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Alzheimer's Talks Transcript

A Conversation about the Drug Pipeline with Dr. Jeffrey Cummings, Director of the Cleveland Clinic Lou Ruvo Center for Brain Health

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George Vradenburg: Welcome to Alzheimer's Talks. This is a conversation about the drug discovery process or nicknamed the Pipeline with Dr. Jeffrey Cummings, Director of the Cleveland Clinic Lou Ruvo Center for Brain Health.

My name is George Vradenburg. I am Chairman and Co-Founder of USAgainstAlzheimer's and a Co-Convener with the Alzheimer's Foundation of America of Leaders Engaged in Alzheimer's Disease, a broad-based coalition of Alzheimer's serving organizations. My own personal connection to Alzheimer's is the death of my mother-in-law and with many of you I'm confident that once you've seen this disease up-close and personal that you, like me, will be engaged in a movement to stop it.

We want to thank you very much for joining. Just as a little introductory matter, if you have any questions for Dr. Cummings during the course of this call, at any point during the call, push star 3 and you'll be put into a question queue. That's star 3 and you'll be put into a question queue and after Dr. Cummings has made his opening comments, we will take you off mute and allow you to ask the question.

This inaugural call of Alzheimer's Talks is the first in a monthly series of tele-townhall calls that will discuss topics of interest to the broad Alzheimer's community. The calls will be presented by USAgainstAlzheimer's frequently in partnership with other organizations. Today's call is sponsored by Shawn Taylor, Trustee of KPB Corporation. Shawn's mother has Alzheimer's, both of her maternal grandparents died of this disease, so she understands the urgency of finding a cure before this horrible disease threatens her and her three daughters. We thank her for her generosity in sponsoring today's call.

As I said today we'll be discussing the drug discovery process or pipeline. What it is, why it takes 13 to 15 years and $1 Billion for a candidate treatment to go through the drug discovery pipeline, why increasing the volume and velocity of drugs through the pipeline is crucial to efforts to stop Alzheimer's. As many of you know, the Obama administration has adopted a national goal of preventing and effectively treating this disease by 2025 and has added money to this year's budget as well as proposed increases to next year's budget to advance that Alzheimer's agenda.

Again, as I introduced Jeffrey Cummings, just want to remind you if you have questions for Dr. Cummings at any point during this call, press star 3 and you'll be put into a question pipeline. We are very pleased to have Dr. Jeffrey Cummings with us today. He has ranked among the top 10 Alzheimer's researchers in the

world. He's an experienced clinical trialist and he is the Director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada. Dr. Cummings, thank you for being with us today. I very much appreciate you being here and very much look forward to your comments on the drug discovery pipeline.

Dr. Cummings: Thank you George and thank you to USAgainstAlzheimer's and to Liz and Ashley who have been working on getting this organized and to Shawn Taylor for your sponsorship. Shawn, it's really really great to have this ability to have a teletown meeting of this sort.

The drug discovery pipeline, it's an exciting enterprise but I will say it's vaguely defined. It refers to all the drugs that are currently in clinical trials and some people might include even those drugs that are working their way through animals. And we frequently hear about Alzheimer's treatment breakthroughs this is a common word and yet we don't have any new treatments and we haven't had any new treatments since 2004, approaching a decade now. So why do we have breakthroughs and there's no follow up, that's the central question that I'm trying to get at today. What happens and why do these breakthroughs not turn in to new therapies most of the time? I know this is a frustration to families. I know that we're always explaining this away to people and so I want to give you my overall perspective on this process.

The point of this lecture is not to discuss all the drugs that are in development, there are roughly 80 drugs in development for Alzheimer's disease right now, but rather to discuss this process and why the process seems so irregular. I'll use several examples of drugs or discoveries that you've heard about to try to illustrate the points and try to help you to understand the pipeline process as opposed to individual compounds. As George said, there'll be an opportunity for question and answer after I finish my remarks. I'll probably talk about 15 or 20 minutes and then I hope to have a really great discussion.

So let me give you an example. In Australia, in July of 2010, there was a breakthrough by Professor's Gotz and Ittner and this made the news, everybody who was following Alzheimer's disease research saw this breakthrough. They discovered that tau protein, one of the proteins that forms the neurofibrillary tangle, mediates the toxicity of amyloid, the other protein that we worry about in Alzheimer's disease. They saw that mice born without the tau protein had no amyloid toxicity and therefore tau must be playing a role. And they went on, they gave a drug that blocked tau and those mice did not develop any cognitive changes and that shows that tau is critically important in terms of the cognitive deficits of Alzheimer's disease and they have a drug right there which they gave to these mice and the mice got better if they were affected or never developed dementia if they were not affected. So this is a typical scenario. This is a breakthrough observation.

