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Alzheimer's Talks Transcript
Can a New Drug Treat Alzheimer's?
with Dr. Michael Rafii

July 14, 2015

Note: This transcript has been edited for content and clarity

George Vradenburg: Welcome to Alzheimer's Talks, a monthly teleconference series presented by USAgainstAlzheimer's, where we connect you with the leaders in research and policy who are working to stop Alzheimer's.

My name is George Vradenburg and I'm Chairman and Co-Founder of USAgainstAlzheimer's, an organization which is a venture, an entrepreneurial and innovative effort, to disrupt business as usual, to transform the fight against this disease with greater passion and urgency.

Thank you so much for joining us today to hear about fascinating new research from Dr. Michael Rafii.

It's been a very busy couple of weeks since the last Alzheimer's Talk.

I just want to give you a quick news flash on what's been going on this week and last. Yesterday I was at the White House Conference on Aging, where we heard from President Obama and numerous panels involving dementia across caregiving, financial security, elder fraud and abuse, and the ways technology can be helpful to our community. At this conference, a new Dementia Friendly America initiative was announced, which is a national effort of about fifty national organizations working initially with six pilot communities - states, counties, and communities across the country.

The objective of this Dementia Friendly Initiative is to increase the range of services and support from each sector of a community for those with mild dementia and dementia disease more generally, or other cognitive impairments, making them both safe and respectful for individuals with the disease and increasing the range of services and a more dementia-friendly character of regular retail services. It will also lead, we believe, to increased willingness on the part of doctors and individuals in communities to have their cognitive impairments detected and diagnosed, and to get post-diagnostic follow-up and participate in clinical trials. And if we learn from the experience in Japan and Canada and the UK with this kind of initiative, it will also increase the mobilization of people around the country to be much more active in talking about the disease, and asking their political leaders to take the steps needed, in order to provide

adequate funding for the solutions to this disease. So from the dementia perspective it was a very successful conference.

Last week, the House of Representatives passed the 21st Century Cures Act. Many of you wrote and called your Representative at crucial points. We thank you so very, very much for your advocacy. It is so important that our elected representatives hear from their constituents on the need to increase funding for Alzheimer's research and to accelerate the mechanisms to get that research to individuals around the country who need it. We worked very hard on this with a variety of other organizations and we look forward to its enactment, hopefully by the end of the year, when a parallel initiative from the Senate will come forward.

To get all the latest updates at any time, please go to http://www.UsAgainstAlzheimers.org and sign up, join us. You will get involved, you will get messages every week on the steps you need to take in order to continue this strong political momentum we're getting with the Administration and with Congress in terms of action against Alzheimer's. We know we can stop this disease, but we can't get there without your help. That's why we call our organization Us Against Alzheimer's. It requires all of us to act. So please join us.

Now for today's call. We have over 1,100 people registered today for this call from forty-nine states, the District of Columbia, Puerto Rico, and countries such as Russia and Canada. Additionally, almost 1,500 people who can't join us at this particular time have asked for all of the materials related to this call, which we will post online, on our website, and send to everyone who registered for the call today.

Just as a reminder, for those who have been on these calls in the past and an alert for those who have not, if you have a question during the call, please press *3 on your phone. By pressing *3, you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff, and then we will try to get you live, on the air, as soon as possible when we open it up for questions for Dr. Rafii.

If you are listening to us online you can type your question in the box on your screen, and we will get to as many questions as possible after the opening presentation. Unfortunately, as always, we will not be able to answer personal specific medical questions during this call.

Today, it is my pleasure to introduce you to Dr. Michael Rafii. Dr. Rafii is Director of the Memory Disorders Clinic and Assistant Professor of Neurosciences at the University of California, San Diego. He is also Medical Director and co-Interim Director of the NIH-funded Alzheimer's Disease Cooperative Study and Attending Neurologist at the Shiley-Marcos Alzheimer's Disease Research Center.

Today, he is joining us to talk about two trials that the ADCS, Alzheimer's Disease Cooperative Study, is running: the A4 trial for those at risk of developing Alzheimer's disease, and the NOBLE trial for those with mild to moderate Alzheimer's disease.

Dr. Rafii, thank you for joining us today. We look forward to your comments.

Dr. Michael Rafii: Thank you, it's a pleasure to be on the line with you today.

I am a neurologist and I work in a Memory Disorders Clinic, and I see individuals with memory concerns, and what we see is that one of out every three people over the age of eighty-five has dementia, the most common cause of which is Alzheimer's disease. And all of our efforts on the research front are really aimed at translating discoveries from the research realm into the clinical realm, where we see patients. There is a little bit of background that I'd like to provide before I discuss the two trials, the A4 trial and the NOBLE trial. What I'd like to do is provide some background and a context of the biology in which new compounds are being tested, to see if we can treat the symptoms and perhaps even prevent Alzheimer's disease from developing.

