UsAgainstAlzheimer's

Alzheimer's Talks Transcript

with Dr. Michael Harpold

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Note: This transcript has been edited for content and clarity

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

My name is George Vradenburg, Chairman of UsAgainstAlzheimer's. We regard ourselves as an entrepreneurial, innovative organization seeking to disrupt business as usual and transforming the fight against this damn disease.

Thank you very much for joining us today to hear from Dr. Michael Harpold about some really important research.

I want to give a special thank you to Karen and Chris Segal and to the Zickler Family Foundation. Their contributions, along with smaller contributions from many of you who support these calls, have made this call possible. We are so grateful for their support, and your suport, so that we can continue to bring you the latest and the best in Alzheimer's research from leading scientists.

We have over 500 people registered today for the call or recap materials, from forty-five states plus some foreign countries such as Greece and Australia. Additional individuals will call in or join the online stream.

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 or if you are listening to us online, you can type your question in the box, and we will get to as many questions as soon as possible after the opening presentation. As you know, unfortunately, we will not be able to answer personal specific medical questions during this call.

Today, it's my pleasure to introduce you to Dr. Michael Harpold. Dr. Harpold is Chief Scientific Officer of the LuMind Research Down Syndrome Foundation, and is also Chair of their Scientific Advisory Board. Dr. Harpold has more than thirty-five years experience in biomedical research, including research focused on neuroscience, and discovery and development of new therapies for neurological disorders, in academia and at pharmaceutical companies. His work has led to numerous scientific publications and forty-seven U.S. patents and additional foreign patents.

We are so grateful to Dr. Harpold for joining us today to speak about why individuals with Do wn syndrome experience Alzheimer's disease earlier and at a much higher incidence, and the n share with us the latest research advances, including a groundbreaking new clinical trial, an d how this work can hopefully help find a treatment for individuals, with and without Down syn drome, who have Alzheimer's. Thank you very much, Michael, for joining us today. We look fo rward to your comments.

Dr. Harpold: Thank you, George, for the kind introduction, and to you and UsAgainstAlzheimer's for a wonderful opportunity to speak today about some very important topics that as yet may not be as widely recognized as they should be, namely, Alzheimer's disease in individuals with Down syndrome, and the implications of that connection for research in the field as well as the development of effective new Alzheimer's disease therapies, not only for individuals with Down syndrome, but also potentially for everyone.

As part of my talk today, as you mentioned, I'm going to provide a brief background on Down syndrome with some historical context, and describe some of the key evidence for the connection between Alzheimer's disease and Down syndrome. I'll also provide a brief overview of selected recent research advances, primarily supported by our foundation, concerning the identification and validation of specific therapeutic or drug targets, and associated pre-clinical studies that are leading to important and exciting new clinical trials, and how Down syndrome represents a unique key in demonstrating proof of efficacy in accelerating the development of effective new Alzheimer's disease therapies.

As many of those on the call today likely may already know, Down syndrome, or trisomy 21, comprises a wide set of cognitive and physical conditions and symptoms resulting from individuals having an extra or third chromosome 21. This third copy of chromosome 21 primarily occurs during the formation of an egg and prior to fertilization. Also note that there are individuals estimated as approximately four percent of cases, in which only some proportion of cells in their bodies contain an extra chromosome 21, and this is designated as mosaic Down syndrome, and results in varying degrees of characteristics of Down syndrome.

Down syndrome is the most common chromosomal cause of developmental intellectual disability, with an estimated population of 400,000, and possibly more, children and adults in the U.S. and four to six million worldwide, so this is not a small population. Research indicates that there are no significant differences in the occurrence of Down syndrome among males or females, or among different races and ethnicities. As recently as the mid- to late-1980s, the life expectancy for individuals with Down syndrome was less than thirty years old. Today, it is approximately sixty years. And this is a dramatic increase, but still significantly lower than the general population. Today, many people with Down syndrome are increasingly able to develop their full potential, attending school and working and participating in their communities. Also today, it's clear that Down syndrome is not monolithic. Indeed, there is variability among the considerable set of Down syndrome associated medical conditions. For example, fifty to sixty percent of individuals with Down syndrome have congenital heart defects. And I'll just add, parenthetically, that this represented a major contributor to the dramatically lower life expectancy, but has more recently been successfully addressed with modern surgical procedures.

Additional examples include impairments in sleep functions; this includes obstructive sleep apnea which occurs in sixty to eighty percent of individuals with Down syndrome. And I'll also note that this may have an impact on the development of Alzheimer's disease in those with Down syndrome, but something I'm not going to have time to go into in more detail today. Individuals with Down syndrome also have increased occurrence of seizures, ten to fifteen percent of individuals of the population experience an increased incidence of seizures, as well as a significant increase of susceptibility to and occurrence of infections.

