What Will It Take to Prevent Dementia?

Kenneth Davis: I'm surrounded here by exceptional people are all experts in Alzheimer's disease. Um, Roberta Brinton who comes from University of Arizona. Paul Hasan leads the program at USC and Alan Levy who leads the program at Emory. Um, so as an ex Alzheimer's researcher, I am stunned that since the colon esterase inhibitors, which, um, a lot of the people in my lab and me had a lot to do with in the late seventies, we haven't had a breakthrough drug since the late seventies. So what I want to start out by asking the panel is what's taken us so long, why are we here almost 40 years later and we still have colon esterase inhibitors as our first line treatment.

Roberta Brinton: Bobby. Ah, so ah, I think one of the reasons why we're still addict is Alzheimer's is complex. Um, it is a disease of a long transition period that Alan will talk about in a moment. Um, and that quite frankly just saying 66% of all people with Alzheimer's disease are women and some of us were in the trenches 30 years ago and are here to tell you it makes a difference. Paul.

Paul Aisen: So can this, uh, this disease is difficult. That's why it's been a long time. Um, for a long time. In fact, when, uh, when you were working in the field, many people thought you'd never be able to treat this disease. You can't see it. You look at somebody who has Alzheimer's, dementia, you don't, you can't tell on physical examination, you can't tell on cat scan or MRI. Um, uh, getting a handle on the nature of this disease has really been slow because it's been invisible. And I think that, wow, uh, your work in others let us to treatments that are really helpful. When we tried to move on to, uh, what we call disease modifying treatments that did more than improve the symptoms that actually get at the root cause. Well we didn't know enough about the disease then. And even as we learned more about the disease in the 80s, we still couldn't see it in people. And it's only been relatively recently in the last 10 to 15 years that we've been able to really look at this disease in living people.

Kenneth Davis: So we'll come back to that cause that's really important.

Allan Levey: And your thoughts, why is it taking so long? Well, I think it's a new disease, ironically enough. So it was discovered, it let know a little over a hundred years ago by Alzheimer. Uh, but what he's really found, his editor was occurring in people with a rare form and aggressive form. And your early onset, but I say it's a new disease because it wasn't until the 1970s that scientists and public became aware and physicians, and this was actually the cause of senility dementia. It wasn't a rare disease. It reads restricted to people in their fifties or sixties this is the major cause in fact that led to the national institutes of health forming a whole institute, the National Institute of aging to start launching, you know, research into what's the cause of the disease. So the real research efforts started only, you're not a little over 2025 years ago I would say, where we moved from the first era that led that can lead to identify colon esterase

inhibitors to what are the causes of the things that Alzheimer himself saw under a microscope over a hundred years ago. And those are the major changes that occur in the brain or amyloid plaques. Neurofibrillary tangles. And we're still today, now just having the tools of science to really understand what those things are made of and how we can think about tackling those in a rational way with new therapies.

Kenneth Davis: You have to underscore what Alan said. Um, years ago, decades ago when I was in medical school and we studied neurology, there was just a paragraph I remember in the neurology textbook on senile dementia and it's just talked about this as kind of some inevitability of aging and Alzheimer's disease was like this rare condition of very early onset people. And we didn't realize until the work by Yo Katzman and Perry that Terry that um, hey the fin on the phenotype and the brain was uh, all these Al's plaques and tangles and it was much more common. So we're here to talk about prevention and um, one of the big breakthroughs that going to help us with prevention. Paul alluded to. So Paul, maybe you can tell us more in the panel, can tell us more about how we can identify Alzheimer's disease. Well before their cognitive symptoms.

Paul Aisen: Well, I, I think, um, if I were to mention what I think is the major breakthrough in the last 20 years, I would say it's the ability to image the plaques and tangles that Allen mentioned. So 15 years ago at the University of Pittsburgh, a method was discovered using pet scanning. So it's not cat a CT scan, not Mri pet scan that allows you to see a molecular abnormality. The accumulation of plaques in the brain plaques are one of the two lesions, the two abnormalities in the Alzheimer's Disease Brain. There are plaques and tangles. And when we started being able to look at plaques in living people longitudinally, um, we, we were able to redraw the map, reformulate our understanding of this disease. And in fact, we discovered that the plaques accumulate decades before all simers disease, dementia. And that has changed everything with regard developing drugs. And now in the last five years, uh, a group has developed methods for seeing the tangles as well. And now we can image the two lesions, the two abnormalities in the brain in living people using amyloid pet and tau pet. Right? And that that makes everything much more work.