One of the key hallmarks in Alzheimer's disease, which I'm sure your audience is familiar with, is the amyloid plaques and the second hallmark is the neurofibrillary tangles. And the development of Alzheimer's disease seems to occur decades before the patient develops any symptoms of memory loss or cognitive decline. The buildup of amyloid in the brain seems to occur not only decades before symptoms develop, but the deposition of amyloid into plaques also takes quite a long time. The amyloid is first produced as a soluble or free-floating molecule, and it's in that state that it really causes the trouble. As it deposits into plaques, it is sequestered and is unable to exert the same impact as it does in the free-floating state.

The second effect that we see in Alzheimer's disease, which seems to be attributable to the presence of the amyloid, is the development of an abnormality inside of neurons. And this abnormality is a molecular change in one of the proteins that holds together the scaffolding of neurons, and this protein change—it's a protein called tau, different than amyloid—and this tau becomes abnormal in its confirmation, in the presence of amyloid, and it leads to a disruption in the scaffolding that holds neurons together.

Once this tau becomes abnormal and the scaffolding breaks down, the development of neurofibrillary tangles occurs. It seems that the development of neurofibrillary tangles is the end stage where neurons are damaged and lead to the diminution in neurotransmitters that allow our brains to carry out its normal functions such as memory, language, problem-solving, and so on. In fact, there are many other forms of dementia that seem to revolve around a disruption in the scaffolding of neurons due to a disruption in that protein, tau. So now what we see in the field of dementia is that there are different elements that lead to neurodegeneration, brain cell death, all of which seem to revolve around tau as sort of the end stage. But there are different causes, some of which we don't even understand.

In Alzheimer's disease, we think we do understand from genetic studies that there are familial forms of Alzheimer's disease that lead to an over-production of beta-amyloid that lead to the development of neurofibrillary tangles. The buildup of amyloid in these individuals with familial forms of Alzheimer's disease occurs decades before they show any neurofibrillary tangles and before they show any symptoms. The development of the tangles, and shortly thereafter, neurodegeneration, is what seems to correlate most closely with the cognitive complaints, the memory issues and the status of dementia, clinically, that we see in our patients in the clinic.

So with that background, we now have different ways to target Alzheimer's disease. One way is to reduce the production of beta-amyloid. One way is to increase the removal of beta-amyloid. One way is to prevent the beta-amyloid from disrupting this protein tau that resides within neurons and holds the scaffolding of neurons together. In addition, once neurofibrillary tangles develop inside of neurons, there are a whole host of other biochemical changes that occur, a cascade, if you will, that also lead to the demise of neurons, and each of those elements in the cascade are also drug targets.

So, one study that I'd like to mention is called A4, which is Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease. This study uses a drug, a monoclonal antibody, which utilizes the immune system's capability of targeting an element that shouldn't be in the brain, and allowing the immune system to remove it. Monoclonal antibodies are used as immunotherapies in other fields of medicine, such as oncology, and autoimmune diseases, and is now being looked at in the field of Alzheimer's disease. There are many different types of monoclonal antibodies, that target different forms of amyloid, whether it is in the fibrillar plaque form or whether it is that free-floating form that I mentioned earlier. These compounds, these monoclonal antibodies, bind to beta-amyloid and they help the removal of amyloid out of the brain.

We think that the presence of amyloid in the brain, even in the soluble free-floating form, is what's really causing damage and injury to neurons, leading to the formation of these tangles. In the past few years, we've seen an enormous development in our ability to visualize these changes that I've been talking about in patients. We now have amyloid PET scans that allow us to visualize amyloid plaques in the brain. We now have tau imaging, still in the research world, starting to come into more advanced stages, where we can see the development of neurofibrillary tangles. These two capabilities allow us to really measure the changes that happen on the molecular level in the brain of individuals with Alzheimer's disease.

By using these techniques, we can utilize clinical trial designs that incorporate this ability to visualize the changes in the brain, and look at these new compounds like monoclonal antibodies and assess: Do they interact with the amyloid? Do they remove the amyloid? And most importantly, do they have a disease-modifying effect? Do they actually affect the course of the illness?