These examples, clearly affecting some but not all individuals with Down syndrome, underscore the variability of the different medical conditions. It is also noteworthy that there is a significantly increased incidence of leukemias in individuals with Down syndrome. In contrast, however, research indicates there is a very much lower incidence of most forms of solid tumors, and further, similarly, a significantly lower incidence of atherosclerosis, a condition research suggests may be exacerbating for Alzheimer's disease. While not the subject of today's talk, research to understand the basis for a lower incidence of solid tumors and atherosclerosis in Down syndrome might yield important new therapeutic approaches for treating these disorders in the wider population.

There are, however, two major medical issues affecting all individuals with Down syndrome. The development intellectual or cognitive disability manifested throughout their lives and the age-related earlier onset and development of the characteristic neuropathology of Alzheimer's disease, including the brain amyloid plaques, in virtually everyone with Down syndrome by their forties. One way to think about this is, it's as if, in this population, the onset and progression of Alzheimer's disease is actually shifted twenty to twenty-five years earlier than in the general population. The majority of these individuals subsequently develop the associated cognitive decline or dementia. It also means there are as many or more than 350,000 people in the U.S. with Down syndrome who will develop or are living today with Alzheimer's disease. This earlier onset Alzheimer's disease can rob people with Down syndrome of the success and progress they have made throughout their lives and is somewhat analogous to the disease in older individuals in the wider population in this respect.

I'm sure many are aware of the developmental intellectual disability in Down syndrome; it may not be as widely recognized that this intellectual disability can also variably manifest as mild to severe with research indicating a median I.Q. of approximately 50. This developmental intellectual disability in Down syndrome has long been thought, at least until very recently, to be intractable, by almost very definition. Although not the focus, again, of today's talk, I will note that our foundation has also supported remarkable research advances in understanding specific biological mechanisms underlying the developmental cognitive disability and which has now led to groundbreaking clinical trials in children and adults with Down Syndrome with drug candidates having the potential to improve cognitive function involving learning, memory, and speech associated with that developmental intellectual disability. Although clearly dependent on success and further research, this might also have a positive impact on that earlier age development of Alzheimer's disease in individuals with Down syndrome.

So, what about the connection between Down syndrome and Alzheimer's disease? Well, it appears that Down syndrome has likely existed through human history. The first formal medical description was made by Dr. John Langdon Down, a British physician, in the 1860s, but it was not until the late 1950s that French researchers identified the association with the presence of an extra, or third, copy of a single human chromosome, chromosome 21. Over the approximately following three decades, medical research to more deeply understand Down syndrome was remarkably quite limited. Even so, there were some reports, that, with aging, individuals with Down syndrome exhibited clinical characteristics associated with Alzheimer's disease. Undoubtedly, during this time, the limited extent of research was not only related to various historical, social, and cultural factors, but also significantly to the complexity of research on a syndrome involving an entire extra chromosome. Although until the late 1980s, there were relatively limited numbers of individuals with Down syndrome living beyond thirty years, it had been increasingly noted that many older individuals, those reaching into their forties and fifties, appeared to experience significant cognitive decline and many of the clinical features associated with Alzheimer's disease. Researchers in the early

1970s, based upon autopsy results, demonstrated that so-called Alzheimer's disease senile plaques were invariably present in the brains of individuals with Down syndrome in their thirties and beyond. Also note this has been further confirmed by very recent studies with beta amyloid specific imaging agents that are able to detect the significant amyloid deposits in the brains of living individuals with Down syndrome, as early as their mid- to late-thirties.

Then, in the early 1980s, researchers successfully characterized the major constituent of the brain amyloid plaques associated with Alzheimer's disease, and this was subsequently designated as the amyloid beta peptide, or A-beta for short. Shortly thereafter, the same researchers showed that this was identical to the major constituent of the plaques found in the brain of individuals with Down syndrome, thus providing the first empirical chemical evidence of a relationship between Alzheimer's disease and Down syndrome. By the late 1980s, researchers had isolated and characterized the gene encoding the amyloid precursor protein, which is also designated APP, and is probably familiar to many listeners today. This is the protein from which A-beta is actually produced. Other researchers mapped the APP gene to the human chromosome 21. Taken together with the presence of the extra chromosome 21 along with its extra dosage of the APP gene in Down syndrome, this research provided a strong connection between Down syndrome and Alzheimer's disease, and further reinforced the idea that APP, and/or its products such as A-beta, plays a major role in the development of Alzheimer's disease, and might represent an effective potential drug target for Alzheimer's disease.