Kenneth Davis: Cool. So suddenly we're able to identify people who are at risk 1520 years before they have symptoms. So that provides a window for treatment. Now we could intervene way before people are symptomatic. So Robbie and Alan, maybe you can tell us about what kind of interventions then become possible and how does this change? We'll start with Alan. How does this change the way we conceptualize clinical trials?

Allan Levey: Right. Well, I just want to add, there are other ways other than pet and pet scanning to do this at. Um, well, you know, we, we also do spinal taps. The problem that I see with pet imaging, when we move this to the public health domain or the rest of the world, we can't afford to do that. I know in my institution it costs sometimes up to $13,000 that a person would have to pay

out of pocket for these police scans. Right? And Insurance won't cover it yet. So we definitely have to, if we're gonna really prevent it, we have to think about a preventing this globally and we really need other means other than pet in my view, including a blood test or other ways. But, but we're not that far from a blood test. Right? We're not. And you know, I guess we can talk about that later.

Allan Levey: But you know, to answer your question, what do we really need to do? It is, you know, following up Paul comment that this disease, the disease pathology starts probably at least 20 years before symptoms begin. Currently. You know, we've been recruiting people into clinical trials by waiting for them to come see a memory specialist or their primary care doctor with memory symptoms. You know, I have a family might notice memory loss that's too late. It's 20 years after the disease has already been affecting the brain. So the real way for us to make progress, we all acknowledge now is to start as early as possible. And we can think about starting what's called secondary prevention. People who have no memory problems, their minds working fine, but their brain is already showing the pathology. So that secondary prevention and then we also can begin to think about primary prevention. How do we even prevent the first pathology in the brain, even pre symptomatic or asymptomatic stage?

Kenneth Davis: Yup. So what makes this so interesting is that there are possible ways to intervene that may not have to do with a pill or a drug. And Robbie has a lot of thoughts about that. So why don't you tell us what you're thinking now that we know we can maybe start 20 years earlier.

Roberta Brinton: So what's interesting, what our research has shown is that the transition state that begins the process of Alzheimer's disease in women can actually begin not at menopause, but at the news years prior to menopause, those five to seven years of the perimenopause and we can actually detect Beta amyloid in the brains went of women who were undergoing this transition. And who are those women? Those women are typically perimenopausal there April we for positive, they have the risk factor. People don't know what they believe for well before is a gene that codes for a cholesterol and lipid transporter. And it turns out that that's a risk factor. It's not absolute. So if you have the April before gene, that's good to know. It's not a determinant. It's a risk. And what's really exciting to the point of therapeutics is wait a minute, what if we did that Beta amyloid scan and found that this particular woman is developing Beta amyloid in her brain and she's April we for positive?

Roberta Brinton: Well we can't change that. She's chromosomally female. We can't change the cheese. April we for positive, but we can change her metabolic health and changing that metabolic health either through introducing, I'm reintroducing estrogen, which is regulates, uh, brain energy production meant metabolism as well as metabolism in the brain, in the body or other metabolic regulators. Um, potentially met foreman. We don't know that for sure. Or One of Alan's a favorites is exercise, right? So I'm not suggesting that exercise is going to be the panacea. What I am suggesting is that exercise actually puts you on the right

path for preventing Alzheimer's disease. And if you're April, we four positive and you're female, you may want to consider regulators of cholesterol, um, synthesis and or metabolic regulators or hormone therapy. But we're going to need something. I know that was started at Mount Sinai in great, uh, you know, terrific.

Roberta Brinton: Uh, enterprise. There is precision medicine. So Alzheimer's disease is a complex disease as Paul set and one size is not going to fit all for all time. There are multiple transitions. So we need to know where that person is in the process and treat them based on their sex biology, whether they're female or male. And on their April we for biology, their risk biology as well as other aspects. So, and what's really, what's really terrific about now is there's good news and encouraging news. And the good news is there's an army of very dedicated scientists and clinicians throughout the world that are working 24, seven on this problem. That's the good news. And the encouraging news is that we have a, we have a strategy and we're going to bring those forward. For 30 years we've been focused on Beta amyloid. But in the meantime, there have been thousands of scientists working on other aspects of the disease and they are coming forward now. So I'm really excited.

Kenneth Davis: Good. And before we let Paul respond, what to say about Beta amyloid, I want you to just come back to a point that you made in passing, which is why do you think the frequency of Alzheimer's is twice in women than males? And, and tell us what that means to you.