Over the last twelve years, where there has been no new drugs approved for Alzheimer's disease dementia, what we have seen is that the treatment in disease modification seems to require an early stage of the disease in order to work. Efficacy requires early intervention. An analogous situation is when someone comes into the emergency room with a heart attack, and you offer that individual, who is having symptoms of the heart attack, something like a statin drug that reduces cholesterol. That medication may not be as helpful in that situation as it would have been, say, five or ten years earlier, when you could measure the amount of cholesterol in that individual and say, 'you know, you have high levels of cholesterol and we're going to lower it because you have a higher risk of developing a heart attack.' That cholesterol level is a biomarker. By allowing us to assess the presence of the disease before symptoms have

occurred is one of the greatest benefits of having biomarkers. It allows for what we call secondary prevention of a disease, prevention of a disease only when the biomarker is positive but when no symptoms have occurred.

And the A4 trial is doing just that; it is using one of these monoclonal antibodies, solanezumab, and looking at whether it engages a target, reduces the amyloid, and provides a reduction in the risk of developing Alzheimer's disease dementia, in fact reducing the progression of the disease. That is the aim of the A4 study: the secondary prevention of Alzheimer's disease dementia.

Again, biomarkers have really revolutionized our ability to look at the disease in its earliest stages and try to intervene with the best compounds possible. But of course, there are five and a half million Americans in the United States who are now in the mild to moderate stages of dementia. Remember that dementia due to Alzheimer's disease is a process that does not occur overnight, it's a process that takes, as I mentioned, decades to develop. In fact, we now have three stages of Alzheimer's disease. The stage that everyone is familiar with is the dementia phase. That's the last stage of the disease. It lasts about seven to ten years, progressive cognitive decline, full care, need for full support. But that is really the last stage of the disease, if you will, the analogous heart attack stage. But before that stage, before the dementia stage, is the prodromal Alzheimer's stage. That stage is when an individual has not developed dementia but certainly has cognitive impairment, attributable to those pathological features that I described earlier, the amyloid plaques and the neurofibrillary tangles.

The prodromal stage, clinically, when a physician sees a patient, is often described as the mild cognitive impairment stage or the MCI stage. This is the stage when the individual has memory problems, but they don't have dementia. They're able to do a lot of the things that they could do previously, but they have a clear memory deficit.

Prior to the prodromal stage, which can also last between five to eight years, there is the preclinical Alzheimer's stage. This is the stage where the individual with Alzheimer's disease has no symptoms at all, no memory loss, no cognitive difficulties, but they have amyloid present in the brain. There's been a lot of work looking at preclinical Alzheimer's disease; it has been informed by many longitudinal studies of aging, including the famous ADNI studies. What the ADNI studies and many other longitudinal studies have shown us is that the presence of amyloid in the brain seems to increase the risk of developing Alzheimer's disease dementia sooner than someone who does not have any amyloid in the brain. By utilizing amyloid imaging, we're able to assess for that risk. And in preclinical Alzheimer's disease, the individual has the presence of amyloid but they show no symptoms. And that seems to be the stage at which these interventional studies for disease modification are aiming to attack the disease for secondary prevention.

But again, there are five and a half million Americans who are in the later stage, the dementia stage, and there are a lot of efforts being placed in developing treatments for those individuals. So that's the second study I wanted to mention, that's the NOBLE study. The NOBLE study involves a compound; it is not a monoclonal antibody. Monoclonal antibody needs to be given

intravenously once a month, typically, and in the NOBLE study, this neuroprotectant is an oral compound, it's a pill. This pill, the compound that makes up this pill, has been shown, in preclinical studies, to provide protection to neurons even if beta-amyloid is present. It interferes with the development of that abnormality in tau, it interferes with that cascade that leads to inflammatory changes in the neurons and subsequent neurodegeneration.

The NOBLE study, though, is aimed at individuals of mild to moderate dementia due to Alzheimer's disease. So these individuals who are in the symptomatic stage are certainly not being forgotten. And this is one of those compounds that is really leading the pack in terms of bringing the latest understanding of the molecular basis of Alzheimer's disease into the clinical realm. But before any compound can be approved for use in patients, not only does the efficacy need to be shown, and the tolerability needs to be shown, but it needs to be shown in a randomized, double-blind, placebo-controlled study. The FDA requires clinical trials that show safety, tolerability, and efficacy for all of these compounds, not only for disease modification but also for symptomatic treatment. And that's what the NOBLE study and the A4 study are doing. They are developing the evidence needed so that we can have a treatment that not only treats the symptoms of Alzheimer's disease but perhaps have a treatment that also has secondary prevention and disease modification.

Now, in order to participate in these studies, the A4 study requires an individual, as I mentioned, to have no memory problems. They can have a memory concern but no signs of mild cognitive impairment and no signs of dementia. They should have a family history of Alzheimer's disease dementia. They need to be sixty-five to eighty-five years old, and have essentially normal thinking and memory abilities. The website for the A4 study is www.A4study.org.

