



**World Dementia
Council** Leading the Global Action
Against Dementia

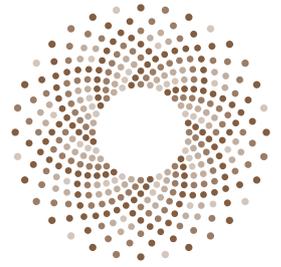
Global dialogue on non-amyloid targets for disease modification: Transcript

The dementia landscape
project

21 October 2021

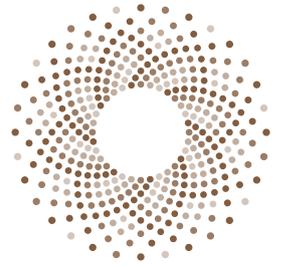


Co-chairs



Dr Maria Carrillo

As chief science officer, Maria C. Carrillo, Ph.D., sets the strategic vision for the Alzheimer’s Association global research program. Under her leadership, the Association is the world’s largest nonprofit funder of Alzheimer’s research — investing more than \$455 million since 1982 — and an internationally recognized pioneer in convening the dementia science community. Dr. Carrillo uses her platform as a noted public speaker to play an instrumental role in the Association’s efforts to lobby for increased funding for the disease. Dr. Carrillo oversees the implementation of the Association’s growing portfolio of research initiatives, including the Alzheimer’s Association International Conference® (AAIC®), the world’s largest and most influential dementia science meeting, and the Research Roundtable, which enables international scientific, industry and government leaders to work together to overcome shared obstacles in Alzheimer’s science and drug development. In addition, she leads the Association’s direct involvement in research by serving as a co-primary investigator for the Association-funded and led U.S. POINTER study, a lifestyle intervention trial to prevent cognitive decline and dementia. Dr. Carrillo earned her Ph.D. from Northwestern University’s Institute for Neuroscience and completed a postdoctoral fellowship focused on Alzheimer’s brain imaging and risk factors at Rush University Medical Center in Chicago.

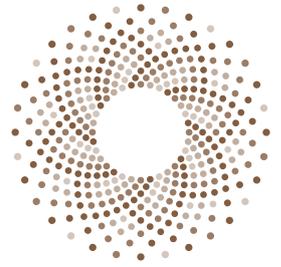


Professor Philip Scheltens

Prof. dr. Philip Scheltens studied at the VU University Amsterdam, Netherlands, gaining his MD in 1984, and PhD in 1993. Clinical residencies in neurosurgery and neurology supported his academic development. He is Professor of Cognitive Neurology and Director of the Alzheimer Center at Amsterdam University Medical Centers. His main interests are early diagnosis, biomarkers, clinical trials and drug development. 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 text books. He is member of the Royal Dutch Academy of Arts and Sciences (KNAW) and served as Secretary General until 2020. 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. Since 2020 he is also managing partner of the LSP Dementia Fund. In September 2021 he was elected chair of the World Dementia Council.



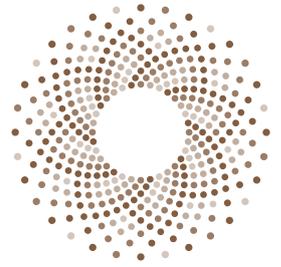
Speakers



Dr Laurie Ryan

Dr. Laurie Ryan is Chief of the Clinical Interventions and Diagnostics Branch in the Division of Neuroscience at the National Institute on Aging, part of the NIH. She oversees the development, coordination, and implementation of the division's clinical therapeutic and diagnostics research programs and infrastructure. Dr. Ryan also directs the Alzheimer's disease and related dementias pharmacological clinical trials research portfolio. Dr. Ryan received her BA in Human Development from St. Mary's College of Maryland in 1986 and her Masters in Psychology from Loyola College in Maryland in 1991. She undertook doctoral training in clinical psychology with specialty focus in neuropsychology at Louisiana State University in Baton Rouge. She completed a neuropsychology-focused psychology residency at the Medical University of South Carolina, Charleston and clinical neuropsychology fellowship at Thomas Jefferson University, Philadelphia. After completing her fellowship, Dr. Ryan joined the Defense and Veterans Brain Injury Center (DVBIC) at Walter Reed Army Medical Center in Washington, DC. In 2003, Dr. Ryan became the Assistant Director for Research where she was responsible for overseeing clinical research development and implementation with a particular focus on clinical trials. In September 2005, Dr. Ryan joined the NIA as the Program Director for Alzheimer's clinical trials. In December 2013, she was promoted to the branch chief position.





Professor Malú Tansey

Norman and Susan Fixel Professor of Neuroscience and Neurology, Co-Director Center for Translational Research in Neurodegenerative Disease and the Parkinson's Foundation Research Center. The research interests of our laboratory include investigating the role and regulation of immune and inflammatory mechanisms that protect against or predispose and individual to develop neurodegenerative disorders. Genetic and environmental contributions to lysosomal dysfunction and alterations in lipid signaling that dysregulate neuroimmune activity and trigger neuroinflammation are a main focus of investigation; as is the role of the gut-brain axis and chronic peripheral inflammation in the pathogenesis and progression of neurodegeneration.

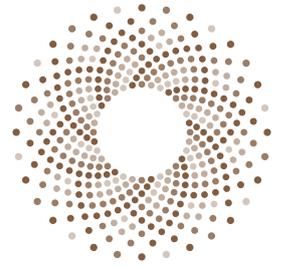


Lenny Shallcross

Lenny Shallcross is executive director at the World Dementia Council. Prior to that he was Head of Community Engagement leading programmes across the UK to establish Dementia Friendly Communities. This includes the Dementia Friends programme which is the biggest health social movement campaign delivered by 10,000 volunteers that have recruited 2 million individuals through a community, digital and corporate offer. Before working for Alzheimer's Society he worked in the UK government as a political adviser at the Department for Culture, Media and Sport and the Department of Health, as well as working in Parliament and for the Labour Party.



Global dialogue on non-amyloid targets for disease modification



Thursday 21 October 2021

06:00 PDT San Francisco
08:00 CDT Chicago
09:00 EDT New York
14:00 BST London
15:00 CEST Central Europe



Discussion transcript

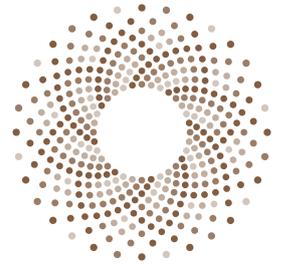


Lenny Shallcross
Executive director, World Dementia Council

Welcome everyone. I am Lenny Shallcross, Executive Director of the World Dementia Council. I realise many of you have participated in one of these global dialogues before or another Council meeting but for those of you who have not, the World Dementia Council was established following the London dementia summit in 2013 hosted by the UK government as part of their G8 presidency.

The Council is now chaired by Professor Philip Scheltens, Director of the Alzheimer Centre, University of Amsterdam. There are 24 individuals who are members of the Council. Alongside them there are a number of government members. We are holding an in-person summit meeting on December 6 in London and at the meeting the Council will publish a paper looking at the progress the international community has made since the 2013 dementia summit. To help inform that, we want to hear from experts around the world on different aspects of dementia policy that were reflected in the communique in 2013.

This is one of a number of occasions where we are hearing from the community on different aspects of policy. Over the last twelve months we have held dialogues on biomarkers, clinical trials, technology, dementia in LMICs, among other topics. Over 400 global leaders have participated in the dialogues. And there are three more meetings coming up those are on psycho-social research, early career researchers and a dialogue just for people living with dementia.



We will produce a transcript of the meeting – which is why the meeting is recorded. For people who contribute live we will check the transcript with you prior to publication.

After all the dialogues we have continued the discussion publishing collections of essays with reflections from people who took part in the meeting and a closing essay from government or international figures who have been active in the field. Early next month we will be publishing a collection of essays on data sharing for research with contributions from those who participated in the meeting and a closing essay from Bill Gates.

All our publications are published on our website. I would encourage you to share your thinking either live in the meeting or in the chat conversation. As you will know from the agenda we will kick off with short opening perspectives and then there is an open discussion which Maria will chair. To contribute to the conversation just raise your hand in zoom. I am sure you all know this by now but to do that click on the reactions button and select raise your hand.

And with that extremely brief bit of housekeeping done I would like to introduce and thank the co-chairs of today's dialogue Maria and Philip for once again co-chairing the meeting and handover to Philip to start the conversation.



