tangles, the protein that makes the tangles is tau, and you need a special form of tau called 4-repeat tau to make the tangles, the mice don't make it. In the dish, the amyloid causes that 4-repeat tau to be made from the tau gene and then that's the stuff that turns into the tangles. So you really recapitulate what's happening in a human Alzheimer's brain.

You can get Alzheimer's in this dish within eight to 10 weeks, full-blown Alzheimer's, and it's relatively inexpensive, we can do this in wells in a dish that now we can start screening compounds 10 times faster, 10 times cheaper and what we want to do next is take all of the twelve hundred or so approved compounds in the U.S. Pharmacopoeia, take all of the 5,000 or 6,000 investigational drugs that already made it through phase 1 that are shown to be safe but are not on the market yet. And these are the easiest ones that you can then shepherd into clinical trials and then try to get those tested. So we have a new program that Cure Alzheimer's Fund is supporting called Genes to Therapy or G2T and we'll be doing this. Well in addition to still making animal models for Alzheimer's Genome Project and not even mentioning here a whole slew of gene mutations we found new ones using whole genome sequencing and we're about to write that paper up introducing those into animal models but our goal is to get to therapy.

So we'll start with the low hanging fruits, start with the drugs that are easiest to get into trials, the approved drugs, the investigational drugs that made it already past phase 1 safety. And start testing them one after another in this, in a high throughput assay in the Alzheimer's-in-a-dish.

Now I just want to end by giving the caveat, there's always a caveat. The Alzheimer's-in-a-dish we have right now allows us to recapitulate amyloid plaques to tangles but it doesn't cover inflammation and we know when we look at brains at autopsy, sometimes you see brains full of amyloid and they came from subjects who weren't demented and in there you didn't see any tangles. We sometimes see brains full of amyloid and tangles, lots of amyloid and tangles, and they died in their 80s without dementia and what you see there is no inflammation. You need all three. You need amyloid, and very early triggering of the tangles, the tangles spread like a fire and in response to all these dying nerve cells, initially the glial cells like microglial cells try to clean up, eventually with so many dead neurons they assume there's an infection and the glial cells part of the brain's immune system overreact and start trying to kill a bacteria or a virus or a fungus that's not there because it has seen so many dead neurons and this becomes an autoimmune, in this case auto-innate immune. It's not antibodies in T cells and B cells, it's the primitive innate immune system of the brain that's getting turned on by the dead neurons by the plaques and tangles. So that inflammatory component is very important, that is not covered in the Alzheimer's-in-a-dish we just published.

However Cure Alzheimer's Fund has funded us to make other models. Now we're making a model with microglial cells to look at how they're activated and as part of our Alzheimer's Genome Project we have found the genes like CD33, another company called deCODE found TREM2. So we are finding these genes that control inflammation in microglial activation, we are going to test drugs to try to turn off the inflammation in response to the pathology as well. So that'll be a second Alzheimer's-in-a-dish that we're currently working on that will also be done in 3D.

And just one last comment, part of Alzheimer's is where the amyloid can get out of the brain through the blood brain barrier. We have another Alzheimer's-in-a-dish model that will mimic the blood brain barrier for trying to find drugs that chaperon amyloid out of the brain as well. So all in all I think we'll need a cocktail. We need to hit amyloid but if you want to hit amyloid you should do that early. And this has been for any type of drug you're going to consider for doing that whether it's the PBT2 or a gamma secretase modulator or beta-secretase inhibitors or immunotherapy, you've got to do it early. Tangles as well, that fire gets lit when the amyloid accumulates. We know that now from Alzheimer's-in-a-dish. So you've got to hit tangles and tangles are spreading early on.

And finally for patients who have this disease right now, that's still not enough. You have to curb inflammation and take advantage of these various innate immunity genes that control inflammation in the brain that have come out of the Cure Alzheimer's Fund, the Alzheimer's Genome Project. So this is what we do for a living, basically learn from these genes, make models. We're very excited that now we can make these Alzheimer's-in-a-dish models, cover these three aspects of the disease: plaques, tangles and inflammation, and start screening. Start screening quickly. And hopefully this will bring in a new era of Alzheimer's research and drug discovery using stem cell derived neurons in 3D culture. So I'll stop there and happy to take questions.