The NOBLE study, which is the neuroprotectant that is being looked at in patients who have mild to moderate dementia due to Alzheimer's disease, is for individuals aged fifty-five to eighty-five years old. The information for this study can be found on www.noblestudy.org.

In addition, the NIA, the National Institute on Aging, has a hotline for education and referral on all Alzheimer's disease studies. This is the ADEAR hotline. This number is 1-800-438-4380. They can provide you information about all of the studies that are available.

So there's a continuum to Alzheimer's disease. There is, of course, the dementia stage, the stage that we're all familiar with, the image that conjures up in our mind when we hear Alzheimer's disease. But Alzheimer's disease has many stages, in fact, three: The dementia stage is the last stage, seven to ten years. Prior to that is the prodromal stage, five to eight years, and before that is the preclinical stage. And these stages are defined by the presence or absence of symptoms in the context of having positive biomarkers for Alzheimer's disease pathology, both the amyloid plaques and the neurofibrillary tangles.

Our hope is that, nationwide, individuals who have symptoms and individuals who are concerned will get involved in research. That is the only way that we can build this evidence

needed, to have drugs and therapies that will help patients. And I think an opportunity to speak to the audience today will help accomplish that goal for everyone involved. Thank you.

George Vradenburg: Thank you very much, Dr. Rafii. I deeply appreciated the explanation of the stages of this disease; the stages of the biomarker cascade was clear and simple and straightforward.

Reminder to everyone, if you have a question, press *3 on your phone, and we will get to your questions as soon as we can. Just a couple of questions from me, if I might. Who is the sponsor of the NOBLE trial, and what is its method of action?

Dr. Michael Rafii: The NOBLE study is, as is the A4 study, an ADCS study; it's being conducted across ADCS sites around the United States. It is a compound that has been developed by a company called Toyama Chemical. Toyama Chemical is the sponsor of the NOBLE study. The A4 study is also being conducted by the ADCS. It utilizes a compound developed by Eli Lilly. This compound is the monoclonal antibody called solanezumab. And so those are the two sponsors that are involved in these two studies.

George Vradenburg: And the method of action of the NOBLE study drug? And what is the symptom that it seeks to treat?

Dr. Michael Rafii: The NOBLE study is looking at their compound that is a neuroprotectant. It acts through different receptors on neurons; there will actually be scientific presentations made about this at the AAIC, the Alzheimer's Association International Conference, on how it acts through various receptors on neurons and it seems to, in preclinical study, prevent the degeneration of neurons and the abnormalities in tau that we see in the presence of amyloid. And so it's in the category of neuroprotectant.

The solanezumab is in the category of immunotherapy, anti-amyloid immunotherapy. There are many different mechanisms that are utilized in these drug trials, but the idea with the NOBLE study is that those individuals who have mild to moderate dementia—can we improve their symptoms? It has been shown in animal models that the compound improves symptoms attributable to the presence of amyloid pathology in animal studies. Will the same be replicated in human studies? That is the goal of this study, to improve cognitive facilities in individuals who have Alzheimer's disease dementia.

George Vradenburg: So the symptom that the NOBLE study drug is attempting to mitigate is cognitive impairment?

Dr. Michael Rafii: Absolutely, the multiple cognitive impairments that are seen in adults with Alzheimer's disease including memory issues, language issues, functioning issues; these are all the aims of the NOBLE study.

George Vradenburg: So I'll ask the question that's on everyone's mind, which is, when are these drugs going to complete their clinical studies, and when will they be, if successful, in front of the FDA?

Dr. Michael Rafii: Yes, this is a very important question. The time course for developing any drug is approximately eight years from idea to approval. There are of course drugs that are a few years shorter and drugs that take longer, but it's quite a long process. The process involves animal models but also clinical studies; clinical studies depending on the effect of the drug can take twelve months or thirty-six months or even longer. In the case of the NOBLE trial, this is twelve months of treatment, and the trial is now ongoing. There are subjects enrolled. There are subjects who are on drug and who are on placebo. There are subjects who are progressing through the study and we hope that we will have a readout when the last subject has been completed, the twelve month period, and then the statisticians have had a chance to go through the data with their pre-planned statistical analyses and then find the evidence and present it to the FDA.

The same is true with the A4 study, but the A4 study is not a twelve-month-long study, it's a three-year-long study, three years of treatment, and there are individuals who are already enrolled in that study, and some are on drug and some are on placebo. And they are committed, they are participants that are wholly committed, in three years of participation that we can get the evidence needed to show the FDA whether the drug has an effect in disease modification. So it really depends on which drug you're talking about, but we hope that we will be getting readouts from many different clinical trials in the field over the next twenty-four to thirty-six months.