Professor Philip Scheltens

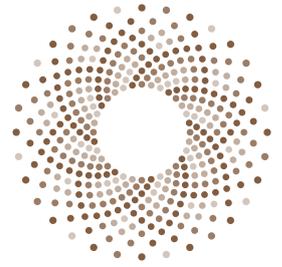
Professor of cognitive neurology and director,
Alzheimer Center, Amsterdam University Medical Centers
and member of the WDC

Thank you very much, Lenny. Welcome to you all. All very familiar faces. This is exciting times in the Alzheimer field I would say and since June 7 the world has changed dramatically. But I think we have to consider other ways of treating Alzheimer's disease and that's why we thought it would be most appropriate to have tau as the point of our discussion for today.

Since the last time many of us got together when we had one of these dialogues actually on biomarkers, I have become Chair of the World Dementia Council which is a great honour but also a big responsibility I must say. The output of this work will be in person meeting on December 6th at the Francis Crick Centre here in London, where I am today, and I hope many of you will be able to attend. It would be very nice to see each other in real life again. Following up on that we hope next year in the autumn of 2022 we hope to host a ministerial meeting in the Netherlands. I think personally that is also very exciting for us to organise.

So, we will have to start the meeting here. I will just introduce and also thank the opening speakers. Dr Laurie Ryan, she is the Chief of the Clinical Interventions and Diagnostic Brain in the Division of Neuroscience at the NIA. Professor Malu Tansey is the Professor of Neuroscience and Neurology at the University of Florida.

Many of you have already participated in earlier dialogues and you all know the format but those of you who have not actually Laurie and Malu will share their perspectives. Laurie will have some slides to share and Malu will just give a verbal perspective. Then



I will hand the baton over to my co-chair Mario Carrillo who will preside over the roundtable discussion which you can do verbally by raising your hands or sending in a chat with questions as Lenny explained everything will be saved for the transcript. The transcript will be used for a formal paper about this particular topic of today. So please use every means you have raise your voice and give your opinion.

So first let me introduce Laurie Ryan and give her the floor to share thoughts on the NIA approach to non-amyloid targets and reflections to where the field lies in this area. Laurie the floor is yours.



Dr Laurie Ryan

Chief of the Clinical Interventions and Diagnostics Branch in the Division of Neuroscience at the National Institute on Aging

Thank you, Philip, and thank you all for having me here to represent the NIA. I am really going to talk about the NIA's pre-clinical and clinical pipeline for non-amyloid targets.

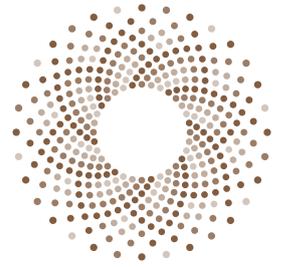
Actually, just to give you a little background. We have a pipeline of funding opportunities for academic institutions and biotech, and really it supports the discovery and development of new drug candidates targeting multiple aspects of the disease. This has been something we started back in 2006, looking to diversify the pipeline understanding even then that amyloid was certainly part of the puzzle but was not going to be the only area that we needed to target.

And in addition to the funding opportunities we have a series of open science, open source enabling programmes to help data driven and predictive drug development approach that the NIA supports.

What I wanted to show you here is really what has happened in the landscape of funding, what has happened in the landscape of drug discovery efforts. This is just for NIA funded projects. This has come from the International Alzheimer's and Related Dementias Research Portfolio or IADRP. And you can search across all the funders. We have 40 plus funders. Many who are on this call today have their grants in IADRP. This is just looking at the NIA's portfolio. And the 2 boxes show 2011 up to 2020 really reflect what's happening in terms of funding. There were some significant increases in funding starting in 2016. While But you can see that amyloid is still part of the picture, you can also see the multitude of targets that are being investigated in the drug discovery space.

We can see a similar thing in pre-clinical drug development. So these are projects that are trying to get to Investigational New Drugs (INDs). And finally, moving into the early stage of clinical development again we are still seeing some amyloid but we are seeing many more targets being investigated in this space.

What I wanted to show you here is that from our preclinical drug development projects we have had 12 receive IND status and are in clinical development now. All the ones in yellow that you see there, dark yellow, are the non-amyloid focused targets. We still have 3 of those 12 that are amyloid but they're next generation targets if you will. A DNA vaccine etc but the overwhelming majority of them are looking at non amyloid



targets. These are the ongoing pre-clinical drug development program. And you can see that actually all of these are Tau or other targets, they are not amyloid focused. So really, while amyloid is part of the puzzle, NIA has for a long time has viewed it as a multifactorial disease. We were going to have to have multiple therapeutics and likely from my perspective, I think the NIA overall, we're really going to be looking at combinations of therapy for people with different risk profiles. Really, we're striving for precision medicine for AD and ADRD. I think that just took up my time and I will turn it back to Philip.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Thank you very much for this very quick but also very elaborate overview of what the NIA is doing. It's clear that amyloid is almost going to the background here and it's focusing on other mechanism, which is good because we know that there are other mechanisms that are playing a role. So, this will ultimately hopefully also translate in phase one or phase two studies as well. So, there will be a flow of new studies coming. As you say, and this is something close to my heart, ultimately the precision medicine approach will be targeting several different mechanism at the same time in one patient. So that's it seems that the, the NIA funding is really targeting towards that work.

So that gives us a good basis for the rest of the discussion. We can see what people think about this and what they think about how ultimately it will play out. So, thank you very much. And we'll be back with you with questions of course.

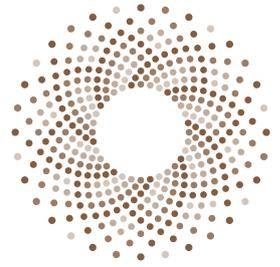
I'm now handing over to Professor Malu Tansey to share her work in the field of inflammation, innate immunity and her experiences with federal and the not for profit funding programs out there to support this particular pipeline. Welcome. And the floor is yours.



Professor Malú Tansey

Norman and Susan Fixel Professor of Neuroscience and Neurology, Co-Director Center for Translational Research in Neurodegenerative Disease and the Parkinson's Foundation Research Center.

Thank you so much. I appreciate the opportunity and the invitation to just give our 2 cents worth about our experiences with not just NIA funding, but private funding from the various organizations that are very invested in funding dementia and ADRDs. We've had from the very early days quite a lot of success, not starting with, you know, the top dogs, like Alzheimer's Association, but AFAR and ADDF and Bright Focus. And what I tell trainees out there is that you've got to start with the seed money funders. You've got to build on that. And so, we encourage them to really start thinking out of the box, be innovative. There are things that are not quite ready for the NIH where reviewers tend to be very risk averse. The solution is to go to the foundations. To put together your best ideas and to shop them around.



And we've been very fortunate. Without the opportunity from these various funding agencies in the Alzheimer's and ADRD space, and in the Parkinson's space, we would not be here today for sure. I say that all the time about the Michael J. Fox Foundation. When we started working on inflammation in 2002, and there was no traction to do that at all.

And from there, I think that once you get a little bit of confidence and you get a little bit of more solid preliminary data, and you de-risk the projects you're in a position to then go to NIH for things that are more mechanistic. Perhaps you have to write an entirely different kind of grant and we help them do that too. Because you're writing not from the disease driven point of the grants that the funding agencies are really looking for. A lot of people call them, you know talking "Foxese" in terms of Michael J. Fox, for instance, you have to really write them in a different way. And then really focus on the mechanism and the questions that are going to form the basis for those therapies in the future for some of the NIH funding. And so we've had a lot of really great support.

And then of course, the partnerships now that foundations and NIA, NIH and NINDS are forming with each other for biomarker discovery and for trials. Also, in the pre-competitive spaces that they've formed with pharma and biotech. I think big kudos to all of them and all of you for, for doing that, because we really would not be able to move as fast as we can without those partnerships. And we have, you know, more than a dozen collaborators through sponsored research agreements. We had that at Emory. Allan Levy, who I know is on the call, is a huge supporter of partnerships with companies, with donors who want to see their dollar stretched. And so really, I would not be in this space if it weren't for his encouragement and his support in making us come from the Parkinson's to the dementia space when I was at Emory. So, thanks Allan for that.

Just to say, in terms of non-amyloid targets and to follow what was just said about the portfolio for NIH, is that I think the field has been moving in the non-amyloid direction for quite some time. It has just not been very loud. And I think we always have to have a complementary strategies, right? I always like to say it's good to have a plan B because you never know, and you have to stretch. And so, I don't have any slides to share with you. But I would like to call attention to an article that we just published with Brianne Bettcher, Michael Heneka and Guillaume Dorothee. It's a roadmap article called peripheral and central immune system crosstalk in Alzheimer's disease – a research prospectus. And we just published it in Nature Reviews Neurology. It really talks a lot about what we think is the most promising, the most challenging, and where we need to go to reconcile some of the findings that still don't quite make sense. But to build on what has been done in the preclinical space, what is starting in the clinical space, to reconcile some of the animal findings with some of the human studies and to build this sort of interdisciplinary studies that are really needed to build the strong foundation for therapies that are going to be effective for patients. So, if you have any questions regarding that, I'm happy to get more specific. Thank you.