Subsequent additional research progress included the development of animal, mainly mouse, models of Down syndrome that actually contain extra copies of the equivalent of human chromosome 21 genes. Depending on how many and which such genes, these animal models exhibit the various characteristics of Down syndrome including the developmental cognitive impairment involving learning and memory and the additional age-related cognitive decline. Also importantly, the Human Genome Project in the late 1990s and into the early 2000s led to the sequencing of the complete human chromosome 21. And this provided critically important structural data to identify its more than 300 genes. However, there was frustration within the Down syndrome community with the significant and disproportional federal underfunding of Down syndrome research, and the relatively slow pace of research, as well as especially the lack of focus to identify and develop potential therapies to improve cognitive function associated with the developmental intellectual disability as well as therapies to address the earlier onset Alzheimer's disease in Down syndrome.

Our foundation was founded in 2004 with that specific focus, to stimulate new research through a pro-active research strategy and increased funding to accelerate the development of effective new therapies in both these areas, to create new opportunities for children and adults with Down syndrome, and with potential to benefit the wider population, particularly with respect to Alzheimer's disease.

In the remaining time today, I'm going to provide a brief overview highlighting some key aspects of the remarkable research progress and advances, supported by our foundation, in recent years, and leading to new clinical trials for potential new therapies to prevent and/or halt the progression of Alzheimer's disease in individuals with Down syndrome, and with significant potential to benefit everyone confronting Alzheimer's disease.

A major operating hypothesis has been that all the characteristics and medical issues associated with Down syndrome result from the over-expression of those genes on chromosome 21, given that they're present as extra or third copies. The outstanding critical questions have been which gene or genes were responsible and how. At the time of the founding of our foundation and even in light of the earlier finding that the APP gene was

located on chromosome 21, this remained a major open question concerning that earlier development of Alzheimer's disease in individuals with Down syndrome.

With initial financial support from the foundation, Dr. Bill Mobley and colleagues, then at Stanford and subsequently at University of California San Diego (UCSD), focused on the APP gene in mouse models of Down syndrome which also includes that third copy of the APP gene as found in Down syndrome. They discovered that the increased or over-expression of APP resulted in the disruption of inter-nerve cell signaling, which involves a specific trophic factor, nerve growth factor or NGF, which is required for nerve cell maintenance and survival. They further found that this disruption led to degeneration of a major cholinergic brain pathway, which is critically involved in memory and also known to be a characteristic Alzheimer's disease pathology. Importantly, they also discovered that deleting that extra or third copy of the APP gene specifically, and thereby reducing the expression levels of APP and associated products in the mouse model for Down syndrome, resulted in significant improvement in the brain signaling, that I mentioned earlier, and prevented the degeneration of the specific brain cholinergic pathway and system.

This provided the first strong evidence of the functional cause and effect between APP through over-expression, such as in Down syndrome, and the development of key aspects of Alzheimer's disease. Follow-on and further research by Drs. Mobley and Ahmad Salehi, who is now at the Palo Alto Veterans Research Institute, and their colleagues, and also with LuMind RDS support, showed that over-expression of APP and its products in mouse models of Down syndrome also leads to the degeneration of another major brain system, the locus coeruleus noradrenergic pathway. This brain system and pathway is critically involved in attention and memory as well as sleep functions, and also has been found to degenerate in Alzheimer's animal models, and is another key characteristic of Alzheimer's disease in people.

These researchers have also gone on to show in mouse models of Down syndrome that these APP mediated neurodegenerative effects and the associated contextual memory deficits can be overcome by treatments to restore norepinephrine levels using two different drugs, both of which are currently approved by the FDA to treat other completely different medical conditions. Namely, these are: L-DOPS used to treat a form of hypotension; and formoterol, a beta 2-adrenergic agonist used as treatment for asthma. This research is continuing and we're hopeful that the results will expedite establishment of clinical trials in individuals with Down syndrome, in the near term.

However, already, based on these studies, Dr. Salehi and colleagues at the Palo Alto Veterans Research Institute have leveraged additional funding, and earlier this year initiated an initial Phase II clinical trial in individuals aged fifty to eight-five years old with mild to moderate Alzheimer's disease to evaluate the potential positive impact on memory functions. Again, I'm going to emphasize, these are in individuals with mild to moderate Alzheimer's disease, not Down syndrome. This trial is currently recruiting participants.