George Vradenburg: So, there is a general question that was asked before this call, and that is: Are you optimistic about our getting a drug on the market by 2020? Are we really making progress in this fight?

Dr. Michael Rafii: I think we are really making progress. I think that one of the greatest innovations in our field has been the development of advanced imaging of Alzheimer's disease pathology. Without a doubt, that has really changed the landscape of clinical trials, because now you can look at the individual, and really be certain whether or not the pathology is there. It's sort of like somebody coming into the emergency room with chest pain, and saying 'ah, well, this is a heart attack.' Well, what's the evidence that it's a heart attack? Where is the evidence? Is there a change on the EKG? Is there a change in the blood level of their troponin, one of the biomarkers for cardiac enzymes? What are the biomarkers? In Alzheimer's disease, we now have validated biomarkers and they have really changed our ability not only to diagnose the pathology but also to intervene at an early stage, where we're now learning that the pathology is occurring a long time before the patient shows any symptoms, and that the cascade has already reached its end stage by the time the person develops dementia.

And so, in my opinion, the development of these innovations of non-invasive imaging of the pathological hallmarks of Alzheimer's disease, has really propelled us into a new arena. And

these are being utilized in clinical trials now, and I think that that is one major thrust that has pushed us forward to meeting the 2020 date.

Will we get there? Will we get there in time? Are the compounds that are being looked at "it"? Well, that's the purpose of the studies. They are the best compounds that we have. There is a lot of evidence behind these mechanisms of action, and we're in that stage now where the FDA is looking at these seriously as late-stage studies. So in my opinion, yes, we've made huge advances, there's been tremendous progress made, and I think that the compounds being looked at are some of the best compounds we have. There are other compounds that are being looked at as well. We simply don't have time to go through all of them, but the enrichment of the clinical studies participants with the biomarkers has truly moved the field forward dramatically, and I think we'll start seeing the fruits of that effort in the next few years.

George Vradenburg: We've got a call here from Sharon, from her cell phone in South Carolina. Sharon, ask your question please.

Caller: Well, you just answered my question. I'm a volunteer in the A4 study here and I was wondering when results would be determined, and you just mentioned that. But while I'm on the phone, I would like to say that I was a little hesitant about being in this study; I was afraid of potential side effects from the infusions. But I have to say after having been getting them since April, there are no side effects for me. It may be that I'm getting a placebo, of course, but it may be that I'm getting the drug. I hope it's the drug. And so, that's really all I need to say. Thank you.

George Vradenburg: Sharon, I'm going to press your question a little harder for Dr. Rafii. The A4 trial is now recruiting but as I understand it, given that it has not yet been fully recruited, in a three-year study, we're talking about the results of that trial not emerging until roughly 2019. Am I right?

Dr. Michael Rafii: Yes. That's true. I do want to address, though, the idea of the side effects and so on. The solanezumab that is in the A4 study, which is a thousand-subject study; that compound has been looked at in thousands of other participants who were in other studies, international studies, that had mild to moderate Alzheimer's disease dementia. That drug was selected to be looked at in the A4 study in patients who have no symptoms at all. It was very well tolerated in those previous studies using the same compound, and so I'm glad to hear this but I'm not surprised that it's well tolerated. And yes, the readout for this study will not occur until, again, probably six months after the last subject has completed their last visit, so we have all the data for all of the participants. Now, that's in regard to efficacy. Remember that in all studies, in all clinical trials, there's always ongoing monitoring. There's ongoing monitoring of lots of things, for example, safety and tolerability, but also efficacy as interim results, so that, are we seeing a dramatic improvement already? There are lots of eyes making sure that individuals are participating and getting the benefit of participating in these studies, so I think it's important to keep that in mind. But yes, the top line results of such a study with all participants for the duration of the study would occur sometime around 2018, 2019.

George Vradenburg: We have some questions that came in earlier. You went though, very clearly, the stages of this disease. Some people are asking whether there are any longitudinal studies, or clinical trials on drugs, for persons at much significantly younger ages, before you're fifty years old or in your fifties, as opposed to these drugs that you've mentioned, which are targeted at sixty-five to eight-five or sixty to eighty-five range. Are there any studies or clinical research going on in much younger populations?

Dr. Michael Rafii: There are no interventional studies in the younger population, other than the familiar forms of Alzheimer's disease, where there's a genetic mutation, those individuals which make up about two percent of all case of Alzheimer's disease, and typically develop symptoms in their forties and fifties, there are no interventional studies for younger adults. The reason for this is that, yes, the pathology does develop decades before the individuals develop symptoms, but again, the developments seem to be occurring somewhere, again, in their sixties, which results in their amyloid scans becoming positive in their sixties and increasing exponentially the older you get. So I think that the current mechanisms that are looking at treatments, secondary prevention treatments, are requiring that there be amyloid positivity in the brain and we just don't see that in, for example, twenty-year-olds and thirty-year-olds. There are longitudinal studies of aging, but again they typically start at older ages, as well.