Chat function

The chat function was available throughout the dialogue for participants to ask questions of presenters and to hold discussion amongst each other. It began just under 20 minutes into the event and is displayed below. It does not necessarily correspond with the adjacent transcript in this document.



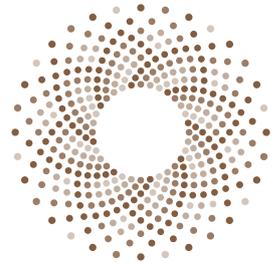
Dr Heather Snyder

ALZ Association funding trends look very similar to NIQ - huge diversification over last several years. Encourage all to check out IADRP. <https://iadrp.nia.nih.gov>



Dr Maria Carrillo

Thank you Dr. Ryan! Great to see so much diversity in the funding pipeline!



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Thank you very much Malu. A very clear path towards drug development. I would say you're stretching the foundations and the collaborations between foundations and governmental bodies. A prominent position, for instance, for the Michael J. Fox foundation, how that enormously helps. And I would just add, you mentioned the DDF. I'm also working, as a managing partner of the LSP dementia fund. I think these funds come in at the stage where the preclinical research has been done, where there is animal proof, and when you are translating it to humans in phase one. That's actually a huge opportunity that is now there. And all these VCs, and specifically the dementia specific funds, they are eagerly waiting for such opportunities. There is a lot of money around nowadays to really invest. And I think the groundwork there is exactly what you described and that gives hope for the future.

So, thank you again, and there will be questions for you later on. I'm now handing over to Maria Carrillo. We've done this together in earlier dialogues, and I think it's, it's a big honour to work with her. She will guide and lead the discussion. Maria the floor is yours.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Thank you . And I'm not going to take any time because I think we have a lot of folks on here that are experts that have perhaps thoughts, opinions on the future.

I know some of you, maybe studying amyloid to a great extent, but understanding that combination therapies and precision medicine is absolutely the future. But I know that some of you also might have a very strong opinions about to the current activities in the field, including accelerated approval from the FDA, at least in the United States. And I think the bottom line to all of that, you know, because disagreement and discourse and challenge of hypothesis, it's actually important for the scientific process we all know this. So that's a good thing! But even though we may not all agree on some things we all agree that we need to do more. We need to do it better. We need to do it faster for all of the people living with Alzheimer's today. And those that may be diagnosed in the very near future and beyond. so that we all know. I think we're all committed to that. Every single person in this virtual room is committed to that. I think that's what really brings us all together to have this type of discussion, to think about what that future then looks like and when it will arrive.

We do know that the lowest hanging fruit is the anti-amyloid sort of approach and closely followed by anti-tau therapies, whether they're small molecules, whether they're also monoclonal antibodies. And so there is a lot of movement in that area. Doesn't mean we don't need more we do need more. I think it's so critical to also think about everything else. That certainly the NIA that you just saw in that lovely slide Dr. Ryan showed with so many different approaches. It is being supported not just by our



Dr Laurie Ryan

Agree, please go to IADRP to see the landscape of funded projects from the 40+ international AD/ADRD funders



Dr Gustavo Saposnik

Dr Ryan: How many of the funded projects target a combination of therapies?



Professor Rik Ossenkoppele

Here's the article: <https://pubmed.ncbi.nlm.nih.gov/34522039/>



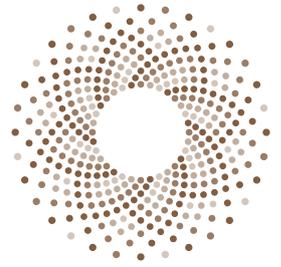
Professor Frank Gunn-Moore

I think we all agreed combination therapy will be the future, but I guess the difficulty is to know which combination? It seems to me we need advice/discussion on how to combine therapies.



Dr Gustavo Saposnik

Thanks Frank. I could not agree



organization but by so many others that were mentioned that are doing the same thing. The future is that combination therapy.

What I want to maybe start with, with this expert group, is to ask all of you, and all of you probably have questions you want to ask of each other, feel free to do that as well – please raise your hand if you want to be the first speaker. But what I would like us to talk about is what is that next lowest hanging fruit? Is it anti-inflammation or looking at innate immunity and stimulating it, whether it's one way or another? Is it going to be another type of protein? Is it going to be TDP43? Is it alpha-synuclein?

And then the other thing that I think is important to discuss, all of you as experts understand it, it is aging itself. Aging itself is a confound that is happening within the context of dementia. What does studying aging add? What can that bring to this? Because many of us are studying this question from the perspective of one particular protein, one particular mechanism of action, one stream. What about aging and what it brings to the table. Who wants to talk first? You're not shy.



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Hi Maria, this is Henrik. One of the things I think we should discuss and study more is brain development. Because I think the tau phosphorylation mechanism is actually a physiological mechanism that is active in the developing brain. There is so much data supporting the relevance of this to Alzheimer's disease and amyloid effects on neurons. We have performed CSF analysis on newborns and they have very high p-tau levels in their CSF, ten to fifteen fold higher than adults. It's amazing and it probably represent pruning.

I think this pruning of synaptic networks is really what amyloid induces in Alzheimer's disease, directly or indirectly via astrocytes and microglia. We could potentially use the brain development models that do exist to better understand neurodegeneration in AD. If phosphorylation of tau could be inhibited, maybe neurons will be less affected by amyloid. These models are so clear and the tau changes are so profound, so perhaps it will be easier to find small molecules and other compounds that could influence tau phosphorylation in a manner that potentially also could be used to stabilize neuronal networks in Alzheimer's disease, also in the presence of amyloid plaques.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

That's a great start. Thank you, Henrik. I appreciate that. Reisa, I see your hand up. And then after that, Gabriel

more. Another issue is that as mentioned most reviewers are risk adverse. Not a way of advancing the field.



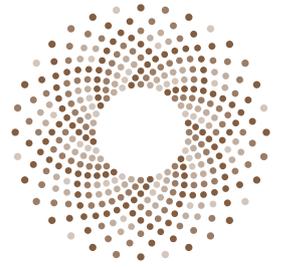
Dr Laurie Ryan

Dr Saposnik, the majority have been single target but not all. Moreover, NIA has a funding initiative on drug repurposing and combination therapy: <https://grants.nih.gov/grants/guide/pa-files/PAR-17-032.html>



Professor Frank Gunn-Moore

I can understand Pharma being risk adverse, they are a business, but it is the governmental funding (in the UK that would be the Research Councils) who needs to be more open. It is noticeable we always have to rely on the charities.



Professor Reisa Sperling
Co-principal investigator, Harvard Aging Brain Study

So, I was actually responding to your first question Maria about aging. But I totally agree with what Henrik just said, it's really interesting data. I don't know if this is the next low hanging fruit, but I think one of the ways we get to the root of the problem is going back to why all of these proteins that accumulate going back to understand the basic mechanisms of how these proteins are dealt with, and especially in aging, because the ability to handle these protein is certainly changing with aging, and trying to go after more ubiquitous mechanisms.

And I think this is really tough because of course those mechanisms are important in every cell. That's how we get to be aged 80 or 90. But you know, I was trying to follow the whole mTOR pathway, and I'm not a basic scientist so I know there's a lot more going on, but I just think it's not going to be going after tau, not just alpha-synuclein, not just TDP 43 and abeta. It's going to be having to figure out how we're handling our proteins. Having said that I have high hopes that clearing multiple proteins, such as abeta and tau, will help us change the system. If you can change the balance in the system with even one of the over-produced or uncleared proteins, whichever it is, we will, we might be able to win.

And then lastly, I wanted to ask people who work on inflammation because in our group we're constantly having a debate about, do we want to zoop up inflammation or tone it down? And I, you know, I really try to follow this field, but I feel that we're getting, it's getting harder and harder to know. And is that a stage thing or is it a hopeless that we could zoop up autophagy without bringing in some of the so-called M2 or more negative pathways that are with high cytokines. But I think that's the other area that's ripe. Inflammation is clearly involved, but we need somehow to get the good without the bad. Sorry these are areas of research that I don't get to directly work on, but I want to ask the experts.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Very important. I think maybe I can, before I get to Gabriel, Dr. Tanzi can you comment a little bit on sort of, since that is your, your area and we just finished, well, we're actually on the last day of the APOE and immunity, a virtual conference of the Alzheimer's Association is hosting, which I think some of you have been speakers, excellent speakers in.