In other research, to further explore the reduction of APP and associated specific products such as A-beta, as a therapeutic approach to prevent or halt the progression of that earlier onset Alzheimer's disease in Down syndrome, Dr. Mobley and his colleagues at UCSD have also been evaluating a number of new experimental drugs, including in mouse models of Down syndrome. As just one example, in research together with Dr. Steve Wagner, they have developed novel modulators of a key enzyme that generates A-beta from APP. These are gamma secretase modulators. Although this research is continuing with ongoing investigations, recent research and preclinical studies have shown that such modulators can overcome the age-related neurodegeneration, and the associated signaling and memory

deficits in mouse models of Down syndrome as well as mouse models for Alzheimer's disease. We're hopeful that this research will lead to evaluation in human clinical trails in the not-too-distant future.

The last additional, and I think, really quite exciting, example I'm going to discuss today concerns a new anti A-beta vaccine, designated ACI-24, which is being developed by the Swiss company AC Immune. Dr. Mobley and colleagues at UCSD, in collaboration with Dr. Andreas Muhs and his colleagues at AC Immune, recently evaluated a mouse version of this same anti A-beta vaccine in a mouse model for Down syndrome. Most importantly, they have shown that this vaccine was able to induce anti A-beta antibodies in these animals, which resulted in decreasing A-beta levels, restoration of the size of the specific cholinergic neurons, and rescue of memory deficits, and with minimal side effects, in particular no inflammatory side effects. Similar results were previously obtained by AC Immune researchers in mouse models for Alzheimer's disease, and AC Immune has an ongoing ACI-24 Phase I/Phase II clinical trial in Scandinavian countries with individuals diagnosed with probable Alzheimer's disease.

I'm also especially excited to be able to tell you today that we anticipate the initiation of an ACI-24 Phase I clinical trial in individuals with Down syndrome very soon, possibly by the end of this year, or in the first quarter of 2016. We're also very excited that this trial will be supported by funding from AC Immune, together with an NIH grant and a LuMind RDS grant, and represents the very first example of a *de facto* private-public partnership to support a clinical trial on a new drug candidate to prevent and/or halt the progression of the earlier onset Alzheimer's disease in individuals with Down syndrome, and, again, also with potential applications to the wider population.

The principle investigator for this trial will be Dr. Mike Raffi at UCSD, and will initially include U.S. clinical trial sites. Many of you may have listened to his Alzheimer's Talks concerning two Alzheimer's disease clinical trials just last July.

For those of you who may be interested in learning more about participating in this planned exciting new trial, please stay tuned to our website and further formal postings and announcements. It's currently in the later stages of finalizing the plan at this stage, so my apologies that more information is not available today, but please do stay tuned and we'll make sure to post information as it becomes available.

In closing, I'd like to emphasize one more very important point. As many of you are aware, results from a number of relatively recent clinical trials on new Alzheimer's disease drug candidates have been described or reported as disappointing, as they do not show significant effectiveness against Alzheimer's disease, particularly with respect to preventing or halting the progressive loss of memory function. It is particularly noteworthy, however, that many researchers and clinicians in the field have more recently concluded that some of these new drug candidates might very well be effective or efficacious, if administered at earlier stages of Alzheimer's disease as the characteristic pathology such as A-beta or amyloid plaque deposition begins and progresses, and prior to symptoms such as the detectable effects on cognitive function.

The major hurdle has been that it has remained challenging and generally not possible to identify individuals at such early stages and who will progress to explicit Alzheimer's disease. As you have heard, during previous Alzheimer's Talks including Dr. Bateman's in September, there is now a trial focused on individuals with inherited or genetic forms of Alzheimer's disease, to provide potential for predictable progression in participants. Researchers and clinicians have been working hard on this issue, but it remains a significant challenge and especially because of the relatively very limited populations with these inherited forms of

Alzheimer's disease. Based in part on what I've presented to you today, I think it's very important to recognize that Down syndrome represents a unique key for determining the potential efficacy of appropriate new Alzheimer's disease drug candidates, and potentially also accelerating their development as effective new drugs not only for individuals with Down syndrome, but again for everyone.

In light of the fact that it's known that virtually all individuals with Down syndrome develop the characteristic Alzheimer's disease neuropathology earlier and within a relatively defined time frame, together with a quite sizable population both in the U.S. and around the world, which represent potential clinical trial participants, we believe this provides a very strong and very important justification for supporting an increase in clinical trials for appropriate new Alzheimer's disease therapies with individuals with Down syndrome.

We look at this as a very important addition to the armamentarium to address Alzheimer's disease.