George Vradenburg: Well thank you very much there, Rudy.

Just a reminder everyone if you've got questions for Dr. Tanzi, please press star 3. Star 3 gets you into a question queue, talk to a member of our staff and we'll try and get you online with Rudy Tanzi as quickly as we can.

So if I understand this Rudy, this goes back a little less to Alzheimer's-in-a-dish, but your description of the sequence of a beta-amyloid, to tau, to inflammation, suggests that you could attack Alzheimer's by going early against, and then regulate the development of, the beta-amyloid. You could go slightly later and attack tau, or you can even allow amyloid and tau to develop as long as you found a way to inhibit inflammation, you can prevent the symptoms of the disease even though you may have this amyloid and tau pathology in your brains. Is that right? So you have multiple targets at different stages of the disease?

Dr. Rudy Tanzi: You do. That was perfect George, but then also even if you have some inflammation early on, that can get amyloid and tangles going. You can have a bang to the head that gets tangles going. So in those three boxes, no matter where you start you get that vicious cycle of all three going. In Alzheimer's, the most common root is, if you don't have lots of bangs to the head or you don't have some type of white matter disease and inflammation, you're accumulating amyloid your whole life, now after 40 years old you have to ask where am I? Just like you have colonoscopy after 50 or you check your cholesterol after 30, after 40 you ask, where's my amyloid level? Is it high for my age? And if I had my druthers and if I could snap my fingers and make something happen, it would be go to the FDA and say look, we can now see how much amyloid someone has in their brain, we can tell them together with biomarkers and the spinal fluid for tangles like phospho-tau. We can tell somebody if they're at high risk for this disease, if they're on their way and if it's being triggered by excess amyloid. And if that's the case, just like you then take a statin to keep your cholesterol down plus lifestyle changes for heart disease, then you would want to take a drug that brings your amyloid down. Now the FDA will say, well wait the minute we don't know that amyloid is really doing this, so you need to show that. Well now I'm hoping that with the Alzheimer's-in-a-dish we can say well here is the first proof of concept guys, amyloid causes tangles and that's the disease. Amyloid and tangles, cell death and inflammation, amyloid causes tangles. If that's not enough to know, that here is someone who has high amyloid levels in their brain and let's say we have a little safe small molecule drug whether it be a PBT2 or beta secretase inhibitor or gamma secretase modulator and they can take that drug and bring the amyloid down right now at 40 years old and that drug is safe to take for 40 years. Why not do it? We took that leap of faith with heart disease. We didn't wait for 10-year prevention trials with heart disease. We knew we had drugs that lowered cholesterol that they were relatively safe, there are some issues with them of course. But if someone had a problem with high cholesterol, we took a leap of faith and said, we're going to lower the incidence of heart disease by lowering cholesterol in those who have too high a cholesterol level and that has largely helped the incidence of heart disease. Now is the time to really push the same thing for Alzheimer's because we have the data from the Alzheimer's-in-a-dish that says amyloid is sufficient to cause tangles, that 30-year debate is over.

George Vradenburg: Let me ask, does everyone who has Alzheimer's have amyloid in their brain? Put aside trauma and the tau but does everyone with a pure Alzheimer's, if there's such an animal, have amyloid in the brain?

Dr. Rudy Tanzi: Well by definition, Alzheimer's must be amyloid and tangles. You can also have just tangles in different parts of the brain and it could be one of the frontotemporal lobar dementias but if it's Alzheimer's, as Alzheimer's is described it is tangles and amyloid together.