Professor Hilikka Soininen

Henrik great notion this brain development.



Professor Serge Gauthier

Can we benefit from the experience of other fields such as oncology or infectious diseases in order to design combination trials?



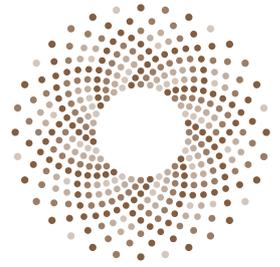
Professor Frank Gunn-Moore

Personally, and we all will be biased, metabolic issues is a low hanging fruit. For example glucose metabolism drops in AD, but there is still glucose in the brain. Why? Trying to convince neurons to go back to using glucose, I think would be a good way of resetting the general health of the brain.



Professor Philip Scheltens

Good point Serge.



Professor Malú Tansey

Norman and Susan Fixel Professor of Neuroscience and Neurology, Co-Director Center for Translational Research in Neurodegenerative Disease and the Parkinson's Foundation Research Center.

Yes, certainly. Those are excellent points, Reisa and Heinrik. I think you hit it. You hit the nail on the head. The inflammation story and the immune activity story is very complex.

The first acknowledgement we need to make is that it does change with age. It's going to be very different during development and during aging. It's not just reversal. But those immune cells, glia astrocytes, they are all aging along with the neurons. And they're changing and they're becoming dysfunctional in ways that we don't really understand yet. And so, their ability to listen to the cues from the neurons, that crosstalk, that conversation really breaks down.

And the other thing about that is that as the disease progresses, the inflammation system and the immune system are playing different roles at different stages, at the beginning the middle and the end. And so, you can't really target inflammation per se, with a one size fits all in the beginning and the middle and the end, because we, it will, it will not work. You can't just immunosuppress the patient. You can't maim and kill microglia. You really have to be extremely careful to identify pathways that are contributing to the selective vulnerability of certain populations be very, you know, in and out targeted. You need to understand how these are changing so that you don't have the collateral damage of just dampening and turning down the volume on everything.

The other really important thing that we don't know, it's kind of the big elephant in the room, is the basic differences between mice and other model organisms, and humans. We just don't know enough about the human immune system, and the brain and the peripheral and central crosstalk that's happening. There's a lot of debate right now. Are their immune cells going into the brain? Is that an artifact of preclinical studies? What are they doing there? Are they good? Are they bad? They're not likely bad. They're very likely to have a function. But again, that function is going to change as a function of aging with disease, different genetic backgrounds, the exposome. And so, understanding that dynamic process, and understanding the central-peripheral conversation that becomes dysregulated, is going to be critical.

The reason I think it matters therapeutically is because if any of these processes do start in the periphery, then I think it's a great opportunity for pharma to come back into the CNS space and not think that you have to get your drug into the brain. Right, that is a huge thing that will change the landscape for patients, for researchers, for everybody. And so just this week also, there's an RFA from NIH for this, the role of multi-disciplinary collaborations for the role of systemic inflammation in ADRDs. And my team is submitting an application. A lot of other teams are. We need to understand that process much better.

The key here was the presence of biomarker, genetic and otherwise, that led the development in oncology



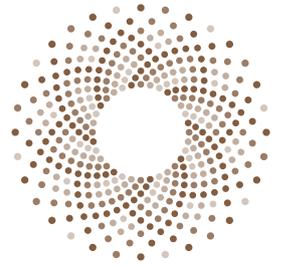
Dr Laurie Ryan

Pardon me, the prior announcement for drug repurposing and combination therapy was the number was the old one. Here is the current one: <https://grants.nih.gov/grants/guide/pa-files/PAR-20-156.html> Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01 Clinical Trial Optional)



Professor Gil Rabinovici

Major breakthroughs in oncology occurred when the mindset changed to patient-specific approaches to characterizing tumors, understanding that



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you. There that's, you know, we have lots of folks that are waiting to, to make a comment. But I think one of the things that is important for all of us, is for government funding in our own countries, and other types of funding, if it is possible, not being as risk averse. This is an issue which I've seen in the chat and should be part of the conversation. And certainly, you know, \$3.2 billion at the federal government in the United States is helpful. And I know that Dr Laurie Ryan who's in charge of the clinical trials program knows that the rest of their team at the NIA is working on advancing those basic sciences. There's so much knowledge we still need. And I think Dr Weninger might speak to some of this as well, because I know they work on this space when she actually also makes a comment, but Gabriel.



Dr Gabriel Balmus
Group leader at UK Dementia Research Institute at University of Cambridge and a Lecturer in Medical Sciences at Trinity College

Although I have worked understanding cancer resistance mechanisms for the past decade, and such new to the neurodegeneration field and Alzheimer's, I would like to mention one or two things.

I was part of Steve Jackson's Laboratory when the PARP inhibitors were approved for various cancer types. I learned from that that there is no golden bullet: I think the success of PARP inhibitors in breast cancer was that we knew how to stratify patients.

So, if we call Alzheimer's disease now what we were calling breast cancer 20 years ago, I think the lesson learned is that we need to carefully stratify before deciding what to treat. I think everybody here has a good heart and thinks, okay, I will find the right target. And maybe their target is correct, but only in the proper context. Before they separated the PARPi clinical trials based on BRACA1 loss, there was no significance, but when they put in BRACA1 only patients, suddenly, you're like, well, we have something. So, I think that that's kind of my first 2 cents.

And the second, ageing. While we look at it from quite a different aspect, you are right; I think we need to look at it. We're looking at this amazing animal called the naked mole-rat that doesn't age and has amyloid in his brain. So, his brain is full of amyloid, but it doesn't have any problems with ageing. This rodent lives for 30 years (while a typical rodent lives on average two years). It's what we call healthy ageing. I think there's much behind that to learn because he has some tricks up his sleeve. We now think a lot about this new concept called synthetic viability: to rebalance disease. Moreover, we talk about phenomics to support genetics and epigenetics. We look at what is the phenotype, and can we find something else that can rebalance the phenotype.

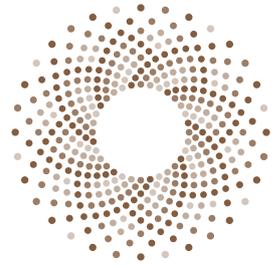
In the end, just a little bit of advertising. I do think that we need new models. We just put a new paper on ALS that comes out today in Nature Neuroscience with a new

different mutations can lead to the same microscopic phenotypes. In AD we are still looking at the disease in a unitary fashion - hopefully biomarkers will help us understand patient-specific mechanisms and therapeutic approaches.



Professor Allan Levey

The cancer field has also successfully addressed the challenge of increasing participation in clinical trials and rapid expansion of early phase trials to test more mechanisms. The number of early phase trials in cancer per patient is an order of magnitude higher than in AD/ADRD. NIH has played a key role in that NCI designated cancer centers are required to report number of patients clinical trials, and this has a huge impact on clinical revenues for health



organoid model containing neurons and glia that we grew for more than 250 days. We need human models to go away from the mouse and be closer to the patients. This is feasible now, and I feel such models will help us better understand the disease.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Those are excellent points. Thank you very much, Gabriel. Appreciate it. And it's great to have fresh eyes, fresh perspectives from other diseases as well. So, thank you for that and welcome to the field, Jane.



Professor Jane Rylett
Scientific Director of the Canadian Institutes of Health Research (CIHR)
Institute of Aging

Thanks very much, Maria. My comments are going to be very short because they're very similar to the comments we've just heard from Dr Tansey and Dr Balmus and really on two points. And it relates to the fact that I think we've been looking at Alzheimer's disease and related disorders as a homogeneous type of process and undoubtedly it is not a homogeneous process.

When you look at ways you can stratify. So, stratification, according to age, stratification, according to other sorts of genetic underpinnings, and I'm not talking about you know APP or pre-synuclein mutations, I'm talking about other types of genetic underpinnings that would be important in terms of considering precision medicine. So, we can't think about precision medicine if we don't understand about the genetics of the individual and then be able to make programs and therapies according to that. So that's the one point in terms of stratification.