So what's happened since July of 2010? It's almost two years. Why hasn't this breakthrough broken through? Well, first of all academics are not generally in the business of drug development. Academic laboratories concentrate most on defining what causes Alzheimer's disease so that they were investigating this tau protein as it related to amyloid protein and to dementia but they had a compound and it blocked tau in the mice but that doesn't really comprise a drug. So what would have to happen if they wanted to make this a drug? Well first of all they just have to repeat their experiments. It turns out that 35% of the time when a scientist repeats his breakthrough experiment, he doesn't get the same result. He or she. So that's the first thing.

The second thing is you've got to test it in a different model. It turns out some models of Alzheimer's disease are much better than others and we usually start off with a model that has had one mutation inserted or present in the genome and that's the easiest. It produces the amyloid that is easiest to manipulate and if you go to a double-transgenic where the mouse is now born with two mutations, the amyloid is much more like the human amyloid but it's also much more difficult to treat, much more resistant. So a drug will frequently have a breakthrough observation in mouse number 1 but will not be effective in mouse number 2. So that's the kind of thing you would have to do.

In addition, animal models are really not models of Alzheimer's disease, they're models of one part of the process. For example, our most common model produces amyloid protein but it does not produce neurofibrillary tangles, it does not produce cell death, and therefore it is not really a model of Alzheimer's disease. Moreover, the mice are quite different than Alzheimer's patients. The mouse that is born in this setting where they've been engineered to overproduce the amyloid is dumb to begin with. So they're really affected right from birth and then they develop something that looks like MCI or Mild Cognitive Impairment and they really never become demented. So both from the clinical point of view and from the pathological point of view, our mice are not really like Alzheimer's disease. So it's not surprising that we often see an effect in a mouse that's a breakthrough observation but it's not able to be translated into human treatment. Now the reason we use the mice is because if the drug did not work in the mice then we would not advance it into humans but many drugs, in fact all drugs that have worked in mice so far have failed to work in humans.

So let's take it the other way, supposing they said yes, I'm really going to work on drug development and I want to see whether this compound that I gave to the mice and prevented the tau and the amyloid toxicity, I really want to see if this can become a drug. Well it's important that this phase of drug development is called the ‘valley of death’. And it's called the ‘valley of death’ for very good reason, it's because it is so hard to move drugs through this process. So scientist now has essentially a white powder that he has given to mice and he wants to know whether this is going to be a drug. Well we don't know whether it's even the kind of white powder that if administered to a person would enter the brain so you'll have to find that out. Also, you can never give a white powder to humans if you haven't looked for the toxicity in animals. And the FDA has very finely prescribed rules for how that animal toxicity must be done and in general it costs about a million dollars to test the required two species to determine whether a drug is safe enough in animals that it could be advanced to humans. Where does that million dollars come from? The government is very unlikely to give a grant for that. Venture capitalists are unlikely to come in because it's too early to feel like they might get a payoff from their investment. Pharmaceutical companies regard this as largely too early in the process and too risky because most white powders fail to ever become drugs. So this is the ‘valley of death’ and it's very difficult to traverse the valley. Eventually maybe you can convince what's called an angel investor who's willing to take high risk to provide some money to do a little bit more of the animal experiments, then you might be able to write a grant to get some of the toxicity work done. You can get a sense for how slow and difficult this process is in order to get what was an active drug in a mouse to become a candidate for therapy in a human being. It's called the ‘valley of death’. So very few compounds survive and most perish in the ‘valley of death’.

Now what about the drug that does traverse the Valley of Death? So now you've got a compound on the other side. Looks like it had pretty good animal safety so now you feel pretty good about that. You've been

working with this compound about a year. It now takes one to two years to finish a phase one study, these are called first in human studies. You take this white compound, you turn it into a pill, it's safe in animals and now you give it to the first human beings, they are normal healthy volunteers, usually young people who are paid to take these drugs. They are very brave, we don't know what these drugs will do and we start with extremely low doses. We give five people a low dose and one a placebo or maybe eight people a low dose and two a placebo. And then if that goes well, then you take it up to the next dose and again you give six people the dose and two a placebo and so on until you get up to what you think is a dose that might have a reasonable physiological effect. If that is safe then at what you think you're target dose is, you would then move it into a population of Alzheimer patients, a few Alzheimer patients, that will be the first affected individuals to see thise drug. In general, it takes two to three years to get through Phase 2 where you see, well does it seem to be affecting the patient in a beneficial way and also, what doses do I want to advance into the final approval process?