Roberta Brinton: So what was typically said about women, and there are two fold or lifetime risk. Again, 66% of people with Alzheimer's are women are women, is that people would say they just live longer. And that is true. They live on average 4.5 years longer than men. And that does not account for a 20 year disease process. And what our work has shown is that it's not because women live longer than men, it's because they start earlier and they do start exactly about 20 years, uh, previous to the average age of diagnosis. And that you run into menopause and the paramedic

Kenneth Davis: and you think that has a lot to do with glucose metabolism. Yes. And measures that people can look at like fasting glucose and hemoglobin a one c. Thank you, Kat. I really appreciate that. I think it's important because when we talk about prevention, yeah. We don't have a pill yet. Yeah. Um, what, what we have are a lot of people in this room who are at the age that things are happening in their brain. So what if your glucose levels may be fasting a little bit high and if your hemoglobin a one C is what it might be a little bit high, it says you better start exercising and you better start watching your cardiovascular risk factors.

Roberta Brinton: Yeah. And so fantastic. And, and obviously Ken has a great memory, um, which I'm pretty impressed by. Um, and that is essentially what we did is think about this even though they're going to be millions of people develop Alzheimer's disease. The reality is is that 11% of people over the age of 65 are predicted to

develop the disease. 89% are not. So we have 11% signal, an 89% noise. How do we detect that 11% signal? And what Ken was referring to is that we can detect women at risk for developing Alzheimer's disease by using simple clinical lead deployable indicators of metabolic health, a fast fasting glucose level, uh, hemoglobin a, one c and know Hdl Ldl, which I think everyone has heard about. And what distinguishes the women at risk? It's not that they're in the abnormal range, it's at that there were on the wrong end of normal so that they're consistently high. When an indicator supposed to be low, they're consistently low when that indicator is supposed to be high. So we need to start having this ability to detect when that system is at its tipping point and move that system back through. I think very standard, um, in, uh, clinical interventions at that that can all read it

Paul Aisen: well. Is it heterogeneous or homogeneous? I tell us. So, uh, we agree on a lot of things. We disagree on a lot of things. Um, I, I'd like to actually step back a second. Um, I agree with many things that Allen and Robbie, I have been talking about things that are good for the prevention of Alzheimer's disease. I don't think they are related to the specific mechanism of disease though I think what they do is improve the brain resilience. I think that if you exercise it's good for brain health. It, it improves the environment in the brain and it helps the brain, uh, resist insults like incipient, Alzheimer's disease, hormonal factors as well, whether it's the perimenopausal period in women or declining testosterone in men. The these hormonal challenges, uh, have a deleterious effect on your brain's resilience. If you go out and learn 16 new languages after the age of 65, that's great.

Paul Aisen: You're building a big network of brain connections that are new and that is going to help you resist the disease. So I believe there are many things, many lifestyle changes, hormonal approaches of vascular interventions that help protect you against the symptoms of the disease, but are not getting at the disease itself. I believe that the disease starts with a specific biochemical event and that ultimately the way we are going to eliminate the disease is with therapies that correct. That's specific biochemical event. What is it? Well, it's the, it's the generation of this amyloid that is the lesion. How little get his trophy. Uh, it, it's, it's a, a specific biochemical event in the brain that leads to this lesion and ultimately in m and we have it in sight. Ultimately, we're going to monitor people in middle age four for changes in the biochemistry and then we're going to intervene with the Alzheimer's Staten, let's call it. And that'll be a drug that you take by mouth that fixes this biochemical abnormality so that you never develop the specific disease. We're still gonna Recommend Robbie, that we address. The other issues, the hormonal challenges, uh, promote exercise, promote healthy diet, promotes social interactions because that's good for your brain anyway. But the specific prevention of Alzheimer's disease is going to be around a biochemical event.

Allan Levey: Oh my God, you are doing a referee here. Go ahead. Go ahead. Let's take a step further back. So what do we think causes a disease? Because that gets to the

root. I think Paul is suggesting that he knows the cause so that he's going to have a single drug that's going to reduce amyloid and prevent the disease from happening. And you know, we all agree amyloid is an essential player in the disease. It's clearly playing a role. The real issue is when you think about a treatment, in my view, that may not be the right treatment. And, and uh, there were lots of reasons for this, but what we do know what causes the disease is that it's a complex disease. Can we agree on that? It's about, most studies suggest about 70 to 80% of the disease is inherited. So genetics plays a very strong role, epidemiologic studies environment, other things sort of fill in the gap for those.