The other is in terms of stratification by age versus pathology. So, is the pathology the same across age? Undoubtedly not. So, the Alzheimer's disease or the dementia that you might see in a 60 odd year old is probably not the same as what you see in someone who's in their mid-eighties and become demented, decades later than the 60 odd year olds. So, I think looking at stratifying and understanding the pathology versus age, what is happening in the earlier time points, what happens in somebody older? So, I'll stop there because my comments were really very similar to Dr Tansey and Dr Balmus,



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you very much. Excellent points to reiterate and reinforce. Dr Weninger

care systems. We need to change the culture of making every patient have an expectation to participate and to get health care systems and payers onboard



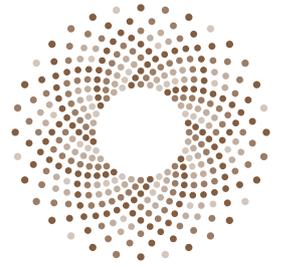
Dr Gustavo Saposnik

Eric made a very good point. It is not only finding the appropriate biomarker, mechanistic approach and combination therapies, but also fighting with our own behavioral challenges-- Group thinking is the one that affects reviewers, policymakers and large committees. Several existing examples in the aeronautic industry, medicine, consumer research.



Professor Reisa Sperling

Agree with Allan's excellent point, and this has to be a culture shift at



Stacie Weninger
President, FBRI

I actually have so much I would like to say with regards to this exciting conversation but I will keep my comments limited. I will start with reemphasizing that patient stratification is so important. And going hand in hand with that is how are we ever going to be able to measure that some of these different approaches, when treating prior to the onset of overt symptoms, are having an effect on the disease without having to wait years and years and years to see somebody's cognitive symptoms develop, or prove a lack thereof?

For the amyloid therapies, we clearly have amyloid we can measure as a direct measure of target engagement. But we need more measurements for some of these other types of drivers of disease that we might be targeting. So, whether that be inflammation or whether it be endolysosomal function, or a myriad of other kinds of targets that we're looking at, we need therapeutic biomarkers to help us have confidence that we are affecting the pathways we are targeting. . In addition, need to understand the genetics driving a particular individual's disease to be able to stratify patients. Genetics are one way, but more broadly, we need to know which patients might benefit from therapies targeting different drivers of disease. And then we need to be able to tell, are we actually affecting the driver of the disease in those patients?

I'd mention a project, led by Henrik Zetterberg (who happens to be present for this discussion) we're working very closely with the Alzheimer's Association to enable. This project is looking across diseases to identify biomarkers that for different neurodegenerative diseases or different subtypes of a particular neurodegenerative disease. In addition to different subtypes of Alzheimer's disease, we are to include Parkinson's, FTD, ALS, et cetera. We plan to look at different genetic subtypes of each disease, as well as sporadic disease. For each, we will conduct an unbiased proteomics screen, under Henrik's direction, and we are working with the Broad Institute to do metabolomics and lipidomics. From this project, we will be able to identify if there are biomarkers that can help us define different subtypes of disease, perhaps with different drivers. What we call Alzheimer's disease is most likely not one uniform disease, but rather can be caused by multiple different drivers and may progress somewhat differently. If we're going to target some of these different drivers of disease, be it inflammation, endolysosomal, et cetera, we need to understand which patients may benefit from different therapeutics, and we need to be able to measure that we are affecting the pathway we are trying to target. . For example, it may be that there are more similarities in terms of response to a particular therapeutic between the subset of Parkinson's patients with an endolysosomal dysfunction and the subset of Alzheimer's disease patients with endolysosomal dysfunction.. So, we're hopeful that this biomarker work will enable across stratification as well as diagnostic markers.

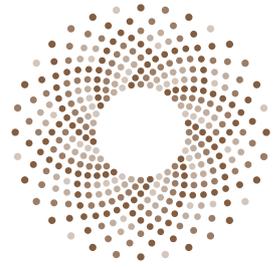
And then the other thing that I will mention-- Malu I loved your comments on the ability to target the peripheral immune system. We all know that the peripheral immune system is playing a role in Alzheimer's Disease. There's just way too much evidence that the peripheral immune system can affect the brain and affect disease. However, a lot of the

multiple levels. Also to Eric's and Stacie's points - cancer did take advantage of common therapeutic mechanisms across very diverse malignancies - such as with checkpoint inhibitor immunotherapies.



Professor Frank Gunn-Moore

If money was no object: as a protein biochemist, I think we need a coordinated project a kin to sequencing the human genome, where we target every single enzyme we can think of and make allosteric and non-allosteric inhibitors. We now can have structures done by alpha fold. We start with enzyme activity but then we can look at protein:protein interactions (there are new companies who have new chemistry to look at this on a large scale eg Bicycle Therapeutics). I know this is a massive task but it



targets that we're seeing come out in the neuroimmune space, microglia targets and so on, are also peripheral immune molecules. And I'm seeing a lot of companies go after some of these targets in a more holistic approach, which scares me, frankly, because I think we're going to run into immune problems by knocking down some of these targets in the rest of the body. So, one of the technologies that I'm really keen to see developed are ways to do brain specific targeting. We're always worried about the flip side, how do we get something into the brain, but by getting it into the brain, we're usually knocking things down or effecting the rest of the body at an even higher level. So, what are the technologies that might allow us brain only targeting? We're seeing a lot of new academic projects in this space. And I think it's going to be really important, particularly for some of these immune targets. So I'll stop there. I could go on for a long time!

would benefit all diseases... You did ask if money was no object...



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

No, thank you. Really appreciate those comments. And I think maybe towards the end of our discussion, cause there's more discussion coming, it would be great just to have an idea from this expert group, if we, if money was no object, where would we start? You know, I want to know that! Because there's just so much great stuff to be done. We're definitely not done. Eric.



**Professor
Linda Van
Eldik**

The therapeutic window for each kind of intervention needs to be defined. Combination therapy may be more than multiple interventions at the same time, but different interventions at different stages of disease. We need pharmacodynamic endpoints for each particular mechanism/target we are interested in. Precision medicine will require development of biomarkers/endpoints that are meaningful for each intervention. And we need to fail fast in early human trials rather than having each trial last for years and be super expensive. Agree with Jeff Cummings about innovations in clinical trial design

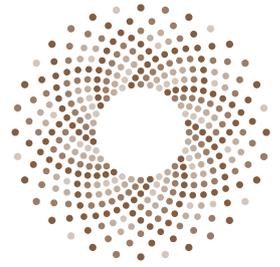


Dr Eric Siemers
Former distinguished medical fellow,
Eli Lilly and Company's Alzheimer's Disease Global Development Team

So, thanks, Maria. I just wanted to bring it back to one of the first comments that you made about combination therapy. But actually, before I do that, there was something in the chat about industry being adverse to risk. And so I might just make a quick comment that, you know, industry has spent billions and billions of dollars on Alzheimer's disease and there's one drug with an accelerated approval and not everybody even agrees with that. So, I think the industry does suffer from group think sometimes, but I don't know that it's just risk aversion.

But anyway, to get back to your point about combination therapies. I think obviously there's more than one form of amyloid, if you're talking about A β or amyloid or oligomers or whatever for Alzheimer's disease. But then if you start to think about the other protein, so tau, I mean, there's more than one isoform of tau, depending on which tauopathy, you're talking about. And then you kind of go down the list alpha-synuclein, TDP43. So that, you know, those targets could be a mix and match with different neurodegenerative diseases.

But the other thing is I think if you get sort of beyond the protein, so not amyloid, not tau. I know there's some people at this meeting today that have mechanisms, and Malu brought it up really well, that may be immune related or may just be different degenerative mechanisms or regenerative mechanisms that work across neurodegenerative diseases.



I've seen more and more crosstalk between Alzheimer's research, Parkinson's research, Huntington's research. And if you can find those common mechanisms now, not every drug is going to have one of those common mechanisms. But you know, you do have the advantage of working across these diseases and it's well, the part about the immune system risk is certainly worth thinking about, but as a group, they at least so far tend to be relatively safe, I think. So, there's an advantage there for some of the mechanisms that may work across neurodegenerative diseases.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think that is absolutely true. And there's a lot of work being done in that sort of crosstalk. I think Stacy alluded to it, but there's so much going on. I know at the NIA and other funding sources that are trying to do that. I think one of the things we just need to hone in on is, you know, how do we get our field kind of more, maybe you don't want group think, but you do want people talking to each other much more. Because pursuing single pathways without that broader knowledge of what those pathways live with, you know, in the brain is not going to get us there faster, as fast as we want at least. Elisabetta, I see that you have your hand up next.