So when you've made those decisions it then takes two to three years to do a Phase 3 Study. So that's where the final study is done to confirm the drug effect and then prepare the drug for presentation to the FDA. If those studies go well, it's taken to the FDA; it usually takes about 12 to 18 months for the FDA to review all of the safety data, all of the efficacy data, and decide whether they are going to grant a marketing approval to take the drugs so it could be available to everyone in the world.

So if you count those years up, a few years to get the drug ready. One to two years in Phase 1, two to three years in Phase 2, two to three years in Phase 3, one to two years with the FDA in answering questions. You have a minimum of eight years and 13 to 15 years would not be uncommon so that observation that Professor Ittner and Gotz made in 2010, we wouldn't expect to be a drug until 2025.

So it's discouraging but it is the way the process works and I want you to understand the way the process works. In terms of drugs progressing through the pipeline, 95% of all drugs fail. Most of them fail for lack of efficacy, that is they don't work, but still about 30% fail because of toxicity, that is they're safe in animals but they're not safe in humans. The total cost, as George referred to in his opening remarks, is about a billion dollars to get a drug through this process that in part is because 95% of drugs fail so the succeeding drug must pay for the 95% that have failed.

So that's an example of a breakthrough observation and it didn't really become a drug. Or I suppose it's premature to say that, but you can see the difficulty of turning it into a drug. I'll just briefly touch on a couple of other things. I don't want to spend too much of my time talking here.

Let's turn to the drug rember. Do you remember rember? This was presented very strongly in the 2008 Alzheimer's Association meeting. There was tremendous fan fair. There was worldwide press. Dr. Wischik presented this as a tremendous breakthrough and it was the cure for all tau-related disorders including Alzheimer's disease. It turned out that there were many unusual features of the trial that made it difficult for the scientific community to give uncritical support to that compound. Skepticism of course made it very difficult for them to raise any kind of capital to proceed with additional trials. Four years later, there's still been no publication that put the rember trial into the public domain. There are residual concerns about safety and no reports of meaningful effects at the human level. So the future of rember is unknown. I wouldn't say it's impossible that rember will eventually be advanced. Only that you can see how

complicated a "breakthrough" becomes and you never hear about it and in this case it hasn't even made it into the literature.

Now let's take bexarotene. I think bexarotene is one of the most interesting observations. The report came out February 9th just almost exactly one month ago, this from Gary Landreth at Case Western Reserve and bexarotene is a cancer drug that he gave to mice. There was a greater than 50% reduction of the amyloid burden in one week. This is a drug that's approved for cutaneous t-cell lymphoma and therefore it's already available by prescription. Now, this is a very interesting situation to be in because we know that it affects a cancer beneficially so we know what it's side effects are, we know how to manufacture it, we know what the dose in cancer would be and we have seen that it has beneficial effects in mice. I think what's important is that we not assume therefore that it has beneficial effects in humans because I've tried to point out the many differences between mice and humans so the fact that it reduced amyloid in mice may not mean that it's going to reduce Alzheimer's disease, a different process in humans. Of course it must be tested and the great excitement about bexarotene is that because it's already available, it can be tested much more quickly and could be available, were it to succeed, in something like three to five years as opposed to eight to fifteen years.

So my point is that this is a long, expensive, complicated process with many players. It's a complex interplay between science and business and I would say that we're not looking for villains here. We shouldn't be looking to blame the pharmaceutical companies. or to blame academics, or to blame venture capital. What we're looking for are better ways to advance drug discovery.

Now there are a couple of interesting solutions on the horizon or I would say at least partial solutions. One is the creation this year of the National Center for Advancing Translational Science as part of the NIH. This is called NCATS and it includes the Cure Acceleration Network, which is designed specifically to find new drugs for patients. It's going to address the scientific issues of drug development and I think this is a really positive step forward to allow the government financing to focus on some of the problems of developing a much more timely, much more effective, drug pipeline.

