Summit 2023

Dementia in a new era: prevent, diagnose, treat

World Dementia Council
Leading the Global Action Against Dementia

The development of future treatments

Transcript of a session from the World Dementia Council summit
20 March 2023

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Alzheimer's Society
Together we are help & hope for everyone living with dementia

Alzheimer's Drug Discovery Foundation | 25 YEARS

The World Dementia Council has 24 members working across six continents. Council members are global leaders who work in research, academia, industry and civil society. They attend meetings, vote on key issues and participate in the organisation's work. The council also includes members who are living with dementia.
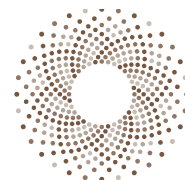
The Council also has multiple associate members consisting of international organizations as well as national governments. They help to ensure that the council's agenda aligns with other global dementia initiatives, providing the council with important strategic advice, guidance and intelligence. As they do not have full membership status, associate members don't vote on issues such as the election of a new chair or new members, or on matters of governance.

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Chair

Philip Scheltens
Professor of Cognitive Neurology and Director Alzheimer Center, University of Amsterdam Medical Centers

Prof. dr. Philip Scheltens studied at the VU University Amsterdam, Netherlands, gaining his MD in 1984, and PhD in 1993. He became Professor of Cognitive Neurology and founder of the Alzheimer Center at Amsterdam University Medical Centers in 2000, which he directed until 2022. Currently he devotes most of time heading the Dementia Fund at EQT Life Sciences, that he started in 2020. He has been the (inter)national PI for over 35 studies, including phase 1-3 multicenter clinical trials. He supervised >75 PhD theses since 2000. He founded the Dutch national plan against dementia and served as chair of the board. He is co-editor-in-chief of Alzheimer's Research & Therapy and co-leads various EU projects. He authored over 1100 peer reviewed papers and > 75 book chapters and co-edited several major textbooks. He is member of the Royal Dutch Academy of Arts and Sciences (KNAW) since 2011. In 2016 he was awarded the European Grand Prix for Alzheimer's Research. In 2020 he was Knighted in the Order of the Netherlands Lion by the King of the Netherlands. In 2021 he was elected honorary member of the European Academy of Neurology and was appointed chair of the World Dementia Council.

Speakers

Dr Heather Snyder
#### Vice President Medical & Scientific, Relations Alzheimer's Association

Heather M. Snyder, Ph.D., is vice president, Medical & Scientific Relations at the Alzheimer's Association®. Dr. Snyder oversees the Association's funding mechanisms; as the world's largest nonprofit funder of Alzheimer's research, the Association is currently investing $310 million in more than 950 active best-of-field projects in 48 countries, including Australia. She is on the executive team for the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) and also serves on the study team for the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), a tool that will collect longitudinal diagnostic and therapeutic clinical data, including measures of cognition, function and safety, from individuals treated with FDA-approved Alzheimer's therapies in clinical settings nationwide. She holds a Ph.D. in molecular biology from Loyola University Chicago Stritch School of Medicine and a bachelor's degree in biology and religious studies from the University of Virginia.
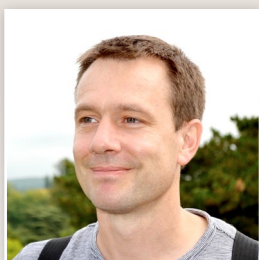
Professor Caleb Webber
Director of Informatics, UK Dementia Research Institute

I am the Director of Informatics and Data Science for the UK Dementia Research Institute. After my PhD between the European Bioinformatics Institute and Cambridge University, I returned to Oxford to work on the first large-scale genome projects. I joined the UK-DRI in 2018 where I lead a team of informaticians and stem cell modellers working across a range of neurodegenerative disorders. I took up the post of Director of Informatics in 2022 with an initial focus on data integration and democratisation.
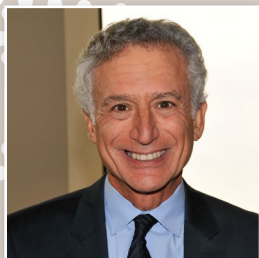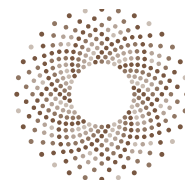
Dr Howard Fillit
Co-Founder & Chief Science Officer of the Alzheimer's Drug Discovery Foundation