But you don't need amyloid to get tangles, you can get tangles with head bangs or other various injuries to the brain. Think of amyloid as a chronic long-term season of NFL Football, where instead of having a few concussions over a few years that triggered tangles, that then spread like a fire for 20 years in the case of head bangs lead into chronic traumatic encephalopathy as the cause of dementia in this other case long term accumulation of amyloid at some point hits a level where there's enough tangles and enough tangles spread caused by the amyloid to cause cell death and inflammation leading to dementia. That's not to say that inflammation early on can also drive the amyloid process higher in the early stages. So that's how I think we have to think about it.

George Vradenburg: So we've got some interesting and very sophisticated questions and questioners on the line. So I'm going to first call on Carla, is it Carla Danesi from East Rochester, New York?

Question: Yes, George hi, how are you? My deepest respect. Carla Danesi, Gloria Danesi's daughter. I have followed Dr. Tanzi's work for quite some time and I'm a huge fan. So I just want to thank him. I have a two-part question.

One is, now I've been following J147 for quite some time and it showed remarkable preclinical trial result. It is not, due to funding in clinical trials as of yet phase 1, it's going into hopefully shortly. Would he be able to test J147 as well? And how long will he be doing these tests because I know he said he's testing some drugs that are already in the pipeline or going into the trials into phase one already, but what about the drugs that are showing promise and are quite there yet?

And then my second part is, as I said I followed Dr. Tanzi's work for quite some time for the Cure Alzheimer's Fund and to this day, I'm unaware maybe I'm wrong, of anyone attending the National Alzheimer's Council meetings from Cure Alzheimer's Fund and I was wondering, I know Dr. Tanzi is extremely busy but either if he could attend or someone or representative from the Fund could attend, that way the lines of communications can be open with his current work. Because his work is vital to the progress of defeating the disease. So I just want to know, his thought process on that if there could possibly be a representative or if he could find time in his schedule, I know he is quite busy again but so what are your thoughts on that?

Dr. Rudy Tanzi: Can you just clarify the national meeting you're talking about, is that government, or a foundation or..?

Question: Well, George knows what I'm talking about because he's actually on the Council. It's the National Alzheimer's Project Act meeting...

George Vradenburg: She's talking about the Advisory Council on Research, Care and Services under NAPA.

Question: Yeah, that's it definitely.

Dr. Rudy Tanzi: Okay, okay. I've attended some of the NIH Alzheimer's summits, I haven't been invited to the upcoming one as of yet, I've had my say here and there. I guess all we can do as scientists is publish our data in good journals, in high-impact journals, and get it read and it's nice to have direct representation but I think data speak more loudly than anything. I'm happy and grateful for your support. I think the data here say that we have a chance now to really hit at this disease.

Let me comment on J147. I'm glad you asked it because I didn't mention a whole other class of drug. We talked about amyloid drugs, tangle drugs, anti-inflammatory drugs. There are also drugs that try to protect neurons, neurotrophic drugs. When things are going wrong they try to help neurons with growth factors like nerve growth factor or BDNF, brain-derived neurotrophic factor. And J147, it came from David Schubert's lab, is intended to induce these growth factors and help protect neurons when they're in trouble. That is a fourth class of drug that could be used in a cocktail. So I think that's a good question. I don't know much about what's happened with that drug or where it's at in trials. But I agree that is worth keeping track of.

George Vradenburg: Thank you very much. The next question I'm going to ask Karen Kaufman of Worcester, Massachusetts.

Question: Hi thank you for letting me speak to such an impressive researcher. I have a number of questions. Well I specified three. In the previous model of Alzheimer's, you're using the ApoE4 gene?

Dr. Rudy Tanzi: No we're introducing mutations that cause familial early onset Alzheimer's. Mutations in the amyloid precursor protein, APP gene, and presenilin genes. However, the human stem cells we're using can have an ApoE background. So when we do these experiments in the future, create more models, we can use, for example iPS cells some skin fibroblasts. Take skin cells turn, those into nerves cells and try ones from folks who carry E4, or one E4, or two E4's, or none and look at the differences. But we haven't done the comparison of the ApoE4 or not in the system yet but we plan to do that.