George Vradenburg: A question here from Chris Carlson online; which stage is the NOBLE study in right now?

Dr. Michael Rafii: The NOBLE study is a Phase Two study. There are essentially three phases to clinical drug studies. There's Phase One which is typically a very short duration and very small number of individuals that's looking at tolerability; this is again after many years of preclinical testing that's been done. Phase Two typically involves hundreds of subjects; it's placebo-controlled and it's for a longer duration, months to years, and then Phase Three is when you have thousands of patients, typically, that are again randomized, placebo-controlled, and it can also be many, many years. So these studies are looked at by the FDA but in conjunction with secondary studies. The FDA typically requires two studies showing the same findings to approve a drug and these studies—both of these studies—would be considered very important in the consideration for approval by the FDA. So, most clinical studies—Phase One, Phase Two, Phase Three—they are all just, as I mentioned earlier, building the evidence that this compound really does what it is supposed to do and meets its end points.

George Vradenburg: A question here, from Karen Sadowsky Kaufman - has solanezumab already failed to show effectiveness in people with mild to moderate cognitive impairment?

Dr. Michael Rafii: Yes, so the results of solanezumab in two studies, Expedition One and Expedition Two, showed that it failed to meet its end points, its primary end points, in patients with mild to moderate Alzheimer's disease dementia. However, there was an analysis done looking at those individuals who are the mild only as compared to those who were moderate, and there seemed to be a trend in those individuals who had mild only having a reduction in the progression of the disease by about thirty-seven percent. Again, this was a pre-planned analysis of pooled data across both studies involving only the mild subjects, but it was only a trend. And

so that is why the A4 study is very exciting. More importantly, there is a study now called Expedition Three, where the FDA has asked the sponsor to run the study with solanezumab only in the mild subjects, and if they show that same effect, then that would potentially lead to FDA approval of solanezumab for individuals that meet the mild criteria only.

George Vradenburg: Let me ask, Shannon, would you like to come on the phone and ask Dr. Rafii your question?

Caller: Sure. So my question is, I am in a long train, I'm fourth in line with a direct history of Alzheimer's; my mom has Fifth Stage, her father had it, and we've traced it up the line, so I understand exactly what my risk is, which is extremely high. For somebody in their early to mid thirties, how can I get involved in some of these studies?

Dr. Michael Rafii: Well, I appreciate that question. In my own clinic, we have individuals who have a very, very strong family history and they have concerns, and they come in for annual memory checks. There are research studies, longitudinal studies, that do enroll younger individuals who have very, very strong family histories.

I would contact the ADEAR hotline, which is 800-438-4380, and provide your location, and ask for those types of longitudinal studies so that you could participate. Some of these longitudinal studies include in them amyloid imaging, cognitive testing on an annual basis, they have MRI and spinal fluid analysis, and so I encourage you to know that there are resources out there and to get involved, but to know that there are many individuals where they have a family history, a very strong family history, and they do not develop Alzheimer's disease dementia. And so although there is increased risk it is not a guarantee. It is very different than the autosomal dominant forms of familial Alzheimer's disease. We are just learning about the effects of healthy diet and physical aerobic activity and so on that have beneficial effects in general health maintenance. So I would at least reach out to the research arenas near you to participate in longitudinal studies such as that.

George Vradenburg: We are going to have a poll question at the end of this call for those people who are interested in studies, and so we'll get to that in another ten to fifteen minutes.

Karen Sadowsky Kaufman seems to be a real questioner today. Curious about A4 trial, is ApoE4 status a criteria of exclusion or inclusion for the A4 trial?

Dr. Michael Rafii: Thank you for that question. I will just take a moment to discuss the A4 story. So, apolipoprotein E is a carrier protein, and it comes in three forms: ApoE2, ApoE3, and ApoE4. You inherit one copy from your mother. You inherit the other copy from your father. And individuals who inherit two copies of E4 have a much higher risk of developing sporadic Alzheimer's disease, about a twelve-fold increased risk. If you inherit one copy of E4, you have an approximately nine-fold increased chance of developing sporadic Alzheimer's disease. If you inherit no copies of E4 and instead have E2, or E3, you do not have an elevated risk of developing sporadic Alzheimer's disease as compared to the general population. So ApoE4 status is thought to be a susceptibility risk stratification gene. It is thought mechanistically that

E4, ApoE, binds to beta-amyloid in the brain as a carrier protein and removes it out of the brain and delivers it into the blood stream; that's one of its functions, or at least is thought to be.