Howard Fillit, MD, is a geriatrician, neuroscientist, and innovative philanthropy executive, who has led the Alzheimer's Drug Discovery Foundation since its founding. Dr. Fillit has held faculty positions at The Rockefeller University, the SUNY-Stony Brook School of Medicine and the Cornell University School of Medicine. In 1987, he joined the Mount Sinai School of Medicine, where he is a clinical professor of geriatric medicine and palliative care, medicine and neuroscience. Dr. Fillit also maintains a limited private practice in consultative geriatric medicine with a focus on Alzheimer's disease and related dementias. He has authored or co-authored more than 350 publications and is the senior editor of Brocklehurst's Textbook of Geriatric Medicine and Gerontology. Dr. Fillit is the recipient of many awards and honors including the Rita Hayworth Award from the Alzheimer's Association. He is a fellow of the American Geriatrics Society, the American College of Physicians, the Gerontological Society of America and the New York Academy of Medicine. Dr. Fillit earned his Bachelor of Arts in neurobiology cum laude from Cornell University and his medical degree from the SUNY-Upstate Medical University.

Dr Laurence Barker
Partner Dementia Discovery Fund

Laurence is a Partner in the Dementia Discovery Fund (DDF) and has supported the funding and formation of numerous DDF companies developing transformational new medicines for dementia. He joined SV Health Investors in 2016 having played an active role in setting up DDF. Prior to joining the DDF, Laurence was Head of Investment Management in Worldwide Business Development at GSK where he was responsible for managing GSK's venture investment portfolio, covering both direct equity positions as well as a venture fund-of-funds portfolio. In addition, he led licensing transactions for the pharma R&D business. Prior to GSK, Laurence worked in business development at biotech companies Syntaxin and MorphoSys. Laurence received his Masters degree in Biochemistry and Molecular Biology from the University of Auckland, New Zealand, his PhD in Biochemistry from the University of Tübingen, Germany, and an MBA from Cambridge.
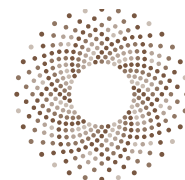
Dr Susan Kohlhaas
Director of Research, ARUK

Susan Kohlhaas is Executive Director of Research and Partnerships at Alzheimer's Research UK where she oversees the charity's research strategy and programme, including strategic initiatives on developing new treatment targets, early detection and supporting research infrastructure. She has a PhD in cancer biology from the University of Leicester and completed postdoctoral work in the field of immunology at the Babraham Institute in Cambridge.

Susan's previous roles include work in the area of multiple sclerosis, as Executive Director of Research and External Affairs at the MS Society where she worked as part of a global initiatives on progressive MS, developed and implemented plans for a large-scale clinical trials programme and worked to ensure innovations in research were implemented into clinical practise.

Discussion transcript

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

So, just like a school class actually. We're going to move to the last session and very appropriately, this session is about future treatments, the development of future treatments. I don't need to remind the audience that even if the monoclonal antibodies will be available, this is only the first step and not the last one. So, we need more, many, many more treatments to treat the whole spectrum of dementia, let alone Alzheimer's disease.

So I'm going to invite

- **Dr Heather Snyder**, Vice President and Medical and Scientific Relations of the Alzheimer's Association.

- **Professor Caleb Webber**, Director of Informatics UK Dementia Research Institute.

- **Dr Howard Fillit**, Co-Founder and Chief Science Officer of the Alzheimer Drug Discovery Foundation.

- **Dr Laurence Barker**, partner of the Dementia Discovery Fund.

- **Dr Susan Kohlhaas**, Director of Research at ARUK.

So difficult to be chair! So, I had promised actually for Susan to give the first opening remarks as long as she does it briefly.
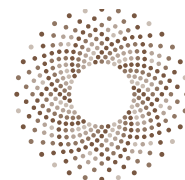
Dr Susan Kohlhaas, Director of Research, ARUK

Philip asked me to do this about a half an hour ago, 45 minutes ago, and I think it's part of his strategy to keep the remarks quite brief because I've got nothing prepared. But I thought I could just talk a little bit about why I'm really optimistic in the field of dementia and Alzheimer's disease and what I think we need to do in order to test multiple treatments, looking at multiple disease areas.

I'm really optimistic because we've got the first generation of treatments coming through. This is something that many people thought was impossible, even just five or 10 years ago, they're modest in terms of their efficacy. They've got serious side effects. But today, for the first time, we've been talking about what this means in terms of clinical meaningfulness, how this is going to impact on diagnosis, and how this is going to be implemented in care.