Question: Okay my question is, how would you try and block the activity of the zinc and copper in the brain without affecting the activity of those minerals in the body because those are critical...

Dr. Rudy Tanzi: Oh I see. So you're talking about PBT2, which is a drug that I've been working on for years from the company I mentioned that I started in my lab back in '97 called Prana Biotechnology. PBT2 is not a chelator of metals, it's a chaperone. Metals bounce around to wherever they have the most affinity. So the drug has a high enough affinity for copper and zinc, that when it gets into the brain, it takes the copper and zinc from the amyloid where it's being sequestered and then the drug takes the copper and zinc and brings it into the cell and then proteins that use those metals then take them from the drug. So, in fact, the drug actually redistributes those metals from where they shouldn't be, which is on amyloid, to the proteins like for example superoxide dismutase 1 that use those metals. So I wouldn't condone using chelators because you don't want to soak up those metals from the body. This is a different class of drug called a metal chaperon that keeps the metals away from amyloid so that it doesn't aggregate and you can clear it more easily from the brain and it actually puts those metal back into distribution so it does the opposite of taking them out.

George Vradenburg: Thank you very much for the question. Lance Stewart from Washington. Lance, could you ask your question?

Question: Hi thanks. Dr. Tanzi, I have a question regarding the gel, and of course it's important for a 3D neuron culture, but do you think the gel prevents the diffusion of the amyloid proteins and therefore boosts the ability to actually have them form into default plaque-like objects and in the sense that if you have the similar cell growing in liquid culture that you wouldn't see it because they would diffuse away. And also whether or not you think those plaques could form with non-familial disease mutations in this gel system.

Dr. Rudy Tanzi: Yeah great question. So yes I think that's exactly what's happening. I think that there's no magic here that if you have nerve cells growing in liquid the amyloid beta-protein floats away, it can't aggregate. The brain is not liquid, it is gel. So when the amyloid beta-protein gets spread out by a neuron in the brain, just like the scan spread out in this gel it doesn't diffuse as far. So if the amyloid gets spit out, the amyloid beta-protein molecules get spit out, they can stick to each other, they use metals to do that and they start to form these aggregates and eventually form plaques.

Now I would say that this 3D model, even though it uses the familial early-onset mutations to make the amyloid, it is applicable to any form of amyloid. I saw some blog pieces and articles saying 'oh this is just for this rare early-onset form' and that's not the case at all because what we did was we used those early-onset genes as tools. We simply use them as tools, where we put them into viral vectors, we do basically gene therapy on the stem cells to make them receive these mutations, so that they can make tons of amyloid. So we're not really studying the early-onset form of Alzheimer's in the system, we're using those mutations to create lots of amyloid in the dish wo we can ask the question, "what happens when you have lots of amyloid surrounding a nerve cell"? And in all cases of Alzheimer's disease by definition there's lots of amyloid surrounding nerve cells. We are just using these mutations as a tool to get that amyloid made and now we know that once you have lots of amyloid around neurons in a gel mimicking the brain, you get tangles. This is something we never were able to show before.

George Vradenburg: We have a question here from the online streaming from John Dwyer, who happens to be a board member of USAgainstAlzheimer's, I have to read this one: Do you have a view on whether low production of progesterone by the brain contributes to Alzheimer's disease?

Dr. Rudy Tanzi: Well there are data on progesterone, on estrogen, on androgen but what we know is that, many of these hormonal proteins have effects on amyloid production. So there are questions about whether, for example during menopause when you have low estrogen levels, is that lead into more amyloid. This is a perfect example for the 3D system, we could not test progesterone, all we could test was estrogen, 17 beta-estradiol and see what happens to amyloid levels. My prediction would be from the literature that both estrogen and progesterone would have effects on amyloid production by shifting APP into what's called the alpha-secretase pathway where you don't make amyloid. But we also have data that say that progesterone and estradiol induced the clearance of amyloid by natural degrading enzymes, that would not be as easy to test in the 3D system as it stands beause some of the enzymes that breakdown the amyloid are made by glial cells and we only have some astrocytes there. So we're making a new model that's going to incorporate the glial cells. So we can ask all of the questions regarding amyloid production and clearance and I think progesterone you'd want to ask both. That was a great question, John.