I would say also that biomarkers promised to help us with drug development greatly. That is you can see a change in a biomarker much more quickly, much more reliably than you can see a change in human cognition. So if you could give a drug to people and see that the Biomarker was benefitted that might give you an answer within, let's say six months where you might have to do 18 months of human observation to see a clinical response. You could then decide in six months rather than 18 months whether you were going to advance that drug into Phase 3 so you could use a Phase 2 Biomarker outcome rather than waiting for a clinical outcome.

Finally, I just want to make a couple of observations from other fields that I think are really interesting and are the kind of thinking that I think might influence the Alzheimer’s pipeline. One is a drug called Gilenya or fingolimod for Multiple Sclerosis recently shown in a very small study to apparently have value in ALS. So they're going to take this MS drug into ALS. But of course ALS shares many of the neurodegenerative features of Alzheimer's disease. So here's an example where we might see a drug that's already approved in one neurological disease being tested in a second neurological disease and certainly we want to see that eventually moving into Alzheimer's disease. Another example is a drug called halofuginone, which I think is

very interesting. It was being developed by an Israeli company for Muscular Dystrophy, but they didn't have enough money to continue doing the work and they were going to abandon the drug. So two families simply bought the drug and they have taken it into clinical trials and it looks pretty promising at this point. So there is an example of two families taking control of the drug discovery process and trying to engineer it on their own. Another example is Kalydeco for cystic fibrosis. This was recently approved by the FDA and the reason it got as far as it did is that an advocacy group for cystic fibrosis worked with Vertex Pharmaceuticals and raised $75 Million to allow Kalydeco to be advanced and it was shown then to be effective for one form of cystic fibrosis.

So I just want to give you a sense that there's a lot going on in the drug development world and there's a lot of innovation in the drug development world with people thinking genuinely out of the box in terms of how to get drugs to patients faster and that what we want, we all want to be able to do a much better job of slowing the disease process or preventing its onset in patients with Alzheimer's disease. So George I think I'll stop my comments right there and open this up for questions.

George Vradenburg: Thank you very much Jeff.

Reminder to those on the phone, if you have a question please press star 3 on your phone and you'll go into a question queue and we'll answer as many questions as possible in the time remaining.

Just to start things off, I have a question. There's been recent discussion; this is keyed off of your comment about mice models not necessarily being predictive of reactions of a drug or a molecule in humans. There's been a recent discussion about whether or not one can use induced pluripotent stem cells taken from Alzheimer's victims themselves, reprogram them to become pluripotent. And then, differentiate it into stem cells against which one can test molecules in human cells of actual Alzheimer's victims. Is that characterization correct? If it is, how promising do you think that is? And then how would that affect the pace of the drug discovery pipeline.

Dr. Cummings: All right, George, I'm really impressed are you going to neuroscience graduate school at night or something here? I'm really impressed with your knowledge of IPS cells. And I do see this as a promising development because when you do the IPS cells, you're taking cells from an affected patient and then you can grow the cells and you can test a drug on those specific cells that are obviously related to that specific individual. Most of the work so far is done in people with mutations. So they have mutation as a cause of their disease and then you look to see whether a drug might potentially help you get around whatever blockage or whatever excess is being produced by the mutation. The great advantage of this is it promises to allow us to individualize therapy to that particular person. However, it's very time intensive, it's very resource intensive and so at this point it's still very much at the experimental level and I'm not aware of an example where we have actually predicted a successful outcome for an individual patient based on the work with that individual person's IPS cells. But I do see this as a technology that promises to get us closer to the right drug for the right patient. I think that's something that is going to reshape drug development. We've tried to give the same drug to everybody regardless of the complexities of their biology. That worked for cholinesterase inhibitors but it's not likely to work for more biologically focus compounds so I think we need to get to this whole concept of the right drug for the right patient and IPS cells are one pathway to that.

George Vradenburg: Again, if you have a question for Dr. Cummings, please press star 3 on your phone and we will put you into a question queue.

Our first question from a listener is from Sheldon Wolf at UCLA. Mr. or Dr. Wolf, please ask your question.

Question: Yes. Hi, Jeff.

Dr. Cummings: Hi, Sheldon. How you doing? Nice to hear from you.

Question: It's again a great privilege and pleasure to be your student again and I want to tell you how much we miss you at UCLA.

Now here's my question and I apologize if you covered this during the time the young lady took me out of the conversation. But the question is this: even if a drug, a potential drug, crosses the 'valley of death' and may work, it may not work if we test it at the wrong time, too late in the disease and perhaps that's a major reason for the gigantic failure in the past decade of the major drug trials. So I'd appreciate if you could comment on what appears to perhaps be a necessity that is to test promising new drugs in pre-symptomatic patients with all the issues that raises of identifying and recruiting patients for those kinds of trials. Take care. Thank you.