And that's the first time that we've been having this conversation that's very real and it's very urgent now so that gives me a lot of hope. And I also think this gives us a chink in the armour in terms of our understanding of the diseases that cause dementia. Once we can start treating, we can then start to see what else is left. It's kind of naive to think that in a brain disorder that has a hallmark of aging that we will be tackling one mechanism and one mechanism only. I think it's really important to be looking at that longer term.

And then just to round off, I'm nearly done, my previous field was multiple sclerosis and when you think about brain disorders and the impact that we had as a field for people affected by MS, I mean, when I was working there, we had on average one new treatment a year. We started with therapies that weren't very efficacious. The figure of around 30% is very familiar! So, we reduced relapses by about 30% in the first generation of treatments. Many neurologists didn't think they worked. They didn't think it was clinically meaningful. But when you used those first therapies long-term, it reduced time to wheelchair by eight years. That is pretty meaningful to patients. I think we need to be looking at these AD therapies long-term.

But what that really did for us as a community is it made people affected by MS come forward for diagnosis. It made the clinical community have a sense of urgency that they hadn't had before. And it made us really organise ourselves around how to care for people affected by MS. It got people into research and now from those first generation of drugs, we have around 20 treatments available on the NHS for people, and I think that's something that can happen in Alzheimer's disease and dementia, so that's why I'm really optimistic about the future. I'll leave it there.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund
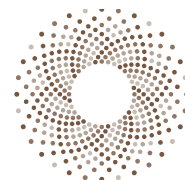
Thank you very much. Susan, I'll go to Heather now.
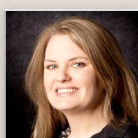
Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

I absolutely echo what Susan said in terms of these drugs being our first. In the US, we have the first two approved drugs. We realise that's not necessarily something that's in the rest of the world yet. But you have to have your first, to have your second, to have your third, and to move forward. And we're at that point now. As we heard in the last panel, we are at that convergence, where we think about these treatments not just as pharmacological, but also as prevention – including non-pharmacological interventions - and how they can work together. Or multiple drugs, multiple combinations of drugs, along with non-pharmacological interventions going forward will be key.

Going back to a conversation in the earlier sessions -- even before we deliver treatments, we need to think about diagnostic tools. We need new tools to identify those that are going to most benefit from whatever that combination of interventions - drugs, lifestyle, behavioural interventions, whatever that combination is – to ask what an individual is going to benefit most from and at what point in the disease do we need to delivery that intervention? Because it might be different for somebody that has the biological changes, but not yet having measurable cognitive changes. Somebody that's having measurable cognitive changes by certain assessments, whatever those might be, versus somebody that's later stages in the disease with more significant cognitive or functional changes.

This convergence, as we think not just about pharmacological and non-pharmacological interventions and ultimately prevention, but also care and across that entire paradigm that we have been talking about today, that's where we are today. And I agree with you, Susan, that's optimistic. We're moving in the direction to put all of that together. I often think about it as a puzzle that we're trying to fit these pieces together. And as we fit more and more of those pieces we have more and more of those pieces at our disposal to go forward with diagnostics, with identifying the right patient for the right trial (and ultimately intervention) at the right time. Success breeds success.

And we need to do this on a global scale. But as we said before, these are our firsts, and we're moving in the right direction. We've heard a lot today about data, data sharing, but also the need for real-world data. That's one of the things that in the U.S. we're looking at because there are people that are receiving some of these treatments today. We need to be collecting that information today in the real world, in clinical practice, and that's why the Alzheimer's Association launched something called ALZNET, to do just that. And we've had conversations with many countries that are starting to think about what treatment delivery will look like in their country and how to gather that real-world evidence to transform the next generation, maybe not the second or the third, but the fourth and the fifth generation as we think about those treatment interventions and that convergence of care.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you very much, Heather. Caleb.

Professor Caleb Webber, Director of Informatics, UK Dementia Research Institute

I'm coming from a bit of a different perspective. I started off my research in the big genome projects, the human genome, moved through into neurodevelopment, and then into CNS degeneration. I've always followed the data, and I've come into topics without being steeped in the orthodoxies or the prevailing hypothesis in the field. What has struck me about this field and its data is that it's very, very difficult to integrate and not enough efforts are made to integrate across these different modalities, and that leads me to have concerns when it comes to understanding how well the models capture the diseases that we're looking at.

So obviously, these are diseases of an inaccessible organ and with aging, which is a very difficult thing to bring into the model. We have to bear that in mind. But nonetheless, unless we can align our models with these diseases then the drugs that we identify won't translate very well. You need to have face validity in the models. The models have to capture some aspect of that mechanism for them to have predictive validity so that he drug that fixes that mechanism will translate into the human population. And my concern about this at the moment is that face validity is done on the basis of the researcher's favourite phenotype in the model, their expertise, and the equipment that they have in their laboratory. It's not done in a data-led way. The construct validity, how the models are made, from the genetics, from the epidemiology, I think that's reasonably robust.