George Vradenburg: I've got a question of my own. So how did you reproduce the gel in a dish that is like the gel in the brain, number one. And number two, are there not more things going on in the brain than simply amyloid-beta and are those other things that may be simultaneous happening in the brain complicating the easy model of amyloid leads to tau.

Dr. Rudy Tanzi: Yeah, first of all for the gel we use a commercial product called Metrogel and it is supplemented with proteins that are actually made by cancer cells that mimic what is called the extracellular matrix or the ECM. The ECM helps the nerve cells to grow but the Metrogel you buy is remarkably similar in density to the type of gel that the brain parenchyma is made off.

In terms of the complexity question, in this system we asked the question, if you have neurons surrounded by amyloid can that cause tangles? Do you need a big black box of events that the amyloid cascade hypothesis from John Hardy and Dennis Selkoe proposed. And the answer was no, you don't need a big black box. The amyloid cascade hypothesis is correct in one sense because you get amyloid to tangles and is incorrect because you don't need a whole lot of events in the middle to get there. It's sufficient to get tangles from amyloid directly. The other events in the brain that are going on is that as the amyloid is accumulating in the brain, and this goes back to John's question, you also have amyloid being cleared by microglial cells that eat it up and degrade it, spitting out enzymes to chew it up. We know that physical exercise increases the number of enzymes that clear the amyloid. So you get this constant, I think it was like a kitchen sink and you have spigot that is turned on and you have a drain that's either clogged or not clogged. And as you make amyloid in the brain, it's being made, it's being turned over, it's being exported out of the brain, it's being taken up by cells and eaten. But in the end I just want to know in the case where there is too much amyloid for whatever reason mimicked in this dish, will that cause the nerve cells to get sick and make tangles and it does. And you don't have a whole lot of other black box items present to explain it, you just have amyloid, you have neurons, you get tangles. So that was a question that we asked and that's what we got answered.

George Vradenburg: So we have an online question here from J.S. Hurley: Will you be sharing samples of this dish technology so that others can do testing at the same time as you do?

Dr. Rudy Tanzi: Yeah, so here's what I would say, we don't have the time and money to become a warehouse for this. We received well over a hundred or so e-mails of people who want the system or want us to test their drugs in the system. You know people are excited about it and we're grateful for that. Like I said we're not a store, a warehouse or a retailer and we couldn't afford to provide everything to everybody, exactly as we do in the dish. What we can do is provide people with the lentivirus vectors, in other words the viruses that we use to express the mutations that allow us to make the amyloid. We could provide those to collaborators and then they could then recreate what we've done. They put them into the human stem cells, they concentrate those with the fluorescent tag, they turn them into neurons, they grow them in the gel, you know we show them how to do it in the paper and they can recreate that system in the lab. We can't recreate our system for everybody but we can at least send them the critical parts they don't have, that they can't buy which would be these lentiviral vectors to put in the mutations. Now with that being said, we've talked to a company who might want to just supply the whole thing for people; they may want to take the whole system and recreate it and send people the whole ready-made system for those who don't want to recreate it and we plan to do that, we want to just get everything out so that people, if they don't want to remake it with the vectors and they want the whole system made for them, they can get it from a company. We are not starting the company, we'll just provide the technology to the company to do that. I think that's the best way to do it because we couldn't possibly keep up with all of the requests and do this for everybody ourselves - we'd never get any work done, and we couldn't even afford to do that and I don't want to start a company to do that. So that's how we're going to handle it.

George Vradenburg: But net you're making available all the know-how associated with how to build the system for people who either want to do it or if a company wants, they could try and create it for others.