Allan Levey: The other 20, 30% and it's complex and lots of ways we know what we really know about the disease. Most comes from genetics right now because we know that there are about 25 different games which so far have been identified, which additively confer the risk for most people to get the disease. It's in my view, uh, what we've learned about those genes is that amyloid plays some role, but a lot of other things are going on including metabolism, bioenergetics the whey proteins move from part to part in the brain. All sorts of different complex cellular mechanisms are, are basically I'm getting enlightened by all these genetic risk factors. We're also learning some of the things that Paul talked about resilience. Um, I agree with the concept of resilience, but I think taking that a step further, it's really critical. Um, if I'm a hundred years old and I get all timers as the symptoms for the first time, I win, that's great.

Allan Levey: You know, shoot me, then I'm fine. I'll move to Oregon. But you know, that resilience can prevent the disease for many people, you know, that's the reality. So making a brain resilient, it has a huge, huge public health ability to prevent the disease. So I think that's really important. The other thing is that some of the behaviors, some of the lifestyle things that we're learning about, including even sleep. So the amount of sleep people get, don't just make the brain resilient. Sleep seems to be playing an important role and clearing out some of the primary pathology, including Paul's favorite amyloid. So there are things that you might be able to modulate during a lifetime that could have a really dramatic impact on the disease. So these are,

Kenneth Davis: these are where we're at a critical pivotal moment here, um, in which, and we are in the field in which we really have to make a decision about how much we invest in amyloid. Um, I'm going to start with Alan and then let all the panelists respond to the following problem. There've been about 35 Alzheimer's drugs that failed. Now what does this say about what we've been doing about the amyloid hypothesis? How has that happened?

Allan Levey: It's one of my favorite questions. Thank you for that. Um, one of the most interesting things that I have been involved in the last five years is an initiative from the Nih who asked that same question. And it was inspired by industry leaders, the same companies that have invested billions of dollars over the last 20 years that funded those 35 failed trials. The industry leaders came together

with the NIH and said, you know what? The way we do science has been flawed in this field. We're all doing the same thing in secret and we go have done the exact same thing. We've all focused on amyloid. We found the exact same things independently rather than learning from each other and using our resources and our knowledge wisely and they decided we're going to change the ecosystem of science by opening it up and having people work together, industry and academics and share all the data and make it public.

Allan Levey: That initiative is called the accelerating medicines partnership program and it's done on for Alzheimer's disease, for diabetes or arthritis, something. The National Institutes of health is trying to change and it's been the most exciting thing that I've been involved in in what we're able to learn is to get really smart people. Like Ken's got a fantastic faculty member, Eric shot at Mount Sinai. There are others around the country that are brilliant mathematicians who know how to put data together, um, in an unbiased way and a data driven way to help us learn from all the genetics, all the molecular phenotype thing that we're able to do now. Unreal, postmortem human brains, including beginning to integrate the imaging that we can do in living people. Um, so that we can say what are the real scientific pieces of evidence telling us about the causes of the disease. And we're now at the transition point. We've already identified as a nation about 200 new targets for drugs to go after for Alzheimer's disease. So there's a tremendous opportunity to go about it, but we've got to think beyond amyloid.

Paul Aisen: Okay, cool. So, um, I feel that it's necessary to point out that we actually all agree on anything. But one of, one of the things we agree on is that we need to test lots of ideas that even those of us who think we, we understand one part of the disease. Until we have an effective therapy, we need to test every plausible strategy. And I think, I think I speak for everybody up here, maybe this will be the only time. This is good that you really need to have an open mind and test many different strategies. So that means anti-amyloid trucks, Anti Tau drugs, hormonal interventions, anti inflammatory interventions, lifestyle based interventions. These are all worthy of testing and are all being tested. So don't get the wrong impression that there are separate camps that are going in their own way. And as Alan said, critical to our success is a culture of sharing and collaboration within the field.

Paul Aisen: And I think amp AED is a great example. It's not the only one. Agni is another great example. We meet together, not just academics as the people on the stage here are, but academics and pharmaceutical companies and small biotechs and regulators and patient advocates. We all meet together all the time and have discussions like this and disagree and agree and share and design the best studies that we can do and continue to work extremely hard with great collaborators, uh, to conduct as many studies as we can to get to effective therapy and primary prevention. So I think on that we all agree right now why to get to the question that you're asking, why do we have 35 negative studies? Um, uh, I think we have a lot to learn. We talked earlier about what I consider a

real breakthrough is being able to visualize the disease and we can visualize it with pet scan, seeing the tangles and the plaques.