But as to what we look for in the models as a translatable phenotype to develop our drugs, I think we really, really need to think about how we can have data-led, rather than hypothesis-led, ideas. It's not that we're not really clever people having great ideas, but those ideas are so often wrong. If we follow the data, we generate the right data, actually I think we'll really make a step change in finding new treatments.
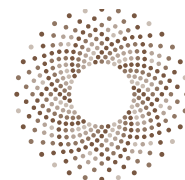
Dr Laurence Barker, partner of the Dementia Discovery Fund

Good afternoon, pleasure to be here. I'm going to bring a slightly different lens again. This time from a venture perspective. At the Dementia Discovery Fund, we're dedicated to building, creating, and funding companies focussed in the field of dementia. And the glass half full, I'll share for a minute, and then I'm going to flip it around and argue it a bit the other way, I think it's important.

So I'm very enthusiastic, as others have said, we've seen such an explosion of novel approaches outside of those just focused on beta amyloid, move forward in our portfolio. We've seen real expansion in terms of number of different programs, and now moving into clinical trials. And that's fantastically exciting, don't get me wrong, it's great.

But honestly, let's flip it around, the glass half empty is, we need to be doing a lot more, this is just the very beginning and I think one thing I'd like to pick up with you all today is almost the non-scientific the non-technical challenges, you know outside of those we think we understand as my fellow panellists have touched on those, in order to really get this novel pipeline accelerated, because that's what we've got to do more of. So, I'll be brief and stop there.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Well, very good, Laurence. Thank you very much. Howard.
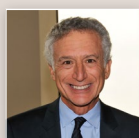
Dr Howard Fillit, Co-Founder and Chief Science Officer, Alzheimer Drug Discovery Foundation
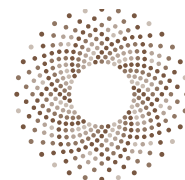
Thank you. I remember the days when we knew nothing about Alzheimer's disease about 40 years ago. I remember when Glenner and Wong first reported on the isolation of beta-amyloid. In my professional lifetime, we've just come an enormous way. We've just had the first disease-modifying drugs approved.

I'm a geriatrician and a gerontologist. I'm not a neurologist, so I've always come from the point of view that aging, is the leading risk factor for Alzheimer's disease and related dementias. And I've been interested for many years in the application of a huge body of knowledge about the biology of aging, which started more than 100 years ago, and translating that knowledge into new drugs for Alzheimer's disease. I thought I'd just go through about eight pathways that form the strategy for our foundation. We've made over 170 biotech investments in the last 25 years on drug discovery and drug development programmes, and altogether about 700 programmes in 19 countries.

So let me start off with beta-amyloid. I don't think we typically think of beta-amyloid as an aging target, but what we've learned recently is that there's multi-morbid pathology in the aging brain, and most people have misfolded proteins throughout the brain, which raises a fundamental aspect of aging as a pathway, which is that the management by cells in our bodies, including the brain, of misfolded proteins deteriorates with age. This is the process of autophagy. And so, to get a parsimonious approach to the multi-morbid pathology that we're seeing in people, in older people with amyloid, and alpha-synuclein, and TDP-43, and tau, and probably a host of many other misfolded proteins, is to target the autophagy pathway, which is difficult. A very simple one that we've recently invested in is to enhance lysosomal acidification as a strategy to enhance the degradation of misfolded proteins in the aging cell.

Vascular disease is critically important. It occurs with aging. We're funding a company that is targeting the vascular fibrin that binds beta-amyloid very tightly and causes local inflammation, maybe even beginning of plaque formation.

Inflammation, which is a hallmark of aging, both systemic and CNS inflammation, has an effect on the aging brain and is important not only in the initiation of disease but also the progression. We know

that people that have plaque without inflammatory cells around the microglia do not progress. And so, we've funded anti-inflammatory approaches, particularly repurposing drugs like anti-TNF and so on, trying to address the microglial activation and inflammation while allowing the microglia to retain their phagocytic function.

Epigenetics, of course, is important and there are many epigenetic changes, such as DNA methylation, that occur with aging. Drugs in development include HDAC inhibitors, to address the changes in epigenetics. And genetics is also important. But genetics is obviously not necessarily an aging programme!