Dr Elisabetta Vaudano
Principal Scientific Manager and portfolio manager for the neuroscience area at the Innovative Medicines Initiative (IMI)

Thank you very much, Maria. And I find with all this conversation, extremely exciting. Just a general comment. I think that going forward that will be extremely important that all the different funders should try to see what is the sweet spot that they can address. Because we all have different opportunity, different types of funding model, different things we can do better. And I think it would be really great to have this overall thought.

As you said, we need a systemic approach to the disease, but we need also maybe a systemic approach to the funding in the sense that it can be so important to fund as many new potential promising mechanism that could be relevant. But also, all the important enablers that can really falsify or validate a mechanism, much faster than has been possible in the past, for amyloid for example. I don't think the patient wants to wait so long.

So then, I think of course as was mentioned already we have an opportunity with new models, that are human based models, IPS cells, the organoid that has been mentioned, or new ways to run a clinical trial. Or bioinformatic approaches that that could be used and maybe are not specific for neurodegeneration, but could be extremely powerful if, as you said, gets together people, because people shouldn't work in silos and need to try to understand the patient globally. Because don't forget that that find me an Alzheimer patient that doesn't have any other concurrent condition like cardiovascular, diabetes. We know hypoglycaemia has a massive effect on the brain.

to accelerate moving forward.



Dr Elisabetta Vaudano

Indeed combination therapy in neurodegeneration most probably is both combination of treatments simultaneously as well as finding the right "longitudinal combination which means understanding the disease trajectory



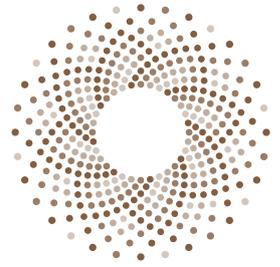
Professor Ricardo Allegri

I agree with Linda, It's very important to determine the therapeutic window for each combination related with the pathophysiology



Professor Serge Gauthier

You can expand the oncology treatment model to clinical practice, such as a course of anti-amyloid therapy when appropriate in the



So I think that there could be benefit both from the strategic point of view and then between funders to talk together and try to see what is the thing that could be done best by each and then put the elements together and also looking at the patient and the disease in a more systemic and holistic way.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you. Thank you Elisabetta. Very, very true. I agree. Jeff.



Professor Jeffrey Cummings
Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health

Thank you, Maria. Thank you, Philip. I think in terms of the whole process, we're focused this morning, we're emphasizing nonclinical study and identification of targets. We need to help all along the clinical development pathway. Phase one is not well supported at this point. You could enter the valley of death and you don't know whether your compound is crossing the blood brain barrier or not, and there are no funds to determine the essential features. For phase two, the platform trials are more productive and more attractive than "rebuilding the soccer stadium for every game". There are many areas where investment could accelerate progress including early development, phase one, and phase two. The infrastructure would accelerate our ability to test compounds, to eliminate them if they're not promising, and to advance them if they are. I think that would be a great help to the field across all non-amyloid targets.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you, Jeff, appreciate that. And you've a lot of expertise in that. I know that there are also so many other things going on in the brain and especially in aging brain that you've studied including neuropsychiatric disorders, that absolutely also contribute that. So, this is a challenge. But you know, a lot of people have been pointing out the cancer has been successful in many ways. They have been at it for decades more. But we can take a page out of that book and see how that was done. So, I think maybe Allan made a point of that in the, in the chat that maybe we can talk about a little bit more, but I'll go to maybe a Maurice next.

course of disease, long enough to normalize amyloid levels,, stopping this treatment during a `remission period', and starting anti-tau therapy when symptoms worsen.



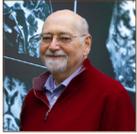
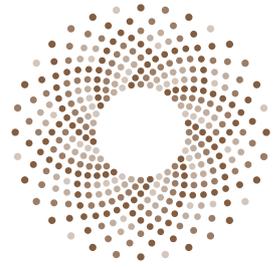
Professor Malú Tansey

Interesting idea Serge! I would add that if we could coordinate that approach with understanding and targeting the dynamic dysregulation of immune system we'd get there!



Dr Christopher Chen

Instead of trying to be oncologists, perhaps we can be a bit less ambitious by aspiring to be endocrinologists ie being able to identify and validate biomarkers of disease which are not only diagnostic but also remediable, predictive and prognostic.



Dr Maurice Zauderer
President and Chief Executive Officer, Vaccinex

Thank you. I want to follow up on exactly that point. You know, we have the example of progress in cancer. So, thinking about what were some of the keys to that, what were the insights in cancer that opened up that progress and how might that apply in neurodegenerative diseases?

One of the keys has been that people have identified in cancer natural regulatory processes that play an important role in health, but that become misdirected under conditions of disease. For example, we all appreciate that the immune system can be helpful in resisting infection and the growth of tumours, but it turns out that immune responses can also be dangerous and the body has a number of ways of limiting the magnitude and duration of immune responses through negative feedback, for example, through induction of myeloid derived suppressor cells. Well, it turned out that those were a key to enhancing immunotherapeutic approaches to cancer by blocking that natural reaction and feedback.

And so, there are parallel feedback mechanisms in the brain, natural processes that are very important in health. For example, the role of astrocytes and microglia is a key function. But, under conditions of stress and disease, they undergo transformations which change their role. Understanding the signals that trigger those transformations and the consequences of those transformations could be a key to identifying targets that could relieve some of the disease-related imbalances that end up causing quite a bit of damage.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Absolutely. Maurice, I think Malu, I think you would probably definitely agree with that.



Professor Malú Tansey
Norman and Susan Fixel Professor of Neuroscience and Neurology, Co-Director Center for Translational Research in Neurodegenerative Disease and the Parkinson's Foundation Research Center.

Yeah, that's exactly right. I think somebody mentioned the fact that there's a lot of amyloid and no degeneration. We think of the neurodegenerative stage as the perfect storm, and we've seen this in our own studies where you can have amyloid and no death but if inflammation comes along or oxidative stress comes along, it's the perfect storm. I think that's what's happening. Right? And so, through a combination of genetics and environment and, and some bad luck or bad lifestyle choices, this is what happens. But the point about understanding how these normal processes become dysregulated during aging with different genetic predisposition and with environmental stressors is exactly what we need to do to understand how to intervene and how to change it. And



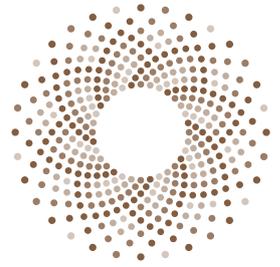
Professor Jane Rylett

Critical point about temporal relationship of changes and how this can be impacted therapeutically. Combination therapy does not always mean giving medications together, but perhaps in a staggered manner to address pathological changes as they emerge.



Dr Laurie Ryan

Open science/open source is key for basic and clinical including trials. It is something NIA has been striving for: <https://www.nia.nih.gov/research/blog/2020/11/open-science-delivers-wealth-ad-adrd-research-data-portal-near-you>; <https://www.nia.nih.gov/research/blog/2020/12/raising-bar-data-and-biosample-sharing-ad-adrd-clinical-trials>



so, I want to give a shout out to say Soyon Hong, who I think is the next generation of investigators who is really focusing on a lot of these basic mechanisms. And, and, and I don't want her to be intimidated to pipe in with all these other established investigators, because she's, she's really doing some critical studies, I want to hear her thoughts on this.



Dr Soyon Hong

Programme lead, Microglia-synapse biology in brain homeostasis and pathology, UCL

Thank you for the shout out, Malu. I appreciate your support. This question is something I think about quite a bit. We need to keep in mind that microglia are tissue resident macrophages. Thus, what microglia do, their major role, is to maintain—and what that means is to help regain and retain—tissue homeostasis. So it bothers me when people say, we need to deplete microglia, or we need to stop their engulfment entirely, and so forth. As someone who studies microglia, I think it is important to understand what regulates microglial engulfment, the functional consequences of the said microglia engulfment, and the specific objects microglia are engulfing. This is what my lab is studying.

I think one of the big questions that we, as a field, are starting to address in the field of neuro-immunology is whether neuroinflammation, broadly put, is a regulated process and how this inter-cell communication between neurons and immune cells alters with aging. And how in the case of pathology, the regulation of the intercellular communication changes to modulate disease progression. So, it goes back to what Reisa and another speaker in the beginning were emphasizing previously—context—and that we need to understand what goes on in a context dependent manner. For me, as someone studying microglia, context is key to understanding the functional consequences of their functions or malfunctions.