Paul Aisen: As Alan said, we can visualize a lot by sampling spinal fluid, which is much easier than perhaps it sounds. And we are getting close to being able to monitor all of the pathology of this disease with blood tests that's coming very soon. So you won't have to spend $13,000 on on scans. But this has given us a wealth of information and a new ability to test ideas. So those 35 studies were done blind, I'm sorry, 35 studies were done blind to what we're trying to treat now. How we can select the right people and we can monitor the impact of our therapies on the disease itself because we can visualize it. We can go 20 years before symptoms and we can see the disease developing and we can intervene and we have ways of measuring the impact of treatments. And this means that we're not going to have 35 more failures. So kind of just add one thing you hit on a really important point. The way we've had to do studies in over the past 30 years is watching people's

Allan Levey: memory change. And there's a real problem with that because it changes very slowly and it changes variably. Sometimes people with Alzheimer's disease have habit changed rapidly over a few years and other times it changes very slowly. And as we now move into an era where we're trying to go early and earlier, the studies are taking six, seven years sometimes before we'll actually have enough change in memory. So these biomarkers are blood tests at Paul's talking about the imaging, the spinal fluid become really critical because we think we can shorten the timeline and and really find the answers much sooner before we do some of these big things.

Kenneth Davis: So Robby would, how would you answer the question that if we had taken some of these 35 drugs and only given them to people before they had symptoms, when they had positive scans, the studies would have worked.

Roberta Brinton: Okay, I'm gonna go back a couple of steps and let's stop and think about how we treated Alzheimer's disease. So we treat it all timers, disease, um, at a point in time for that person. And Alzheimer's disease is a progressive disease. That means the disease is changing, right? And you know, it changes because things are getting worse. And the idea has been that you start here and it's linear, right? What our work has shown is that it's not linear. It is a series of transitions. I did a series of transitions, so to here to get your point, it's a series of transitions that that essentially what we see is that the brain is trying to stay alive and it's adapting and then it runs through adapt adaptation number one and drops to adaptation number two and dropped adaptation number three. And so imagine now we think that we can give a drug at this point and move everybody back to that point when the fact is the biology has changed and you know, the biology has changed because the symptoms of the disease has changed. So imagine what we now have is a portfolio of therapeutics that move this person back up to stage from three, two, two, two, two, two, one from one to health, right? And so that's why we're going to need this broad portfolio of

therapeutics that can treat the right person at the right time. We're developing something that was completely and totally unmanageable on imaginable in the past that the brain can actually re generate itself, right? So these are the kinds of bold new ideas, the encouraging new

Kenneth Davis: ideas that are coming forth that had been in the pipeline for 2030 years. And we're here now. We're ready, we're ready to launch.

Roberta Brinton: And so we're very excited about the new frontier that is exists now in Alzheimer's disease.

Kenneth Davis: We're going to take questions soon, but I'm going to ask the panel, each of them to address one other question. Um, years ago there was a not very well done epidemiological study that talked about people who have antiinflammatories in their medicine cabinet. We're less likely to get Alzheimer's disease and those that did presumably saying that those people who are taking a lot of Advil and Aleve are somehow delaying the onset of Alzheimer's disease. I took some twin data that said that and then there's a lot now of genetic data that suggests an inflammatory pathway. Can you each talk about inflammation and the role that may play in this disease and what it says about therapeutics but briefly and then we'll get to people's posts

Roberta Brinton: first because they the first signal that we see coming on lie in the aging female brain and potentially in the male brain. Let me just say that what we've learned from the female brain, some of it applies to the male brain, but what we learned where the right questions to ask from the female brain and what are those questions comes back to the inflammatory piece, which is the first sign that we see that is coming online is actually inflammation and it comes online early. It comes online as the first sign of a disease progression and that is happening in the peri menopause pay.

Paul Aisen: Um, I agree that inflammation is important. In fact, I am a rheumatologist by training so that the study of inflammation has always been part of my life. And actually I entered this field when Ken recruited me as a rheumatologist to help target inflammation in a d back in the 1980s

Roberta Brinton: just to say rheumatoid arthritis is primarily affects women just then.

Kenneth Davis: Okay.