And if you have E4, your carrier protein is not very efficient at binding to beta-amyloid, and removing it out of the brain. So the amyloid sits in the brain for a longer period of time, hence the increased risk of developing Alzheimer's disease. Moreover, individuals who do carry an E4 allele have higher amyloid depositions in their brain compared to those who don't. If you have ApoE2, ApoE2 is very efficient at binding to beta-amyloid and getting it out of the brain, very efficient, and therefore beta-amyloid does not have a lot of chance to free-float around in the brain and cause its deleterious effects. And that is thought to underly the basis of the protective effect of having ApoE2 status.

Now, having E4 homozygosity or heterozygosity or having ApoE2 status, these are susceptibility genes. But I can tell you, there are patients who have ApoE2, who do get Alzheimer's disease, or who have ApoE4, and don't get Alzheimer's disease. So again, it's harking back to the previous question, with the individual who is thirty years old who has a family history; it is increasing the risk but it is not a guarantee.

And to answer your question directly, E4 status does not serve as an exclusionary criteria to these studies. It is tested, it is looked at in the research study, it is stratified, it is used to compare different groups of individuals in the studies, but it does not preclude someone from participating in these clinical trials.

George Vradenburg: So, Ellen Rodwick has sort of a related question, that is, are there any clinical trials in existence or planned for persons who may have two E4 alleles?

Dr. Michael Rafii: There are clinical trials that are actually targeting the E4 molecule, and again, I would recommend going to the ADEAR hotline. There's another resource that's available called clinicaltrials.gov. At clinicaltrials.gov, you can put in the disease state and you can put in key words such as ApoE or ApoE4, and based on your location in the United Sates, find out what studies are available to you. The ApoE4 story is very interesting because in animal models, there have been some very exciting results published, showing that there can be dramatic impacts on risk by directly impacting the ApoE4 protein confirmation. By changing the E4 protein and making it look like an E2 protein, you may have a beneficial effect and so there's a lot of work being done in the preclinical space on the E4 mechanism. There are other mechanisms for the removal of beta-amyloid out of the brain that are also being looked at in clinical trials, both preclinical but also in early stage studies, trying to sort of prime the ability of the brain to remove beta-amyloid.

George Vradenburg: Could you just refer to, and describe, the homozygote trial that Banner and Eric Reiman are planning?

Dr. Michael Rafii: Yes, so the Banner Alzheimer's Institute led by Eric Reiman and Pierre Tariot, based in Arizona, is running under the umbrella the API, Alzheimer's Prevention Initiative, two different studies. One study is looking at individuals who have a familial form of Alzheimer's

disease due to a genetic mutation, and this is being conducted with participants in Medillin, Colombia, in South America, and it is utilizing different treatment strategies to again remove beta-amyloid or reduce the production of beta-amyloid in those individuals. That is one study.

A second study is looking at individuals in the general population who have E4. And by utilizing again mechanisms that remove beta-amyloid out of the brain or reduce its production, in individuals who are at a higher risk of developing Alzheimer's disease pathology by virtue of the fact that they have ApoE4, and again trying to have a disease modifying effect. Again, all of these studies are targeting amyloid, and are either reducing its production or increasing its removal.

And there are a lot of studies now that are looking at other compounds that target other elements within this amyloid cascade, including tau, including the inflammatory cascade that develops subsequently. But most of the studies including the E4 homozygote study are again targeting the removal of amyloid, and are using E4 as a way to enrich that population of participants.

George Vradenburg: So I'm going to ask Nicole from Mobile, Alabama, to ask her question.

Caller: Yes, I wanted to know why was most of the research aimed at the pre-symptomatic, mild to moderate symptomatic, patients, and will research and medication be available, or possibly available, for those with moderate to severe stages or the last stages of Alzheimer's, or are you trying to do the research ahead of time to get medications and get things available for people in the moderate to latter stages of the disease?

Dr. Michael Rafii: The question is, are we targeting mechanisms in the moderate to severe stage of dementia due to Alzheimer's disease. The NOBLE study is targeting the mild to moderate stage. Remember that in Alzheimer's disease, that dementia stage, that last stage, involves not only the amyloid plaques and the tangles, neurodegeneration, and atrophy, but there are neural circuits that are being disrupted by that atrophy and those neural circuits produce neurotransmitters. There are over thirty neurotransmitters in the brain; one of the neurotransmitters that becomes abnormal in Alzheimer's disease early on is acetylcholine. But there are many others that become perturbed, and there are many clinical trials that are being conducted that are neurotransmitter-based. So there are clinical trials looking at serotonin and changing levels of serotonin; there are clinical trials looking at norepinephrine, again these are in earlier stages but they are moving forward towards later stages based on the compound and its brain penetrability and its tolerability and so on, but there are drugs that are being looked at that affect neurotransmitters that seem to be perturbed in the later stages of the disease. There's been a tremendous amount of work being done on behaviors and managing behaviors pharmacologically in the later stages of disease.