Another thing I really wanted to point out is the need for earlier biomarkers, especially targeted at microglia. And I say this in a very cautious manner, because I'm not a cancer biologist, but based on my limited understanding of cancer research history, one key phenomenon that revolutionized the field is the advancement of biomarkers to detect the disease early. I feel like this concerted effort to push early detection, which I think will revolutionize AD, is missing in the field.

I personally think, and this is likely because I am passionate about microglia, that this is where neuroimmunology will be key because microglia, as tissue-resident macrophages, are the first responders. They are the first to turn on the sirens at the earliest signs of danger, damage or injury. I mean, that's their job to protect and raise the alarms! If we understand what the molecules that are up-regulated in these immune cells are, if we understand what those markers are, I think that's going to, for me personally, what's going to revolutionize how we detect the disease and whether we can detect the disease in stage one or stage two, rather than stage five and stage six.



Dr Hans Moebius

Concur with Jane - the past decades have seen more emphasis on ever more specific interventions while the phenotype that needs to be “balanced” is less well understood



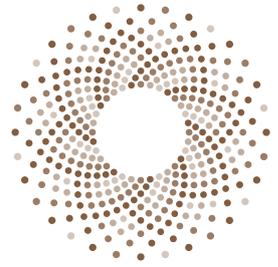
Tim Boyd

Relating to Dr. Diaz-Castro's comments, here is a link to a recent publication of plasma GFAP levels as a sensitive biomarker with AD progression: <https://pubmed.ncbi.nlm.nih.gov/34661615/> To add to Dr. Siemers's comment earlier, a therapy targeting astrogliosis may be helpful from a common pathology across several neurodegenerative diseases



Professor Charles Scerri

Following on what Hendrick highlighted (on consent and the like) there



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Absolutely. I think Gil said something very similar in the chat. And I think that is a very important aspect of what we need to be stimulating more of. And, and those biomarkers of all this across the board. But one of the things that I think we need to also do is find places where we can have these types of discussions with a broader community. Because, for example, when we did the Tau 2020 meeting, it was a fantastic conversation around all of the aspects and all the different ways to target tau when, how, the confirmations, including all the way from the biochemistry, all the way to genetics and beyond including therapeutics, of course.

And I think now we're, we're trying to create the same thing with the immunity meeting because innate immunity, immunity, immune response, doesn't also happen in isolation and also impacts all of these other proteins. So how do we study that systemically instead of sort of again you know, bring your discussions Soyon into conversations with other experts that can really understand how it fits in that bigger picture. I think that's exciting. That's exciting. We need to do more of that in order to ensure that we're all talking and there that there is crosstalk but thank you very much for that contribution. Congratulations on all of your great work.

remains a challenge in presenting research protocols to prospective research participants. Most often the language we are using is one that they cannot understand...it's too 'scientific' for them. We need to present what we are doing, the research aims, possible outcomes in a way that that they can understand



Dr Soyon Hong
Programme lead, Microglia-synapse biology in brain homeostasis and pathology, UCL

Thank you. I think technology, all the wonderful recent advancements in technology, is allowing us to understand that, right? There are now many tools to profile and further utilize and incorporate multiple sequencing, proteomic, epigenetic, lipidomic and other kinds of omic data to understand the big picture of how the intercellular communications change across space and time, sometimes at subcellular levels. So I think now is a really exciting time for neuroimmunology.



Dr Elisabetta Vaudano

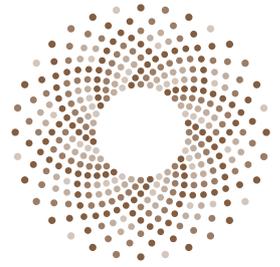
In addition to biomarkers there is also need for work on endpoints that reflect better what really matter for the people with neurodegeneration

I just want to say, you asked earlier about what we'll do if money was not limited. I'd love to do such a multiomic approach; really trying to understand really complex cell-cell communication that changes with normal aging versus with pathology and early stages. But for that to be realized fully, I think it's not just money that we need, it is some of the things that were mentioned by other people in this talk as well as in the chat – we need real collaboration at multiple levels, including collaboration between funders, specialists sharing early data and samples, as well as a real need for brain banks of excellent quality. We need multi-level efforts across materials, money and funders to allow deep phenotyping to understand the complexity of human disease across age.



Dr Rodrigo Cataldi

That's a great point regarding data/sample sharing. As part of the Dementia Research Blueprint, WHO is exploring how to support countries and people with dementia and foster data sharing. Many of the experts in this conversation



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Very true. Very true. Thank you very much, Blanca. I see that you have your hand up.



Dr Blana Diaz-Castro
UK Dementia Research Institute Fellow, University of Edinburgh

Thank you for the invitation. This is very exciting. I'm learning a lot. I wanted to follow up on Maria's comment about investigating how physiological mechanisms transform in the context of disease. I come from the astrocyte field and sometimes I feel in neuroscience, glia research is compared to neurons or immunology, which have been studied for more than a hundred years. For non-neuronal brain cells like astrocytes, we still don't understand very well what its physiological function is. We may be rushing into understanding how they become dysfunctional when we still don't know enough about its own function in physiological conditions. Hence, another point to make is that investment needs to be made towards the understanding of basic cellular functions to then investigate how they go wrong in the context of disease.

The second point is following Soyon Hong on the biomarkers, and also Malu on the interaction between periphery and the brain. We often forget that one of the main mechanisms by which the periphery and the brain communicate is through the blood-brain barrier. I just want to point out that the blood-brain barrier could be a huge source of biomarkers because it is where an important fraction of the brain-periphery communication and exchange of substances is occurring. Many of the molecules resulting from these interactions, will be released into the bloodstream. It will be a worth looking into it further.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you. Very good points. Absolutely. Stacey.



Stacie Weninger
President, FBRI

I just wanted to make a quick plea here as much as anything. Soyon you really triggered some thoughts when you were talking about some of the needs in the field and brain banks and biomarker data, et cetera. One of the big challenges that I think this field is facing right now, and I'm going to ask that the World Dementia Council perhaps has a role here in helping, is the ability to share data. GDPR rules are making things very

are already involved and we will be reaching out to WDC and members for further inputs. Looking forward to working with the group on this.



Dr Blanca Diaz-Castro

Thanks Tim!
GFAP is indeed upregulated in many neurodegenerative disease, however astrocyte reactivity is a very wide concept, highly context dependent. Not all reactive astrocytes are the same, so no single therapy will work. For more info: <https://pubmed.ncbi.nlm.nih.gov/33589835/>



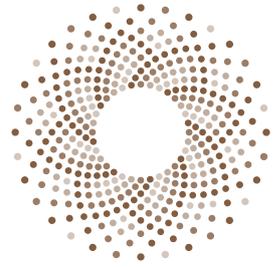
Dr Elisabetta Vaudano

Maybe is not really so critical that a mechanism is so brain specific?



Professor Serge Gauthier

DIAN is a great example of global approach for



difficult--even just understanding what is allowed and what isn't allowed is making people hesitant to share it all. Unless we can share data across large datasets, we're never going to make progress here. So, how do we protect privacy while also enabling these critical data sets to be shared across the global research community so that we can really make progress? When we're talking about stratifying patients in subtypes of genetics et cetera, these all require large numbers of patient data and deep phenotyping to be able to make sense of them. So, I would think that the World Dementia Council might be in a position to help us here as a field, figure out how to handle this issue.

observational and therapeutic studies.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yeah. I think that is very important. I know we have some of our European colleagues on that might be able to, to address that, but Henrik, I see your hand up. I don't know if you want to comment on that.



Professor Henrik Zetterberg

Deep phenotyping of the CSF cells is also very interesting! Many of us throw away the CSF cell pellet after centrifugation...



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Yeah just a quick comment because what we need to do, I think is this is a global thing: to change the informed consent form because when we meet patients and families here, most of them want their samples to be investigated by leading researchers across the globe and they want their data and samples to be shared and it's unethical not to follow their wish.



Professor Henrik Zetterberg

They are easy to collect.

So, I think that to some extent the pendulum has gone too far, and I know that European Union is looking into this now, but I do not know where one should lobby. I think this is, I almost get angry when I think about this, that the patient's and family's wishes are not followed, which is unethical and it's not good to be part of unethical work. But I do not know the best way of getting this message across.



Professor Malú Tansey

@Henrik: indeed! We don't and can spin down a good amount of cells from 20mL of CSF :)

Of course, the informed consent should make it possible not to approve data or sample sharing but we should facilitate the individual's own wish to come true. But if anyone has any ideas regarding how we could lobby regarding this stuff, that would be great. The starting point is that patients' wishes are not followed at the moment and that I think would be extremely powerful.