Paul Aisen: We followed up on, on, on study an epidemiologic studies that pointed to nonsteroidals like Advil and our results were quite discouraging, but we kept thinking about antiinflammatory drugs and tested several others that also had disappointing results. I think now what we're doing is we're taking a much more specific look at inflammatory mechanisms. Protect really, I would say microglia activity in the brain that is, that is, uh, uh, um, uh, pointed to by specific genes that influence the expression of AED. And we now think that Microglia play a, a

big, these cells in the brain, inflammatory cells in the brain play a big role in managing changes, whether it's amyloid or Tau or other things. And we need to now develop specific therapies that encouraged the beneficial activity of these inflammatory cells while tamping down the adverse effects of brain inflammation that we think actually contribute to symptoms. So it's a hard nut to crack, but very important.

Allan Levey: So, um, I completely agree. Um, we've profiled over 2000 human brains now understanding the genetics and all the gene expression in the protein changes. And we see, uh, over a 400 proteins that are part of the inflammation network, which are activated in these presymptomatic sages. Just complimenting what Robbie said. Um, and other several other groups are seeing this and we're seeing it in brains from across the country. Um, Robbie, we're seeing it in men too. Yeah, sorry. Oh, wow.

Kenneth Davis: Yeah. So let's take, let's take some questions. Go ahead. Stand up. We need a mic. So we'll get everybody to be patient so we can hear what you have to say.

Audience Member: Thank you. Um, I thought, I heard everybody say that one of the ways we're going to stave off the disease is by developing new connections in the brain. I think there's some pretty good evidence about the olfactory sense being able to do that. And I was wondering if the panel could comment about current research or what your thoughts are about utilizing the olfactory sense this disease.

Roberta Brinton: That's a very interesting, the very, very interesting point. Because the olfactory neurons are one of the sets of cells in the brain that regenerate throughout life. And so one of the key elements, the question is, is can a loss in the ability to regenerate those olfactory cells actually tell us something about what's happening in the regenerative capacity in the brain? Right. So, um, I think it's a great question. Uh, there is an association between loss of Olfaction and risk of Alzheimer's disease. Um, it's, uh, it's not well studied, but I think it's an area for future study.

Kenneth Davis: Maybe we can talk a little more about the connectivity and the point that Paul was alluding to about learning languages. Is there some data around people who were bilingual and their risk for Alzheimer's disease?

Paul Aisen: Yeah, I mean I think there, there's the brain is that as a large collection, a very large collection of brain cells of neurons, and there are many, many of these connections and brain function, uh, requires all of these connections and having a very rich network makes you resilient. Uh, when you start to lose that network, you, there are various manifestations, one of which might be a sensory failure and all smell seems to be particularly notable as an indicator of early neurodegenerative disease. Not only Alzheimer's but Parkinson's, uh, very much so as well. And I think yes, it points to a connections to the network, to the synapses in the brain that need to be protected to protect everything. Since

everything in the brain ultimately is at risk in a disease like Alzheimer's, it starts with memory, but it spreads and affects everything. And learning about both lifestyle changes and hormonal changes and, uh, potentially medications that build connections and protect against loss of, of, of, uh, neuronal connections are going to help. They're going to help in all neurodegenerative diseases, including Alzheimer's.

Allan Levey: One of the most exciting things we've learned about brain science and the things I had to make these connections texted the same Microglia that regulate inflammation that Paul was talking about that we're all talking about, we think is a really important contributor to Alzheimer's disease. And what happens is they say, Mike Quigley, when they get activated, they can tear apart the synopsis is the connections. So there as we learn about this, those are the ways that we're going to regenerate connections as well.

Audience Member: Yes, we go to the Shamba land. I just like to clarify this, this idea that um, anti Tau antiamyloid uh, initiatives to failed in my view if they haven't failed yet. Um, animal data shows they clear the amyloid animal data shows that sometimes they clear the amyloid with attended brain damage while trying to remove these toxic components from the neurons. Trials in humans have shown very good improvement in the amount of amyloid in the brain, but there have been side effects. So to say that amyloid antiamyloid is fail, I think is disingenuous. I'd say the same thing about in Flint, inflammation, right? Tried the, the nonsteroidal anti inflammatory drugs. Tried prednisone, didn't work to abandon it though inflammation is part of almost every neurological disease and it's an Epi phenomenon or took away that the body tries to clear the scavenge, um, things that are toxic in the nervous system. So these are still very vital approaches. None of them should be discounted, but it troubles me to say, oh, 45 trials of antiamyloid failed when they're getting so close to something that's actually effective and not so toxic. Paul, thanks you for that comment. It's a massive plan. I'm going to be too polite to return to that.