Dr. Rudy Tanzi: Yeah bottom line is all the know-how is in the paper and in the supplemental data. We might even put a video online if we have to, to make it even easier. The only thing that's not commercially available to do this are the viral vectors, the tools we use to put in the mutations so that these neurons can spit enough

amyloid out to recreate the disease. So we will provide those collaboratively to anyone who wants them. The rest of it they have to build or if they don't want to they can get the readymade system hopefully from a company who takes the technology.

George Vradenburg: I congratulate you for that, for making the know-how available and then allow people to either build it themselves or to have it be built for them.

Next question we have here is from Tina Rogers from California. Tina would you like to ask your questions.

Question: Yes, hi Dr. Tanzi. Thank you so much for your amazing work towards curing Alzheimer's and sharing your research with us. My question is two part. First, it's my understanding that the plaque precedes the tangles but you also need inflammation, you need all three to have the Alzheimer's and that some people postmortem have the tangles and plaques but no dementia and I'm guessing that's because they didn't have the inflammation?

Dr. Rudy Tanzi: That's right

Question: Okay, so given that understanding and that you are also working to recapitulate that inflammation component...

Dr. Rudy Tanzi: That's right.

Question: ... so until you do and until these drugs are approved, for say a 50 year old like myself with a dad with Alzheimer's, can I do something holistically that will minimize this inflammation and prevent overworked glial cells from causing this - exercise, fruits and vegetables...

Dr. Rudy Tanzi: Well, we say anything that is good for the heart is good for the brain...

Question: Okay.

Dr. Rudy Tanzi:... for inflammation there are lots of antioxidants that people try, you have to make sure they get into the brain. You know we heard about chocolate this week and we've heard about blueberries, there's lots of ways to get antioxidants out there. There are no guarantees, right, even curcumin we published on curcumin but the problem is curcumin is very effective in a dish but it doesn't get into the brain very well. So you may have to spend your whole life at a Indian buffet to get enough curcumin and maybe even that won't be enough. We're working on drugs that mimic curcumin that do get into the brain, for example one of our Cure Alzheimer's projects. But I think for the tangles and plaques there's some interesting data on an ayurvedic root powder called Ashwagandha. Douglas Labs sells it and we tried it and it actually seems to help, actually very much seems to help amyloid get out of the brain. As the amyloid builds up in the brain, the way it gets rid of it is either the microglial cells eat it or enzymes spit out to chew it up or it is exported out of the brain across the blood brain barrier and the Ashwagandha seems to help that happen. There's another supplement called cat's claw, it's a Peruvian leaf that's sold as an organic herb. There's data that helps block the amyloid from forming, they even help block tangles from forming. None of this stuff is guaranteed, but, for example in South India they've been chewing the Ashwagandha root for senility going back thousands of years, so it's up to you if you want to try some of these more traditional remedies.

I think the main thing to remember is what's good for the heart is good for the brain, in terms of exercise, diet, antioxidants in our diet, so omega-3 DHA, but again there is no one thing that's going to guarantee that you will prevent this disease. It's again, it's a healthy lifestyle and a healthy diet.

George Vradenburg: I have a question here on line from Mindy, who asks have you had any discussions with the FDA yet to see if they'd be open to using your discovery to just prove that basic concept of amyloid to tau?

Dr. Rudy Tanzi: I have not yet. I would love to. I plan to. Maybe George you can help me with it. But I think the FDA needs to know what this paper means that we've heard, yes well on one hand you can image for the amyloid and you know who's in trouble. Yes we may soon have safe compounds that lower amyloid but are they going to make us wait to do 5 or 10 year prevention trials before they let us start using anti-amyloid drugs in those who'd need them who have too much amyloid in their brain based on imaging. Are we going to have to wait for 5 or 10 years trials that drug companies may never do because current patent laws would say that their drugs are already generics by the time the trials are done. I mean this is a quandary and I really think that we need to rally based on these new data to say look now we know amyloid causes tangles, we know tangles kills neurons and neurons dying leads to inflammation this is the disease. That original amyloid hypothesis George Glenner put forth 30 years ago was correct. If the amyloid is too high, we need to lower amyloid, it will lower incidence of this disease. Just like we took that leap of faith with cholesterol and heart disease. I truly feel we have to push this now and any help I can get doing that I will appreciate.