Dr. Cummings: Okay. Thanks Shelly. Thanks for the comments. It's nice to hear from you.

And you put your finger on an important point and again it comes back to this idea of the right patient for the right drug and part of the right patient is that they be in the right phase of the disease. So there is a lot of worry now that using particularly anti-amyloid agents later in the disease course may be well after the amyloidogenic process is established and a second phase of the illness has been launched in which there is more neurodegeneration more tau protein abnormalities and therefore maybe anti-amyloid treatments are most effective and perhaps only effective in the pre-symptomatic or minimally symptomatic individuals. Now that's still a hypothesis, but it's a hypothesis that deserves to be tested and the failure of our anti-amyloid agent so far although I would say none of them has been rigorously tested by the trials accomplished so far, but still they're acknowledging their failure thus far might be because they're being used to late in the illness. We can see from amyloid imaging that people are laying down amyloid in the brain before they become symptomatic and that essentially plateaus by the time they become symptomatic even with very mild symptoms. So it may logically be that an anti-amyloid agent must be administered at that very early point in order to have its maximal or beneficial effect.

So I think that's a really important question Shelly and one that's unresolved by empirical evidence at this point but certainly there's a movement in the field to move to earlier and earlier clinical trials. There's again the secretase inhibitor that is in patients who specifically have an amyloid abnormality but do not meet criteria for dementia. And then there are at least four prevention trials that I am aware of in which, three of them will involve anti-amyloid drugs where people who are carrying a mutation that will definitely and inevitably cause Alzheimer's disease will be treated before they develop symptoms to see if the onset of symptoms can be prevented or delayed. So there is a movement to act on this idea that we must be treating earlier in the disease process. I think it is also possible that drugs focusing on tau,

neurodegeneration and other cell processes may still be useful and beneficial later in the disease process. I think it speaks to the need to diversify our portfolio of drugs that are being tested.

George Vradenburg: Thank you for your question Dr. Wolf. Our next question comes from Melissa McCaughey of Rancho Mirage, California. Melissa, what is your question?

Question: Good morning, Dr. Cummings. I think Dr. Wolf kind of covered my question partially. But my question is with the drug Seroquel I run an in-home care agency and my clients all range in levels of diagnosed Alzheimer's. And I'm wondering is there a drug besides that? I feel like that drug kind of delays the reactions to things that they're trying, they put them on multiple drugs. And the ones that have been high functioning seem to do better than the ones that weren't necessarily high functioning and I'm just wondering if there's anything else out there that may help slow the progression because I see within a six month time span how quickly they deteriorate where before they are high functioning, now they're not. Once Seroquel and one other drug is implemented, and if you have any commentary on that?

Dr. Cummings: Sure. Thank you for your question Melissa. So Seroquel is an antipsychotic medication that is used for treating agitation and psychosis in Alzheimer's disease. It's commonly used because there is some evidence of efficacy that is that it works and it also has a very broad dosage range so doctors like it because they can start off with a small dose and then manipulate the dose upward to try to get a behavioral response. All antipsychotics, like Seroquel but also like Haldol or any of the others carry an FDA black box warning that the risk of death is increased by two fold from about 2.5% to about 4.6% by dementia patients who are treated with antipsychotics. But there are certainly times when I use these drugs and other doctors must use them because patients become very behaviorally disturbed. We try to avoid them, we try to find explanations for why patients become very upset but in some cases we have to resort to them. We try to use them in the smallest dose for the shortest period of time and with full informed consent of the caregiver and to the extent possible of the patient. So these drugs do reduce cognitive function. There's been a recent review of that from the CATIE study so your observation that that this may adversely affect cognition has been empirically supported.

So this is just one more area of drug development for Alzheimer's disease where we have tremendous unmet needs. We need companies to work in this area to find drugs that would help with patient's behavior and be safe. And very few companies are working in this particular area of drug development. So you put your finger on something that's very important in terms of the drug pipeline and the very few agents that are in this aspect of the pipeline.

George Vradenburg: Thank you Melissa for your question. Our next question comes from Zaven Khachaturian of the Campaign to Prevent Alzheimer's Disease by 2020. Zaven, your question please.