Audience Member: Hi, I'm doctor Alison Ball bag at the University of southern California. Did a wonderful study about the effect of music and that 64% less dementia Alzheimer's is found in musicians. So I'd like for you all to address a little bit of that if you would please.

Kenneth Davis: Well, let me start and then others will talk about this. Um, thanks to lorry Tish and the Illumination Foundation. We're actually studying music at Mount Sinai. Um, one of the things that I found remarkable, uh, and has encouraged us to look at music is that, um, even at the end stage of Alzheimer's where people have lost their ability to speak, have lost their language, they can suddenly speak again the songs, you know, they can't verbalize, but yet the capacity to verbalizes there and it comes out in another brain connection and they start to sing an old song. So there's lots to be learned from music and whether those musicians are like people who have another language and they have more

connections and that protects them and gives them some resilience. I don't know. I'd like to hear what the rest of the panel thinks about that.

Roberta Brinton: So I, what are the interesting things is that when you think about music, right? It's, it's a sensory experience and it's a sensory experience that activates not only the right hemisphere but the entire brain, right? So, and it is also very interesting and, um, that there is a difference between how the two hemispheres are affected by Alzheimer's disease. Alzheimer's disease preferentially begins to affect the left hemisphere, right? And then the right hand sphere. So that's one part. The other is a, I would agree with um, 10 statement that it may well be this aspect of language. Uh, and it's, I think it's a fantastic area to study.

Allan Levey: Anybody? Alan? Any thoughts? Yeah, well it's just something that's really out of the box is just emerging is um, some, some investigators have found recently that if you flicker the lights at a certain frequency or you play sounds like music at a certain frequency, it has to be 40, 40 hertz for 40 times per second. The lights flash or a certain frequency of the sound, the brain, the brain neurons change their rhythm into that activity and it actually seems to activate these resilient mechanisms and actually can clear out amyloid in animal models. So it's really cool. So things like, like, uh, music might actually be changing brain physiology. Yeah. So over here, go ahead.

Audience Member: So is there any truth to the fact that the brain develops the amyloid plaques as a response to toxins piercing the blood brain barrier and some of these drugs have eliminated them all together, which is an accelerated the disease because some small amount is necessary. Do you want to take over protection? Yeah, so I think there's a lot we don't understand and they're certainly is credible work

Paul Aisen: that points to beneficial effects of forms of amyloid. We know that certain forms of of amyloid diffusible Alago Americ forums would be a tech technical term, but some forms are highly toxic, but other forms seem to play some protective role under certain circumstances. Um, does that mean that the amyloid accumulation is actually a protective mechanism against an infection, for example, like a virus crossing into the brain? There are credible scientists who have proposed this. I don't think the evidence is convincing yet, but we certainly have learned that sometimes when we hit amyloid too hard with drugs trying to get rid of it, we see adverse effects that might be consistent with knocking down some of the beneficial effects of forms of amyloid. What I'm trying to say is that we have a lot to learn, yet we have to be open to these ideas and continue to explore the impact of many different types of interventions.

Roberta Brinton: Um, way in the back. I was just wondering if you could speak to the interest in Keto genic diet as a treatment for these diseases. Uh, so the, uh, so there is, I think the potential for ketone bodies to be those who don't know, tell us what they're talking about. Ketone bodies and cute, what does a ketogenic diet and ketone bodies, yeah, so a ketogenic diet increases the ketones in blood, for

example, in ketones can be used as a fuel for generating energy ATP in the brain, right? So where I think, uh, this is a very traumasing area, uh, because what we see is that the brain is trying to generate those ketone bodies, uh, and that may actually lead to some deleterious effects in the brain, but we're still in early stages. And this is again, where I think it's critical that we look at all timers, not as a magic bullet kind of disease, but one of complexity.

Roberta Brinton: So the idea is that ketone bodies would be beneficial, but that also requires that you can get ketone bodies into the brain and that you can metabolize those ketone bodies, that the entire system is working. And I don't think that is the case. However, um, I think nutritional interventions are going to be absolutely necessary. The brain has to recover from this disease and the brain is dependent on nutrients to generate energy and to generate, you know, all the cells that are necessary. So I think this is an untapped area really in the field of nutritional can add a little bit. So

Allan Levey: when I was a trainee at Johns Hopkins in Neurology, um, one of my professors invented the ketogenic diet basically. And what it is, it is feeding large amounts of butter and fat and the, I mean, it's really hard diet to have. It's totally unpalatable. Uh, but it was developed for kids with epilepsy. Right? And so whether the ketones get into the brain or not, I mean these were kids that basically had a life that they didn't have a life, they were bed bound because her seizures were so frequent. And some seizures just were completely eliminated. So there can be dramatic effects on brain function and that's well established now.