As in so many cases, there are rate limiting factors. One major factor is funding, which I alluded to earlier. While there's been some progress on this front during the past few years, Down syndrome research remains dramatically and proportionally underfunded. For the most recent fiscal year, in 2014, NIH funded only twenty million dollars for all research on Down syndrome and that includes Alzheimer's disease in Down syndrome. For context, that represents approximately $60 per individual with Down syndrome. And in contrast, among many other examples I could provide, NIH funded more than forty times that amount per individual with cystic fibrosis. So, there's still a long way to go to increase the amount of NIH, as well as private, funding for Down syndrome research.

There's also a need to facilitate potential recruitment of individuals with Down syndrome in clinical studies and trials. In this regard, I lastly want to draw attention to DS-Connect. This is the Down syndrome Registry, recently established with the generous financial support of NIH, through the Down Syndrome Consortium, a private-public partnership with NIH and a group of Down syndrome organizations and stakeholders. This registry has been designed to be very patient-centric and a valuable resource for individuals with Down syndrome and their families, as well as a way for researchers and clinicians to connect to those individuals with Down syndrome for clinical studies and clinical trials. I encourage everyone in the Down syndrome community to learn more about, and consider registering and participating in DS-Connect. Just as one final point: At present there are fewer adults registered and this is certainly an important need. So I certainly encourage anyone listening with loved ones that are adults with Down syndrome to please, consider registering.

There is much additional progress being made today which time just doesn't permit discussing. I certainly encourage everyone interested to explore further information and more details on our website. However, it is my hope in this short time that I've been able today to provide you with a greater understanding of the strong connection between Down syndrome and Alzheimer's disease and how this research is leading to effective potential new therapies not only for the earlier onset Alzheimer's disease in the majority of individuals with Down syndrome but for everyone.

My sincere thanks to everyone joining today's call and again to you, George, and everyone involved with UsAgainstAlzheimer's for this opportunity. We look forward to continuing our work together with the greater Alzheimer's disease community and organizations in our shared quest to develop effective new Alzheimer's disease therapies. I will be happy to address any of your questions.

George Vradenburg: Thank you so very much, Michael, that was clear and that was thorough. I know that you couldn't get to all the topics on the subject but you did a great job in a relatively short compressed period of time.

I've got a few questions to start. Let me explore, if I could, some questions about the relationship between Alzheimer's in individuals with Down syndrome and Alzheimer's in individuals without Down syndrome. Is the biomarker progression and evidence with respect to Alzheimer's in Down's victims the same or similar to what you see in an Alzheimer's victim without Down syndrome?

Dr. Harpold: Well, that's a great question, George, and unfortunately at this stage I don't think we've got definitive answers. Again, there's a bit of a paucity of research on that front. However, the studies that have been done so far certainly reflect that a number of the biomarkers that are observed, for example, in ADNI studies, you can actually detect in individuals with Down syndrome, again it's shifted to earlier age groups. And I mentioned to you, I think probably the most definitive data that's emerging at this stage of the game is with the various amyloid imaging agents. Again, these have been more heavily studied in individuals with Alzheimer's disease or the development of Alzheimer's disease in the non-Down syndrome population. There are a number of studies that are emerging that can see the build-up of amyloid beginning actually beginning in the mid-thirties of individuals with Down syndrome.

Just to say again, there's some work with some markers in the blood to reflect some of the studies that have been done in individuals in the Alzheimer's disease research arena; this is actually an area of intense current investigation, I think, in individuals with Down syndrome. One of the things I can mention is that we've had challenges in getting funding for such studies, and one of the things that I'll mention is that just this year, the NIH particularly the National Institute of Aging and the National Institute of Child Health and Development have allocated and have just awarded funds for grants looking at biomarkers for Alzheimer's disease in individuals with Down syndrome. I think this is a start, it's not complete, but I will say that I do think it's further reflective of progress.

The final thing I'd like to say is, in these emerging imaging studies there appear to be some differences in regions of the brain where amyloid deposition occurs. This is still, as I said, early stages. I don't necessarily not expect that there may be some differences but I think the bottom line is, you're still getting essentially that same neuropathology which leads to neurodegeneration and ultimately the impact on memory.

George Vradenburg: What's so interesting as you pointed out, is that the Down syndrome population is, by its nature, a higher risk for Alzheimer's than the general population, and this provides a potentially richer population to study. But one of the things that Randy Bateman emphasized in his studies with the dominantly inherited form of Alzheimer's, is that with those families, you can generally predict that the child with the mutated gene will convert to Alzheimer's symptomatology at about the same age as the parents. Is there a similar pattern in the Down syndrome population, so that you could predict roughly when it is that someone with Down syndrome might convert to Alzheimer's symptomatology?