Metabolic disturbances, such as insulin resistance in the aging brain is important. Several clinical trials have repurposeddrugs like liraglutide, semaglutide, and metformin to treat Alzheimer's disease. We've funded clinical trials in all of those areas. Metabolism is critically important to the brain. It's 2 percent of the body weight and at any given time uses 20 percent of the body's energy. So, any deficit in insulin utilization and glutose utilization has a profound effect on neuronal function.

Mitochondrial disorders occur with aging, such as the failure of mitochondrial fission to occur, and the impairment of free radical management. We're funding a clinical trial with a company named Treeway in the Netherlands to repurpose edavarone , which is an ALS drug that helps to manage free radicals.

And finally, senolytics are an emerging class of anti-aging drugs. We're all populated with senescent cells. These are cells that refuse to die. They're in every organ in the aging body. The problem with senescent cells that refuse to die is that they cause inflammation. And there are drugs that can try to kill these senescent cells, much as cancer cells won't die. And so, we're funding a clinical trial repurposing a cancer drug, using a combination study of dasatinib and quercetin to see if we can kill off the senescent cells in the aging brain and reduce inflammation.

We talk about comorbidity risk factors and how diabetes and hypertension might be affecting the aging brain and being a comorbid factor in developing dementia. I'd like to say that the process of aging itself is a common denominator in why older people develop multiple comorbidities. And I think that's a slightly different perspective on thinking of diabetes and hypertension as examples, as purely risk factors, but rather taking a holistic approach. These are signs that all of us, as we age and as we get into our 70s and 80s, we're going to develop multiple comorbidities because this process of aging affects all of our organs. And in some people, for whatever reason, there's 10% of people over 65 that develop dementia, about 25% that develop diabetes, about 60% who develop hypertension, 80% that develop atherosclerosis. There's a fundamental process going on here that we need to address, and I think we can only understand it by going back to that 100 years of research in gerontology, specifically biological gerontology, the mechanisms of aging that there's so much knowledge about that there's just a huge garden of possibilities there for our work in drug development for Alzheimer's disease.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund
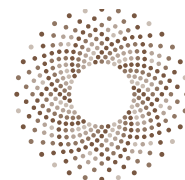
Thank you very much, Howard. I got a little bit depressed when you talked about aging, but it's fine! So, we have a question from the audience.

Participant

Thank you. I am health journalist and I've been interested in Alzheimer's for about 10 years now and the question I'd like to ask is there is something lurking on the good side, something that might be done about Alzheimer's. But as far as I can tell, none of the main bodies, organisations, foundations, and the rest of it have actually picked up and run with it. And it's something that's fantastically cheap. It's doable. It's got a good evidence base. It's been studied for 10 years.

So this is something that I'm no doubt that it's not a final definitive cure in any way, but it seems a really interesting avenue given the risk of side effects is zero, it's very cheap and the evidence is there now. And I'm curious as to why homocysteine, B vitamins and omega-3 has been completely ignored in this whole meeting and for the last 10 years.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

But Howard, there you go.
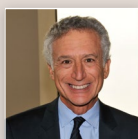
Dr Howard Fillit, Co-Founder and Chief Science Officer, Alzheimer Drug Discovery Foundation

I don't think it's been ignored at all, quite frankly. When I see patients, I always get their homocysteine, and if it's too high, then I'll prescribe folate for them. And we know that B12 deficiency, as an example, can cause not only neuropathy, but memory loss, and it's part of the routine guidelines for evaluating patients. Thiamine is also really important.

We funded a clinical trial of a preparation of thiamine that gets into the brain much better called benfotiamine. It had positive results and the investigator just got about a $30 million grant from the NIA to do a much larger study.

About 90% of the omega-3 fatty acids in the brain are Docosahexaenoic acids and it's been shown that people in the lowest quartile of DHA in their blood, which can be measured in by commercial labs now, have some memory impairment which can be ameliorated by DHA supplementation. So, I don't think these supplements have been ignored. It's part of the part of the drug research that's being done. And I think it's quite common actually.
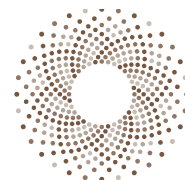
Dr Susan Kohlhaas, Director of Research, ARUK

I can talk to that briefly. So, I think for treatment of MCI or Alzheimer's disease, a definitive trial would be needed. The way to do that would to be to get funding for that definitive trial. We have mechanisms to do that in the UK. And then we have guidelines to look at what those recommendations for treatment should be taking from the literature.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you John.