Question: Jeff, I was asking a question about pipeline whether that might be one of the culprits that we don't have enough ideas to go through the process. And second related question is whether our conceptual models of the disease and the animal models on which we're testing are correct or adequate, perhaps

that's where the fundamental problem is. The question of conceptual models is a difficult one because there is such an orthodoxy in the field about what causes the disease that new ideas usually find difficulty in getting received or heard or tested. Would you care to address that issue?

Dr. Cummings: Yes. Thank you Zaven. Great to have you on the line. And nearly everyone knows Zaven but if you don't, he's one of the foremost architects of our current scientific enterprise to address all Alzheimer's disease so thank you for your question Zaven. And your comments are exactly right on, of course, our models, let's take the transgenic mouse models, are models of amyloidosis of the brain and so they stem directly from the widely health belief that amyloid is the principal culprit in causing Alzheimer's disease. And of course there's a lot of evidence particularly genetic evidence that amyloid is an important component or maybe the first component or at least a bystander component. There are many ways of viewing amyloid in the brain but I think it is absolutely true that we need a more models, more diversity in terms of neurodegeneration, tau models, mitochondrial failure, why cells die. We need a much broader horizon of the models and therefore the targets. Models simply represent targets for drug interventions and we need a larger horizon of models so that we can explore many more targets and the effects of many more types of drugs. In addition, a point that you've made to me in private conversations that I'll capitalize on here is that the whole idea of one drug may be far too limited. We know that in cancer, in AIDS, we've made substantial progress because we have multiple drugs in the kind of cocktail approach that affects many of the different pathways that are active in the Alzheimer's disease process. One of the things that really impresses me is the awesome complexity of Alzheimer's disease as we get to know it better and better. And I think we're going to have to have a therapeutic regimen that reflects this awesome complexity. So, yes Zaven I endorse the idea that our conceptual models are impoverished compared to the complexity of the illness and therefore approaches to treatment do not match the complexity of the disease.

George Vradenburg: Again a reminder, if you have a question for Dr. Cummings, please press star 3 on your phone.

Dr. Cummings, this is George Vradenburg. I do have a question relating to an earlier comment. You mentioned with respect to certain drugs that have been approved by the FDA for one purpose and found potentially to be effective against Alzheimer's as another purpose. On the assumption that they have been tested for toxicity and on the assumption that we don't have to do that again but still have to go to the FDA for the next purpose. You mentioned that in fact you could get the clearance time down from 8 to 15 years down to 3 to 5 years. Is there a systematic effort being undertaken today to examine all of the drugs that may be on the market for one purpose and to test them against Alzheimer's disease and thus shorten the time-line by being more systematic and assessing the possibility of reprogramming existing drugs

Dr. Cummings: That’s a really great question George. I know that many pharmaceutical companies are reexamining their approved drugs to see whether they might be active against specific targets. The way you screen a drug is you say well I understand that enzyme X is very critical to the process of Alzheimer's disease. So I now setup an assay where I have an ability to measure whether enzyme X is inhibited and now I screen all of my library, that is all of my compounds that I have available to me, against enzyme X. And the pharmaceutical companies might have somewhere between a hundred thousand and a million compounds that they would be screening to see whether they can get a so-called hit that would indicate that the

enzyme is inhibited and therefore this drug might move up the pipeline. So I know that some pharmaceutical companies are systematically doing this. I think it's the kind of thing George where we need a national consensus on this to make sure that we have looked at all of the drugs and we've looked at them against many of the available targets and again we come back to Zaven's point that the targets that we're testing against, may be too simplicity or too ruled by a certain scientific orthodoxy in regard to what targets we're looking at. I think repurposing is a big opportunity because we know that at least 30% of all approved drugs have effects on other systems that might be therapeutically important. So we always think about monitoring drugs for side effects that were unanticipated but we hardly ever think about a systematic way to look at benefits that were unanticipated and I think there is a huge opportunity there. I'm not aware of a wide-scale systematic effort to go back and look at that and to explore the repurposing opportunity more than it currently is. Do you know about that George? You might know about something that I don't.

George Vradenburg: You're the expert Dr. Cummings. I'm just a moderator.

Our next question comes from Patricia Overgard of Bayside, Texas. Patricia, what is your question? Patricia?

Question: Oh yes. I had Anemia in my 40's and had such a severe brain issue and I think that's when I woke up my Alzheimer's, would that happen?