Dr. Harpold: Well, I think the data is still being developed on that. I will say, I think one thing seems incontrovertible, and that is that virtually every individual with Down's syndrome will develop that amyloid, the same neuropathology seen in Alzheimer's disease by their forties. So it's relatively much more compressed and you can predict that they're going to have that neuropathology. What's more difficult and which there's less data on at this stage of the game is that rate of conversion. I can tell you that the studies out there—again, there could certainly be better data—but the studies out there suggest that between the ages of fifty and sixty, at

least fifty percent of individuals with Down syndrome will convert to that dementia. And beyond the age of sixty, as much as seventy-five or more percent will also develop it. There are not many individuals that have lived beyond the age of seventy-five, but I will say that there's some intriguing evidence to suggest that maybe ten to fifteen percent of these individuals, while they've developed the neuropathology, do *not* develop the dementia. And I think that's one of the things we're certainly interested in pursuing; if one could make some correlations there, to do the studies, it may be that this population could be helpful in identifying protective factors which may be applicable not just in individuals with Down syndrome but everybody.

George Vradenburg: I think what is so intriguing is, if there is no difference in the nature of the pathology between the Alzheimer's in a person with Down syndrome and the pathology in a person without Down syndrome, that the result that you would get from the treatment may be, in a population with Down syndrome, could be extendible to the general population. So, it is a fascinating proposition and clearly in a sense, one would think, that it would be useful through your DS Registry or otherwise, to begin to insert people with Down syndrome into ADNI, into amyloid studies, more generally, so that we could get, could discern whether there are any differences, it could validate the proposition that we could test drugs in the Down syndrome population and have some basis for believing that those drugs would be efficacious in the general population.

Dr. Harpold: Absolutely. And the reverse is true too. The work going on in Alzheimer's disease outside of Down syndrome certainly has potential applicability to individuals with Down syndrome.

George Vradenburg: Let me ask about the drugs that may treat the symptoms of cognitive impairment in individuals with Down syndrome, whether there are any drugs that do that, with respect to sleep apnea or hypertension or other symptomatology of Alzheimer's in Down syndrome which have been successful and which might provide a hint about what might be successful in the non-Down syndrome population.

Dr. Harpold: Well, really, there's not anything out there and on the market that has an impact on that cognitive aspect, particularly with respect to Alzheimer's disease. I will say that there are physicians who prescribe cholinesterase inhibitors; those are already used with Alzheimer's patients out there, and in some cases, that can show some improvement, maintenance of function, but not in everyone. I guess I'd point to what I had mentioned, the work of Drs. Mobley and Salehi, with these drugs that can restore norepinephrine levels. I think, the jury's still out on whether or not that's going to impact progression of the disease, but certainly the idea there is, and it's what's been shown in the animal models, both Down syndrome animal models as well as Alzheimer's animal models, those drugs certainly would be directed towards the symptomology, particularly the memory aspects of the disorder. You would think, and again, this is a question we talk about all the time, at least in our scientific advisory board discussions for the foundation, that there should be data out there on such drugs, although again, one of those drugs, L-DOPS, has only been on the market in the US for a short period of time. But formoterol, the beta-adrenergic agonist, that I mentioned for asthma has been around for a while. The problem is, there's just no surveillance data that would allow us to be able to judge whether or not any individuals with Down syndrome taking that medication for asthma also see any sort of impact on cognition. So I think again, it's hopeful but at the present time, there are just not any drugs on the market that I can point to, and say, they have a major impact on cognition and particularly with respect to Alzheimer's disease.

George Vradenburg: We have a question that came in before the call from Richard Mohs who, if it is the Richard Mohs that you and I know from Indiana, is a prominent executive on

the scientific side of Eli Lilly. He asks: When would be the best time to intervene with drug treatment to prevent Alzheimer's-like cognitive decline in patients with Down syndrome?

Dr. Harpold: Well, that's a great question and currently one for which answers are being sought in ongoing scientific discussions and investigations. I think, this is going to be telling from some of the results of the clinical trials. And I think the problem is, as yet, there is no real definitive answer. It's currently thought that such intervention should probably be evaluated by or before the time the individual gets to their mid-thirties, but certainly at earlier ages and later stages as well. So, again, I think that's a great question but one that is still lacking for empirical evidence, but based on what we know about the development of that neuropathology that I'd mentioned to you, and also the subsequent cognitive decline, I think that's probably the best target that we have available today.

George Vradenburg: What is the average age of intervention in the DIAN study, do you know?

Dr. Harpold: The age range for the DIAN study is 18 to 80.

George Vradenburg: You're talking about roughly the same time period for an intervention with Down syndrome.