Participant | **John Harrison**, Chief Scientific Officer ,Scottish Brain Sciences

Professor Weber, you dangled that wonderful phrase content validity in your presentation which I'm going to pick up. We're not good at getting people to cover content validity in the exploratory and confirmatory phase of trials. There's a lot of evidence that if you look after the facts Donepezil seems to be really good for fixing executive function and actually not memory as we thought originally. Good empirical work on that. Is there any kind of carrot we can give to the drug development community to get them to look at other facets of cognition to see where there might be extra value?

Professor Caleb Webber, Director of Informatics, UK Dementia Research Institute

Thank you. I was talking about construct, face and predictability. It could be that actually your drug works, but you didn't see it. Ultimately the value of sharing clinical trial data is that you get to go back, look at it, identify a population in which the drug works that you didn't see at the time, work out the biomarkers to identify that population, and then it's all go. And obviously, given the amount of money that's been invested, that should be quite a good carrot.

Participant | **John Harrison**, Chief Scientific Officer, Scottish Brain Sciences

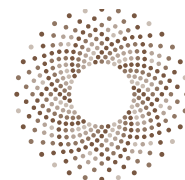It's very hard to resurrect drugs, I've discovered thank you.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Questions from the audience? Other questions? Art Toga, just arrived, fresh from Los Angeles, ready to ask a question. You'll get a microphone, you'll get a microphone.

Participant | **Arthur Toga**, Provost Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California (USC)

Thank you. One of the ways you can get dementia is to get off an airplane after sitting there for 14 hours, or in my case, 24 hours, and try to speak lucidly, so don't do that. Just kidding.

I'm struck by a couple of things, both in the last panel and this one, and that is that we don't really have any recommendations for common data elements in data collection protocols. So, what would

be the kinds of data that all trials, all observational studies, might include as a minimum set? It would facilitate both the testing of the efficacy of treatments, but also would allow us to look at the differences between population-based and disease-based trials. And I think, if we could, as a body, make some recommendations about what data should be collected, and how it should be labelled and defined, it would greatly facilitate data aggregation and give us a better handle on answering some of the questions that have been posed just now in this panel and in the previous one.
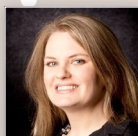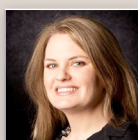
Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

Agree fully, Art, and you know that because we've talked about that about an hour ago.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Oh, this is all pre-set up, come on!

Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

It's not just what's in clinical trials and what are we collecting in clinical trials, but then also how are we doing some of the analyses and some of the follow-on.

For instance, in US POINTER which is taking the FINGER model and applying it in a diverse and representative population in the United States. We're fully recruited now with over 2,000 participants and 30% from underrepresented communities, which is really great. POINTER harmonised some of its outcome cognitive measures with FINGER, but also US POINTER harmonised with A4 and some of the other pharmacological and non-pharmacological trials that are going on- and harmonized for the very reason Art mentions. So, all of that data, particularly cognitive baseline data, but beyond that you can look at imaging data and other types of data. You're going to be able to say, well, what are the elements that are most informative, particularly in an earlier population, in a population that might have biological signatures but not yet have cognitive signatures. What about those that progress and those that don't. And so, looking at some of that commonality to get to what should be those data elements.

But that's just in one part of that spectrum of disease -- we have to get across all of that spectrum of disease to say what are the data elements that we should be studying and at what timing in the spectrum of the disease and the disease pathway.
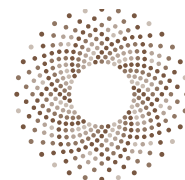
Professor Caleb Webber, Director of Informatics, UK Dementia Research Institute

So can I just add a bit more of an abstraction, but a few hundred meters that way is the Turing Institute. And we were over there a couple of weeks ago talking to them about what would data look like that was interesting to them? Could they specify that data? And so that means making data sets, and this is part of data democratisation, not just for the bioinformaticians who can start with the raw data, but also for the data scientists who don't know really about the molecular modalities and need to start with processed data and will go where the processed data is. So if you can ask the Turing Institute, a great AI machine learning institute in the UK, what interesting data would look like to them, and then bring your data to their standards so that you can attract them and say, okay, here, we've got all this data together now, run a challenge on it, tell us something we don't know, but prepare your data to make it more attractive and easy to use by those people who might be able to tell you something you didn't know.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Question from there?