So to answer your question, the mild to moderate dementia stage of Alzheimer's disease has not been forgotten by researchers and there are drugs that are being developed that treat neurotransmitter abnormalities, but also provide neuroprotection and are being looked at in particular in the NOBLE study that will provide symptomatic benefit and perhaps even

stabilization of one's function in the later stages of the disease. However, there is also a clear understanding that for disease modification to occur, you really need to treat the disease much earlier to prevent it. That is the same we find with cancer. If you imagine treating a patient with metastatic cancer, that's widely metastasized, that person's prognosis, when you start treatment in the metastatic stage, is very different than treating someone with the same type of cancer but in the very early stage when it has not metastasized or involved any lymph nodes. The staging of the disease using biomarkers has revolutionized cancer treatments. It's revolutionized heart disease, and it's revolutionizing Alzheimer's disease. So, yes, the individuals with the later stages of Alzheimer's disease dementia are certainly going to benefit from research that's taking place with new therapies, but there's also a tremendous effort being placed on secondary prevention. By secondary prevention, by delaying the symptoms of Alzheimer's disease dementia by five years, we would reduce the incidence by fifty percent. And so secondary prevention is a major effort that's taking place, but knowing that there are individuals who have mild to moderate dementia that need symptomatic treatments now.

George Vradenburg: Dr. Rafii, thank you so very much. You mentioned two significant trials and people on the phone have also asked about other trials. So we're going to try something today as a starter and that is, if people are interested in one of these studies we heard about today, or you think you, or someone you know, might be eligible and would like some more information, I'm going to ask you, in just a second, to push a specific number on your phone, and we're going to share your information with Dr. Rafii and his team at ADCS, and they can follow up with you.

So if you're interested in the A4 trial, please press 1 now. As a quick recap, the A4 trial is for those aged sixty-five to eighty-five years old, with normal thinking and memory abilities. So if you think that you are interested in or know someone who would be interested in participating in that trial, press 1 now.

If you're interested in the NOBLE trial, we're going to ask you to press 2. Again, as a quick recap, the NOBLE trial is for those aged fifty-five to eighty-five who have mild to moderate Alzheimer's disease. So if you, or someone you know, is fifty-five to eighty-five years old and has mild to moderate Alzheimer's disease, and is interested in participating in, or asking questions about, the NOBLE trial, please press 2.

If you aren't sure which study you'd be eligible for, or if you're interested in both, please press 3. So, please press 1 if you think might be eligible or like more information on A4, press 2 for the NOBLE trial, press 3 for both, and someone from ADCS will be involved.

Dr. Rafii, thank you so very, very much. There are many questions we couldn't get to today, but you have been very, very clear on these two trials and more generally on the stages of the disease, the different mechanisms of action that may be involved in each stage of the disease based upon the cascade of pathology, and so we thank you so very,very much for your clarity and for your time.

Thank you to everyone on the phone or online for participating in this Alzheimer's Talk. In about a week, we'll have a copy of the recording and a transcript for you to share with your friends.

For our next call, we have a special edition of Alzheimer's Talks on Wednesday, July 29, from 4 to 5 p.m. Eastern Standard Time. We're excited to have Jonathan Kozol, the award-winning author of Savage Inequalities, Death at an Early Age, and many other books from his fifty years of working with children in inner-city schools. He's doing to discuss his newest book, The Theft of Memory: Losing My Father, One Day at a Time, which actually I'm in the middle of right now. Kozol's book is a heart-wrenching chronicle of his own father's decline from Alzheimer's, along with glimpses of his father's past, and stories from his long career as a respected psychiatrist and neurologist. Jonathan will share his experiences caring for his father, his insights on memory, and the difficult questions we all have about whether our father stays at home, goes to an assisted living facility, the impact on the rest of the family, in his case his mother, herself in advance stages of a variety of chronic diseases other than dementia. So I'd encourage you to pick up a copy of the book today, and join us on July 29 for a discussion with Jonathan Kozol.

As always, please stay on the line if you'd 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 and again information can be obtained online under A4study.org, for the A4 study, and NOBLEstudy.org for the NOBLE study.

Dr. Rafii, thank you so much for your time and for your clarity of explanation today. We deeply appreciate not only your time today but what you're doing every day in the fight against this disease.

Dr. Michael Rafii: My pleasure, thank you.

George Vradenburg: Take care.