Dr. Harpold: Right.

George Vradenburg: We have a question here from Marilyn Flint. Marilyn, would you please put your question to Dr. Harpold?

Caller: Yes, there's a doctor Gary Wenk, professor of neuroscience, immunology, and medical genetics at Ohio State University, who has studied Alzheimer's extensively, especially brain inflammation, and he said throughout all his research, cannabinoids have been the only class of drug he's found work and in my study of omega-3 and the impact on the brain, I find that it's been a very powerful force in preventing in vitro and throughout life and in treatment, cannabinoids and the omega-3s in things like salmon, and I know your interest is primarily in pharmaceutical drugs, but I'd like you to comment on what people around the world are finding about natural remedies as well.

Dr. Harpold: Right. That's a good question. There's clearly many studies, this is not just in Down syndrome but as you point out in Alzheimer's disease, with omega-3s, there's been some work on cannabinoids; there's some connection, and again I didn't have a chance to talk about it today, between some of the work we're doing really on the developmental cognitive disability and mechanisms involved there and the relationship with cannabinoid systems. I think some of that work certainly looks promising at this stage, but I would just say that a lot of that is still ongoing and ultimately, I think what is needed there, are solidly designed clinical studies or clinical trials of such agents to determine the extent of potential effectiveness and more definitive answers.

I just want to add to this, that while we focused on a variety of pharmaceuticals, that's certainly not our only focus. One thing I didn't have a chance to talk about today, which George just briefly touched on in his earlier question, is sleep. And I'd mentioned that individuals with Down syndrome, for example, experience a variety of sleep issues and particularly sleep apnea. Some of the work by Dr. Jamie Edgin and her colleagues at the University of Arizona that we've supported—again, this is mainly in younger individuals with Down syndrome, adolescents, some work now going all the way back to toddlers, but up to young adults—that have shown there is a tremendous influence of sleep apnea on cognitive function. There are other studies which you may be aware of that are ongoing on sleep

issues and sleep apnea in particular in individuals without Down syndrome, and a correlation with the onset and severity of Alzheimer's disease. So, there's a case where there are various existing therapeutic interventions, non-drug interventions such as CPAP, that could be applied in those cases and I think in the short term is one way to have a major impact in individuals with Down syndrome. Again, I stress, we've seen this, mainly, in our case, in the studies with younger individuals but again, the goal there would be to, if we could correct that, improve cognitive function there; that also may impact the ultimate onset, or subsequent onset, of cognitive decline that's associated with Alzheimer's disease in individuals with Down syndrome.

George Vradenburg: You mentioned earlier that the life extension that you've been able to achieve or has been achieved in the Down syndrome population has been the result of surgical intervention and treatment. Is that right?

Dr. Harpold: Yes, and I think it's also better medical care in general. I mentioned the surgical interventions for the heart defects. That was certainly one of the major issues involved, but in reality I think it's a collection of a variety of things. As I mentioned, this dramatic difference in life expectancy has occurred just since the 1980s. I mean, frankly, that's a fact that in a sense blows me away still, when I think about it today. So in that amount of time, you've had more than a doubling of life expectancy there. But I do think it's a collection of things. Since that time, it's not just been the surgical interventions that have been brought to bear, and other medical progress, but as I think many of you are aware, it's a greater inclusion of individuals with Down syndrome in communities and society and schools etc., etc., and I think it just underscores one of the points that we make over and over, and that is, if you stimulate people, that's a good thing. It helps preserve cognitive function, and, as I said with respect to some of the research that's going on in the Alzheimer's arena at this stage of the game, we'd like to see in individuals with Down syndrome, whether or not that could in fact delay or impact the onset of Alzheimer's disease, particularly the cognitive decline, and maybe even reduce the severity. So I do think that all of those things are really key factors.

George Vradenburg: It's fascinating; is there some sort of study or set of studies on the reasons for the life expectancy improvements in Down syndrome in just that short period of time?

Dr. Harpold: You know, George, I hate to keep answering these to say, really, there are not many solid evidence-based studies on this. It's clearly observable, and clearly those are the conclusions we can draw. But I think it just underscores the paucity of funding that's been available for Down syndrome research, but at the same time, the importance of that information not just for individuals with Down syndrome but I think in general, with respect to the wider population's health care.

George Vradenburg: It is fascinating. One last set of questions I have is around ACI-24. This notion that there could be a vaccine, which I think most of us just in the vernacular associate with the ability to get one shot, one shot a year, that actually would cause you to be immune to a disease, you know, you get a flu vaccine every year, to be immune for a period of time. Is that what we're talking about here? With a possible vaccine for Alzheimer's in Down syndrome patients?