Participant

Yes, there seems to be a bit of a catch-22, and that is the idea that if you take the omega-3 B vitamin connection researchers have not been able to get funding for longer definitive study. Here in the UK, the government is doing a dementia moonshot and yet we have the best clinical evidence and no money to continue to do proper, randomised, clinical controlled trials. I say we have to divest into areas where there is a non-profitable treatment, whether it be B vitamins, exercise, lifestyle or anything else we can talk about prevention but until there is actual money made available to research things are non-patentable.

Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

So just to address that a little bit, I can say that from the Alzheimer's Association, we've funded well over 60, 70 trials and a portion of these are investigating natural products. We have a lot of mechanisms to fund this sort of work, and so does ARUK. I would suggest reaching out and having that conversation off line.

Participant | **Ruth McKernan**, Venture Partner, SV Ventures

So, a question to the panel, I'd like them each to say what they think is the most promising new mechanism that they have seen or are involved with.
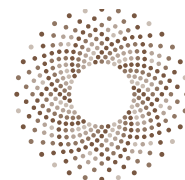

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Okay, good. That's a good… and in the meantime, Rhoda remembers the question again and I will come back to her. So very quickly, Howard.

Dr Howard Fillit, Co-Founder and Chief Science Officer, Alzheimer Drug Discovery Foundation

Well, one mechanism I didn't mention was neuroprotection. And so, if you look at the many ways that cells can get injured with aging, of all the eight or so pathways that I mentioned, there's an evolutionarily conserved common mechanism for neuroprotection. This is instructing a cell either to go through cellular death or apoptosis, or to try to induce survival pathways in the cell. And this neuroprotection is mediated by the NGF receptor, which is a heterodimer of trkA and p75. We helped

to spin out a company out of the University of North Carolina, founded by Professor Frank Longo currently at Stanford, that has P75 ligands that promote neuroprotection and have gone through phase 2A, with very promising biomarker results. And he's trying to raise about $100 to $200 million now for the Phase 2B. And I do think that neuroprotection as a common denominator in addressing all these different pathways could be revolutionary.

Dr Laurence Barker, partner of the Dementia Discovery Fund

Ruth knows me too well, so I'm going to pick something different. It's hard just to pick one! I think selective targeting of aggregated proteins while preserving the non-aggregated form, for the right disease, I think, could have real impact (increased efficacy, lower side effects). Just one approach to pick off some forms of disease. I will not expand on my interest vascular mechanism and pathologies for this conversation, but I had to mention it.

Dr Susan Kohlhaas, Director of Research, ARUK

I mean, I think, Ruth, you're causing trouble because I've got two of our CSOs of our Drug Discovery Alliance in the audience and if I pick one mechanism, I'll upset the other. But I think one of the things we're really interested in at Alzheimer's Research UK is understanding the question of resilience and what promotes resilience in the brain, I think that's going be really exciting.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Yeah, good point.
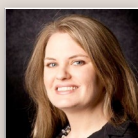
Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

I don't know that I would pick one because the mechanisms/ biology we've been discussing today, they are not new. I think these are things that we've funded some of the phase one studies several years ago and they're moving through the pipeline now and we're seeing that. But it's actually going to be the combination, or the approaching of multiple biologies with combination approaches – looking at metabolism, or specific aspects of the metabolism, with the vascular pathway as an example. And we're seeing that emerge now. I would not pick one pathway, but more, it's where we're seeing the convergence across multiple pathways in treatments being designed right now or in trials being designed right now.
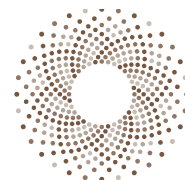
Professor Caleb Webber, Director of Informatics, UK Dementia Research Institute

I'm an expert in Parkinson's disease, and a post-mortem human brain atlas study last year reported that in Parkinson's brains the dopaminergic neurons that are lost are marked by the presence of AGTR1, angiotensin receptor one. And you can actually see the whole renin-angiotensin system is switched on in these neurons. And last year, two 10-year studies looking at cardiovascular drugs identified that RAS inhibitors, renin-angiotensin system inhibitors, reduced your risk of Parkinson's by half. But only those RAS inhibitors that crossed the blood-brain barrier. Could those RAS inhibitors be crossing the blood-brain barrier and directly acting on those vulnerable neurons in Parkinson's disease? I'd like to know.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Yeah. Good. Rhoda.

Participant | **Rhoda Au**, Professor Anatomy and Neurobiology, Boston University

All right. I remember. Okay. This is in response to Art Toga's question and Heather's response as well. And bringing in the fact that we're supposed to be thinking about world and equity. When we're thinking about what are those common data elements that they both mentioned, we got to think about what's going to work around the world. And most of what we talk about isn't going to work around the world. I'll do the little spiel for DAC! In our global cohort initiative, we're focused on two things, digital and blood. And the reason we picked those two is because we wanted to think about how do we do this equitably? How do we do equal opportunity science and bring everybody to the table? And so, I want to encourage people to think outside. Don't think outside of the box, because even what happens if it's not a box? You got to think beyond that. And we got to think about how we're going to do this in a way where we include everybody.