George Vradenburg: I'll help you do that, we can also do it for the NIH.

I got a last question here from Ken Dychtwald in Orinda, California. Ken is also a member of our board and he's got a question.

Question: Yes, first Dr. Tanzi thanks for your science and your commitment and also your enthusiasm. It's terrific to listen to you.

Question, you talk about determination of the progression of Alzheimer's disease through checking the spinal fluid. Can you envision any simpler, less invasive approach?

Dr. Rudy Tanzi: Well I would love one. Right now we have to image for amyloid in the brain because even the spinal fluid test isn't good for amyloid. Actually you see lower levels of the A beta 42 in patients because it's getting sucked up by plaques in the brain before it can get out into the spinal fluid. What you do see in the spinal fluid is the phosphor-tau that's what makes up the tangles so the combination of seeing high amyloid in the brain with imaging and then you see the high phosphor-tau and lower A beta 42 presuming it can't get out of the brain because it's getting stuck on amyloid that's what allows you to see if somebody's in trouble 10 to 15 years before symptoms. It would be great to have a blood test that could do that and there are many, many groups who are working on a blood test that could also show us these things. I think we'll probably first see a blood test that will show us whether you have tangles because it should be possible to see a reflection of that phosphor-tau in the blood if you have a sensitive enough assay. I think it's going to be more difficult to know whether you have a lots of amyloid in the brain based on a blood test and we may be stuck with imaging for a while. But hopefully that will change.

George Vradenburg: Rudy, thank you so very much. We have a number of additional questions and a number of online questions and quite frankly we've run out of time. I think we may have to have you back, we'll wait a few months to see if we can get some more exciting stuff out of your work or at least a greater concreteness in funding for your plans going forward or something. But we're going to have you back just because of the demand of questions and comments that have come online. Many comments have come in simply thanking you for your work so you ought to know that...

Dr. Rudy Tanzi: Hey you're very welcome. And George you know, USAgainstAlzheimer's and Cure Alzheimer's Fund and other interested parties should get together and visit the FDA or other governmental agencies who can influence them and say, hey have you heard about this? We have data that we need to take this leap of faith in lowering amyloid levels.

Dr. George Vradenburg: I assure you that the NIH knows of your work because there is a senior NIH official on the line, I'm going to mention the name but I know he's on because I have seen his name.

So I just want to close this afternoon and honor people's time. Thank you again to Dr. Rudy Tanzi for joining us today and again, thank you for your commitment to finding a cure and Ken Dychtwald is absolutely right thank you for your enthusiasm, which leaps through the phone so I appreciate that.

Thank you all for participating in this Alzheimer's Talk. In about a week we'll have a copy of the recording and a transcript on our website for you to share with your friends.

Our next call will be on Tuesday, November 18th from 3:00 PM to 4:00 PM Eastern with Olivia Mastry. She is the head of ACT on Alzheimer's and she is in Minnesota, and now I believe here in the United States as whole, we're going to be helping her work on creating a dementia-friendly community, a dementia-friendly society. This is a movement that started in Japan, has picked up in the UK, and is now being taken up and announced in Canada and now other European nations and it's a completely new approach to how to assure that we in society can recognize those that may have cognitive impairment and allow them to come out into the community even with their cognitive impairments and not be fearful but also provide them support. As someone has put it - how are we going to create the equivalent of a curb cut for those who are mentally impaired? So she will be talking with us about her work in pilot communities and how we can begin to develop organizations in your community to make your community dementia-friendly.

As always please stay on the line. If you would like to leave us a message with a question or comment. We're particularly interested in what you would like to discuss on future calls. Thank you so much for joining us today. Have a good afternoon and Rudy, thank you so very much for a very clear and very spirited conversation about your research.

Dr. Rudy Tanzi: Thanks for having me.

George Vradenburg: Thank you. Goodbye.