Kenneth Davis: Okay. In the back on this, yes, yes. Go ahead. No, you, yes. Um, exercises almost universally recommended. What'd you come in and bid on the mechanism, how exercise may be helpful and when you went to on the published evidence that in fact it is, it is helpful.

Allan Levey: Yeah. Well there have been several studies of exercise in the many more to go. I'm going, it's a really exciting area and the, and at least my sense is there, it's probably what we would call pleiotropic. There are probably many different ways that exercise could be beneficial. I think I completely agree with Paul. It might be a very general way to make the brain more resilient. Uh, we're learning the blood vessels play an important role in not only Alzheimer's disease, but a variety of these brain diseases. Exercise seems to make the blood vessels healthier. It lowers cholesterol typically and changes our cholesterol metabolism in ways that are healthy as well. Um, there's also a very interesting research that shows that, um, when people exercise, there may be some factors released into the blood which get into the brain, which caused new brain cells to be born so called neurotrophins. So, and I'm sure there are other ways as well. And so I think there's a lot to learn but it ready, it's clear that there are lots of positive things with the only downside being people get, you know, aching knees and need to see a rheumatologist.

Kenneth Davis: Okay. We have time for, go ahead.

Audience Member: Yes, nope. You were right there. Yes. First of all, the presentation was fascinating. Not terribly optimistic that fast as a 73 year old clinical psychologist whose mother had this disease for 11 years, I'm not so sure from a psychological perspective, I want to know that I have a 48% chance of getting this disease in the next 15 years. So speak to the issue of should you really work up somebody to that point when we don't have the panacea or how you manage the psychological piece of this disorder. Right. So essentially you're asking, since we have a way of detecting these plaques before you get symptoms, do you want to know?

Kenneth Davis: Yeah. And, and we, you and I have talked about this and I've got a mother and a grandmother also wet Alzheimer's and I don't want to know, but go ahead. What? So I would, but I, I lead my life as if it's going to happen and I do everything I can to prevent it.

Roberta Brinton: Yeah. So, and, and I would, I would emphasize that, right? So for late onset Alzheimer's disease, yes, there are genetic risk factors. So having a mother with Alzheimer's disease is a risk. Having a father with Alzheimer's disease is not a risk. Well, why is that? Well, we inherit our mitochondrial DNA only from our mothers. Well, what that tells you is that, wait a minute, I need to work on generating energy. And how do I do that? Exercise is one of those ways. Exercise and, and regulating diet and sustaining cognitive activity are all ways to enable the brain to help to survive. And the part about exercise in the vascular chair, the vasculature is the highway of nutrients to the brain. Keeping that vasculature open and freely moving is critical. So I think for late onset Alzheimer's disease it is very encouraging. We we'd have sufficient evidence to suggest what we actually should be doing. Do we have evidence that says absolutely a, B and C or for another person c, D and e? Right. We're not there yet, but I think I would be very encouraged.

Kenneth Davis: Can I note on the go ahead and then we'll have to be an encouraging note.

Paul Aisen: [inaudible] I was going to actually question your premise. I am very optimistic even having lived through the last 30 years of disappointments. I am very optimistic. We understand this disease to a level of clarity that is a complete game changer and the trials that we're doing now are based on on this new knowledge that's vastly increasing our, our likelihood of success. Coupled with the fact that NIH funding for this disease has quadrupled in the last few years. When you couple that with the kind of vigorous exchanges that we all have working together to vet ideas and coming up with the best ideas and the best specific trial designs. I think we're going to see success soon. I think that we're going to have effective therapies in the coming years, five years, and I think we're going to get to prevention of Alzheimer's disease in the next couple of decades. I'm very optimistic.

Audience Member: We have a Nice Cup, right?

Paul Aisen: But you probably have children and grandchildren, and I would not recommend testing for amyloid unless you're willing to participate in a clinical trial. Right. And we have lots of clinical trials. What slows us down is not enough volunteers. And so I hope more people just want to volunteer to have tests and then join clinical trials. And that'll mean that it won't take us 20 years. All right. Thank you all for coming. Thank the panel. [inaudible].