Professor Caleb Webber, Director of Informatics, UK Dementia Research Institute

I think one of the responsibilities of a genomic data institute is to wrangle their data. Most data challenges are 80% data wrangling and 20% application of some clever algorithm. I think we get that data wrangling done, and then we can open up our data to the world. You've made your billion in the stock market, you now want to do some philanthropic exercise, come and deal with our problem, our data is ready to go. So, I think we should prepare our data to attract all the data scientists, wherever they are, to come and tell us something we don't know.
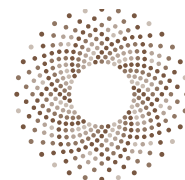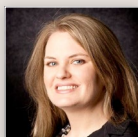
Heather Snyder, Vice President, Medical & Scientific Relations, Alzheimer's Association

Yeah, maybe just one comment on that, because I think we learned a lot during COVID about how to do some of that, about how to actually develop processes or methodologies that we could apply in different ways with perhaps different levels of what might be the resources or the availabilities. Now we're applying that and some of those learnings into how we think about Alzheimer's, and all dementia because we keep mixing those terms up, but we really mean all dementias as we sit here today.

Dr Susan Kohlhaas, Director of Research, ARUK

I've just heard a few times today people saying, don't let perfect be the enemy of good. I like that phrase, but I prefer to say, don't let perfect be the enemy of good enough. And I think we need to know what is good enough. I think the thing to think about is what is the minimum clinical data set, and to focus on that. Everything else is nice to do, but I think that's really key.

Dr Howard Fillit, Co-Founder and Chief Science Officer, Alzheimer Drug Discovery Foundation

You know, I just wanted to go back to the gentleman's question about the money and so on. I think intellectual property is critically important to the development of new drugs, and when you consider it's upwards of $2 billion to develop a drug, 12 to 15 years, there has to be a return. And intellectual property protection, I think, is critically important.

But what you're talking about supplements and the application of supplements, I think in the ecosystem of drug development, that's not the place for big pharma or necessarily even industry, but for groups like ours, the three nonprofits that you have here, and government, to support clinical trials so that we can determine whether DHA for example or Thiamine supplements, such as Benfotiamine or any of the many supplements that are out in the market, are effective. We have a strategy that if there are supplements with good data, let's put them in clinical trials and see if they really work. And if they really work, then that becomes general knowledge, but it doesn't necessarily create the marketing that would lead to widespread market access and patient adoption. So, even with supplements, there are challenges in making sure that everyone gets them. But I think we need to do the clinical trials. When you go into any pharmacy now, you see so many supplements. How many of them have actually been through clinical trials? Very few.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you very much. I feel a little bit like sort of fatigue in the room and longing for a forbidden lifestyle intervention which is called alcohol. Yes, Miia. Where's the microphone for Miia? Come on. Then I will finish.

Participant | **Miia Kivipelto**, Professor in Clinical Geriatrics, Karolinska Institutet

Yes, just final one. I just want to come back to the question about data harmonisation and data sharing, because I really think it's important. And Heather, you mentioned already the WW-FINGER and how we work. We are trying to use prospective harmonisation with 45 countries. There is a way to try to harmonise, not exactly the same measures, but close enough. And I think if we have that view, that joint data, we can use federated data set, in FINGER we have the support from ADDI to really do it more easily. And you can ask questions that you can never answer in one single study, like gene-environmental interactions, sex differences, many of the questions we now think about, but one trial is too small to answer. So, I just want to highlight once again, the importance of prospective harmonisation and data sharing and creating that attitude. Thank you. Thank you very much.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

And very appropriately, you have the last question indeed. Any comments from the panel towards this? No, it's all true. Yeah. So we are going to end this a little bit early for a bit of good news from the UK Science Minister who you can see is waiting to speak next. So first of all, I'm going to thank the panel very much. Howard, Susan for coming in so late, Heather, Caleb, you can join your colleagues again. You are released.

The World Dementia Council (WDC) is an international charity. It consists of senior experts and leaders drawn from research, academia, industry, governments and NGOs in both high-income and low- and middle-income countries, including two leaders with a personal dementia diagnosis. The WDC has an executive team based in London, UK.

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