Dr. Cummings: Thanks for your call Patricia and I'm not aware of a specific relationship between anemia and Alzheimer's. One of the things that we have learned over time is that anything that reduces your so-called brain reserve will make it more likely that that individual will exhibit the symptoms of Alzheimer's disease. So we know for example that brain trauma makes it more likely that one would have Alzheimer's disease later in life or stroke patients have a greater risk of developing/manifesting Alzheimer's disease after a stroke. And so again, this might fall into the general category of reducing the brain reserve that protects us against Alzheimer's disease but I'm not aware of a more specific relationship.

George Vradenburg: Thank you for your question, Patricia. Again if you have a question for Dr. Cummings, star 3. One other request, if you are willing to join in a fight to find a cure for Alzheimer's, press 1 on your phone and we will be in touch with you to determine how best you might engage in this effort to stop Alzheimer's. So if you want to ask a question, star 3. If you want to engage in the fight against the Alzheimer's, please press 1 and we will get in touch with you.

Our next question comes from Dan Perry at the Alliance for Aging Research. Dan, what is your question for Dr. Cummings?

Question: Hi George, actually it's Cynthia Bens, my colleague who's here with me listening to this and she had a response to your back and forth with Dr. Cummings about efforts to repurpose existing drugs and the war against Alzheimer's. So let me defer to Cynthia.

Question: Sure and hi. Thank you for your time. I just wanted to add that while it's not a large-scale effort, as part of the National Center for Advancing Translational Science at the NIH that Dr. Cummings mentioned at the beginning of the call, there is a pilot program on drug repurposing that would allow the National Institute of Health to enter into cooperative agreements with pharmaceutical companies with drugs that showed potential promise for use for another disease area. So I would say with respect broadening that, it

would all be dependent on the ability for the NIH to get a larger portion of the budget. So I would say that that's one point of advocacy is using that pilot project to expand across all the institutes of NIH.

Dr. Cummings: Thank you Cynthia and thank you Dan and for those of you again who don't know Dan and Cynthia, they're real leaders in terms of developing bridges between the FDA and the Alzheimer's disease drug development community, so they've done terrific work.

Just to respond to that Cynthia, one of the things that comes to mind is that the Michael J. Fox Foundation had given several specific grants for looking at repurposed agents and Parkinson's Disease. So I know that there are several efforts relevant to Alzheimer's disease because all of these degenerative diseases share some features and you're absolutely right we need the advocacy. I think an important part of the National Alzheimer's Project Act would be to make sure that the Institutes such as the new NCATS are devoting a substantial amount of their energy efforts and programs to working on the Alzheimer's disease related programs because the NCATS is promising but it's only going to help us solve the Alzheimer disease problem if it focuses a lot of its efforts on Alzheimer's disease.

George Vradenburg: Thank you. Again any questions, press star 3 and you'll be put into a question queue.

I have one question that follows up on a comment, I think of Dr. Wolf. He mentioned that if we are going to target some potential candidate drugs to populations that do not yet show any symptoms of Alzheimer's, that we are going to have a more difficult task of recruiting people into clinical trials. So my question is whether or not there are any changes in industry or academic practice, which might accelerate or ease the process of recruiting people for clinical trials particularly in those who do not yet have the symptoms of the disease.

Dr. Cummings: Well I think George that there is a lot of awareness raising going on in this call and your new program and USAgainstAlzheimer's is one very important example of that.

And I think people are realizing that if they had a mother or father, grandmother, grandfather who had this disease that their risk has increased. And that if you had to choose a group of people to get into to screen, to get into a pre-symptomatic trial. You would start with people who have a positive family history and a substantial number of those will be carrying the e4 genotype but some won't and they will have family risk of other types that perhaps we haven't fully defined yet. But I think there is an increasing awareness that there is an important genetic element to Alzheimer's disease and that those people who have come from families where there was an affected member are now realizing that they are also at risk or their children are at risk. So that's the easiest pathway into getting people to come in for volunteering for clinical trials at a point where they are still without symptoms.

George Vradenburg: Again, any questions please press star 3 and if you'd like to find means of engaging in the movement against Alzheimer's disease, press 1 and we will be in contact with you.

Our next question comes from Donald Conner. Mr. Conner, what is your question?

Question: Dr. Cummings, could you comment in the reporting of trial outcome, how statistical significance versus clinical significance is being handled?