Dr. Harpold: Yes, this is essentially just that. It is using a piece of the A-beta protein, and the vaccine is constructed in such a way that when delivered to the individual it will induce an immune response and essentially induce antibodies within the individual themselves. We don't know until the studies are actually done, will this require a set of vaccinations? In some cases, even with other vaccines, that's necessary, you get a booster periodically, we don't know that. But again, I'll contrast that with a number of the current Alzheimer's drug

candidates that are in clinical trials, and I'm sure many of the listeners are familiar with, of the monoclonal antibodies which are made in a laboratory and directed against the A-beta protein or the amyloid plaques. These are already in clinical trials in individuals with Alzheimer's disease.

In those cases, those are actually described and can be thought of as passive vaccines, because you're delivering the antibodies; you're not asking the body to generate its own immune response. Now, I think both methodologies, or both approaches, could be successful. However, I would say in the case of individuals with Down syndrome, in general one thing that they don't like, I mean, many of us are like this, but they certainly don't like to be stuck with needles. And that's true of a lot of people. So I think in this case, there may be some pragmatic rationale behind thinking about an active vaccine which might require much more limited dosing than something like the monoclonal antibodies or passive vaccine approaches that are going to require multiple doses throughout their lives.

George Vradenburg: Well, that's very promising. And you said that ACI-24 is now in Phase I/II? Describe the differences in those two studies, please.

Dr. Harpold: The Phase I/II is an ongoing clinical trial that AC Immune began a couple of years ago in individuals with mild to moderate Alzheimer's disease and this is now still an ongoing trial in Scandinavia. And this is in individuals with probable Alzheimer's disease. So that's not in the Down syndrome population and that's a Phase I/II study. That's really a combination study of looking at safety and tolerability and dosing as well as efficacy measures.

The new planned Phase I study in individuals with Down syndrome that I was talking about is the one that's not yet begun; this is the one that we're excited about getting started quite shortly and this is going to be in individuals with Down syndrome. In this case, this represents a Phase I clinical trial; the primary outcome measures in that trial are going to be related to, again, safety and tolerability, and looking at dosing. But there will be secondary outcome measures, which are designed to provide preliminary information concerning potential efficacy. The situation with Phase I trials—generally they are using many fewer subjects, and they are not designed to be powerful enough to actually obtain statistically significant results with respect to efficacy. So I think this represents a first step, and the first step with virtually any drug.

I didn't emphasize this but I want to make sure to emphasize it—this is a vulnerable population and should be considered a vulnerable population when thinking about clinical studies or trials. So we want to be sure before we go into the clinic with anything, that we've got a view of safety and side-effects potential from other studies including in healthy individuals that there are no or sufficiently acceptable potential side effects, such that individuals with Down syndrome are assured the highest safety possible, as well as to then move towards actually establishing the efficacy of something in a clinical trial which is mainly what a Phase II trial is designed to do. But certainly during Phase I you may be able to get some hints that help design those and optimize those subsequent clinical trials.

George Vradenburg: That's all very, very exciting and it's exciting for the Down syndrome population but exciting for the general Alzheimer's population.

So thank you so very much, Michael, for this very interesting conversation today and for all of your work in this area.

Dr. Harpold: Thank you again.

George Vradenburg: I want to thank Karen and Chris Segal and the Zickler Family Foundati on for their generous contributions which together with your contributions make these calls possible. And thank you for all of you on the phone who have contributed as well.

Our next call will be on Wednesday, November 18 at 2 p.m. Eastern and will feature Dr. Larry Goldstein, Director of the Sanford Stem Cell Center and Distinguished Professor in the Depar tment of Cellular and Molecular Medicine at University of California San Diego. He will discuss stem cell based models of the disease and their work in using stem cells to fight against Alzheimer's. If you would like to register for this call on November 18 at 2 p.m. please click here.

If you have not already joined UsAgainstAlzheimer's, please go to www.UsAgainstAlzheimers.org and sign up. We will send you important updates and simple ways that you can get involved personally in raising awareness and urging our members of Congress and the Administration to increase their focus and resource for Alzheimer's and for related diseases such as Down s yndrome. We know we can stop this disease, but we can't get there without your help. So ple ase, join us.

Thank you to everyone on the phone and online for participating in this Alzheimer's Talks. In a bout a week, we will have a copy of the recording and a transcript on our website for you to s hare with your friends.

As always, please stay on the line if you would like to leave us a message with a question or comment. We are particularly interested in what you would like to have us discuss on future c alls.

Thank you for joining us today and have a good afternoon.