Dr. Cummings: Yes, thanks Don. This is like all my friends are on this call so this is great. Yeah, so this is a very relevant point when we think about a clinical trial, how do we decide whether or not the drug has worked? And in general the FDA requires that there be a statistically significant difference between the drug and the placebo on two outcomes. One of those outcomes has to be a measure of cognition, such as memory, and we usually use a scale called the Alzheimer's Disease Assessment Scale. And the other has to be a measure either of global function or of activities of daily living. So we usually use either the CDR, the Clinical Dementia Rating, or the ADCS, Activities of Daily Living ADL Scale. The FDA has said that movement on either the global or the functional scale is a measure of clinical significance. So a drug that moved only the cognitive measure and not the global measure for example would not be regarded as having had a clinically significant effect. Whereas a drug that moved both of these measures would be regarded as having achieved the goal of improving cognition relative to placebo and of having a clinically meaningful amount of benefit. So all of the drugs cholinesterase inhibitors and hementin that are approved and on the market have met those dual-outcome criteria and it's fairly common to see other drug trials meet only one of those two criteria. For example, the recent nicotine study that was published showed a cognitive benefit but it didn't show any global benefit and therefore it wouldn't meet FDA criteria and it wouldn't meet the usual criteria for clinical meaningfulness. But Don, as you know these are very nuanced arguments and what we would really like are drugs with very robust effects, not these small statistically significant effects even if it affects two outcomes and meets formal criteria for clinical meaningfulness. So we're really looking for drugs that really make a difference for our patients and have much more robust effects than what we currently have and what we have seen in the emerging trials.

George Vradenburg: Last question today. I think in the queue is from Sue Crow of Alexandria, Ohio. Ms. Crow, what is your question?

Question: Hi, hi can you hear me?

George Vradenburg: Yes we can.

Question: Okay. I'm not a healthcare professional. I'm a lot like you where I have family members that have been affected by it and I also volunteer for the Central Ohio Chapter. And what I'm finding is that we are becoming the most popular booth at a lot of the health fairs. What can we do just as everyday people to help push these trials either farther or what can we do to just help the cause as an everyday person.

George Vradenburg: Well let me try the answer to that. I would say that there are many Alzheimer's serving organizations that are active on your behalf. The Alzheimer's Association is of course one of the major organizations to do this. USAgainstAlzheimer's is another such organization and that giving your voice to those organizations enables us here on Washington to both be urging more resources be applied to the disease and also urging other elements needed to fight this disease.

We have been successful in getting the Obama administration to commit to preventing and effectively treating the disease by 2025. We've gotten the Obama administration to propose additional funds for Alzheimer's research. There are number of other steps that need to be taken and that we are urging in connection with the development of a national Alzheimer's plan. One of those effective steps is what we can do to shorten the time and cost of getting drugs from the laboratory, from those @#$% mice that aren't doing a very good job predicting the outcomes, through the drug development process. So both your

association, USAgainstAlzheimer's, and a number of other organizations are being quite active in that fight. So I would urge you to press 1 on your phone and we'll be in contact with you to follow-up with you to how you can be engaged to yourself and also those people that you touch.

Thank you very much for your questions today. I would like to wrap up by saying thank you very much for participating on our inaugural call, Dr. Cummings. You're experimenting with us on how it is that we can engage more people and inform more people about this fight against Alzheimer's.

We welcome any suggestions anyone has on the topics of interest to you in the Alzheimer's world that might be dealt with in coming calls. We will have an Alzheimer's Talks call every month on a topic of interest that is timely and relevant to the fight against Alzheimer's. Some will be from scientists, some will be from policy makers, but we intend to try to both responsive too and inform the Alzheimer's community about the current topics of interest in the Alzheimer's world.

As I said, we are making good progress in developing a national plan. It is a critical time in the Alzheimer's movement - the development of a national plan, the commitment to a national goal to stop this disease, to increase resources and reforms on how to care for those people and those families with the disease and providing additional resource. But this is a marathon not a sprint, even as we are sprinting as fast as we can, we know this battle will take some time. Dr. Cummings is on the frontline in the research field and USAgainstAlzheimer's and other organizations very much on the frontlines in terms of advocacy.

We very much appreciate your participation on the call today and look forward to having you participate in future calls. As I said press 1 if you'd like to talk to us directly on how you might get engaged or give us any topics of interest that you might have or suggestions you might have for speakers in the coming months. I hope you'll participate in these calls in the future, share the information with friends and colleagues. Please stay on the line if you would like to leave us a message, for even as we sign off in fact you'll be able to leave a voicemail for us on suggestions of future calls, future speakers, or other ways in which we might be able to help mobilize the Alzheimer's community. Thank you very much for participating in the first inaugural Alzheimer's Talks call. Thank you.

Dr. Cummings: Thank you all.