Dr Laurie Ryan

As funders, we have to make data and sample sharing requirements for grants



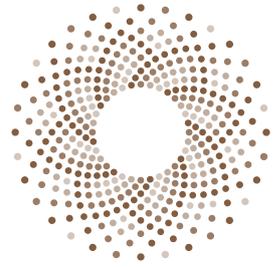
Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yeah, absolutely. Absolutely. Very important. And we all have that. That is something that perhaps the World Dementia Council can look into, we'll touch base with of course with Lenny and Philip as current chair, I believe so Phillip something you can take



Professor Henrik Zetterberg

Yes, there are 1-5 mononuclear cells per microL of CSF



back to the council itself and the trustees. But something I wanted to also follow up on is, you know, Allen if I can call on you? You talked a little bit about sort of the cancer model. And I just wanted to dig into that a little bit more because I think others have referenced it as well. You know, from the BRAC example that Gabriel started with and Gil talking about biomarkers really advancing that field. We have biomarker envy for cancer. I mean there's no doubt. But what are your thoughts? I know you're involved in a lot of partnerships, federally funded as well. What are your thoughts about that?

(without frank neuroinflammation).



Professor Allan Levey

Professor and Chair of the Department of Neurology at Emory University and Director of the Goizueta Alzheimer's Disease Research Center

Well, thanks Maria. It's been a great discussion. I think that cancer has a lot of benefits. One is as I was putting in the chat, healthcare systems have tremendous pressure to make sure every cancer patient possible is engaged in research. And it's changed the culture. Certainly, healthcare in the United States is just completely different as a result of that.

And I think we've also learned in the AD field how important it is to follow a data-driven approach, similar to the roadmap that cancer has laid down. I think Gabriel's comments were really spot on. And I'm excited as we're seeing biomarkers emerge for all of these different pathways that people are talking about that go beyond amyloid plaques and neurofibrillary tangles. I feel strongly that we urgently need to broaden the net. And it's going to take, you know, basic research and translating it into early phase human studies very fast. And that's where it's currently too slow. I'm involved in the Accelerating Medicine Partnership that NIH stood up about seven years ago to broaden the target list. The teams in the AMP-AD consortium are all taking these multiomic approaches to profile over 2,500 post-mortem human brains. Our Emory team has additionally profiled the proteome of about 3000 CSF samples and moving quickly into plasma samples. These data from AMP-AD are all publically available to enable broad community study using advanced analytical tools, i.e., to accelerate the discovery and validation of novel therapeutic targets. And the target list just grows and grows. There's so much biology that needs to be explored that hasn't been studied previously, or at least in the context of AD.

One of the things that's emerging very clearly to me is there a common set mechanisms of disease. There are a plethora of pathways involved in cancer with many also emerging in a data-driven manner as highly relevant for AD, including hot topics like inflammation but also many other specific signaling pathways. Much like genetics research which has highlighted a large number of risk genes and disease complexity, that there are a lot of different that pathways involved in the disease that are emerging from molecular profiling of the brain. We now need to develop biomarkers that are indicators of how these pathways are altered during the disease progression in living individuals, and how these pathways are perturbed by drugs.

I'm wondering whether we can even go a step further in clinical trials and begin to facilitate sample sharing from patients that are participating in cancer clinical trials or diabetes clinical trials, for example, because now that we're beginning to see emergence



Dr Elisabetta Vaudano

We need to understand which could be incentives for sharing of data and even more of precious samples



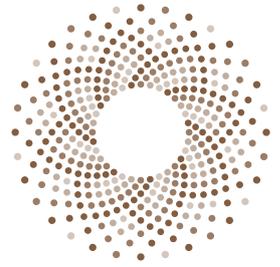
Professor Linda Van Eldik

Mixed pathologies and co-morbidities also increase as the individual ages. So treating a 65 year old will likely require very different approaches than treating an 85 year old. In our elderly cohort, we see lots of quadruple misfiled proteins (Ab, tau, a-syn, TDP-43) and vascular, and the cognitive decline is faster when you have multiple pathologies.



Dr Hans Moebius

Wondering whether the group thinking leads to circular logic ? A drug with a highly specific effect on a singular



of brain-based biomarkers of AD pathologies that are available in biofluids, interrogating large databases would improve knowledge of how drugs in perturb various pathways, on – and off-target, and then use this information to accelerate testing a lot of disease mechanisms.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Well, I think that's great too, Allan, thank you very much. No, I appreciate it. And I think there is a lot of examples in cancer that has, that we can bring in. And perhaps is there a way to have a conversation with, certainly breast cancer experts who have been able to sort of use that BRAC gene to really hone in on how to separate patient populations in terms of what works and doesn't work. Maybe some of our drugs that have not worked perhaps in phase three trial can indeed work. There is the example of Solanazumab maybe, starting off in participants who did not all have amyloid when that was the target moving into now drugs that are at least enrolling the people they're intending to treat. So, I think that that part of it is critical and finding those biomarkers is going to be a very important contribution.

But what do others think about that? I think that there's a lot of you here working on those types of biomarkers, and I know Henrik you're working on several different types, not only from sort of his scans, but in particular fluids. And what are your thoughts about that? Because those more accessible markers can revolutionize the way we work and making us work faster and certainly with more incentive to invest because they won't cost as much money.



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Yeah. I agree completely. I mean, biomarkers in blood look increasingly promising and that works well. For the other disease processes, it's harder, especially microglial activation is such a difficult biomarker category in blood because of macrophages that contaminate the blood. But here one could potentially hope for innovation in terms of enriching for microglia-derived exosomes in blood. That is not easy either of course. But here we need to do a lot more work. I would encourage continued work on biomarkers also for categories that we perhaps have had little hope for before, given their high extra-cellular expression. Now, we have methods separating different subsets of biomarkers and the analytical tools have become more sensitive. The development in this field has been very fast during the past one or two years. So, I think this is very important. I would also like to underline the feasibility of doing CSF studies as well. I mean, it is possible to do it, although it is harder to implement globally and at large scale. But if there is inflammation microglial activation, astrocyte activation to be studied, these processes are perhaps still a little bit hard to study in the blood, in a CNS-relevant way. And there it is easier to do it in CSF, but we shouldn't give up, we should continue to work on this hard.

aspect of the pathophysiology may change the response biomarker (whether fluid or imaging) - but does cognitive improvement follow? Like AChEIs after giving scopolamine?



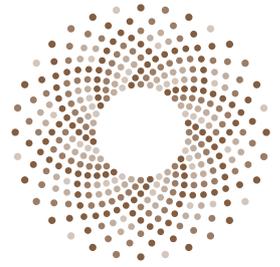
Dr Soyoon Hong

Yes! And re: comment above about need re: brain-specific.. I don't think necessarily think so because we now know that brain is not immune isolated. Key is to find changes in "peripheral" immune cells that are being influenced by "central" brain immune cells (microglia, BAM/PVM) etc. is there a way to compartmentalise lymph fluids in a organ specific manner?



Professor Malú Tansey

Yes, David Gate first author is now at Northwestern - the T cell paper that Henrik mentions.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think the brain well, it certainly is a very unique organ, right? Its a little harder to sort of biopsy and take a look at what's happening inside. That has been, I think, one of the things that has been in the way. But technology as it advances will address this. You know, many of us have pointed out today technology advances being made are really critical to being able to understand a lot of the mechanisms now. So, you can recognize that. And just in terms of being able to do different types of assays and deep phenotyping, Henrik, you know, we didn't think we would be able to measure any of these proteins in the blood just a few years ago. It was like, how is that even possible they are in such small quantities once you separate from, you know, brain and spinal fluid, but it does look like some of that is possible. Cancer is spearheading in many ways can be brought into the field to really help us understand brain. Not to mention the fact that we shouldn't forget that the periphery is a critical component, cause all this is all, this is connected.



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Yes. I always have to remind myself of the last thing you said here, because that is of course important. I always forget to emphasize that.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

No, very important here that it's been mentioned as well. And I think Malu started that conversation, but Hans, I see your hand up. I'm sorry, go ahead.



Dr Hans Moebius
Chief Medical Officer, Athira Pharma

I just wanted to make a comment regarding biomarkers and the breathtaking advances that we have seen over the last couple of years. And I think that will enormously support identifying the phenotype that you would like to address. I think it's also important that these are not necessarily bound to high-tech installations like a PET scanner and are more accessible both for diagnosis and monitoring of therapy.

And then another remark I wanted to make is that I'm kind of surprised that I mean the core phenomenon of the phenotype is really memory. That is what we're talking here. And there are biomarkers, electrophysiological biomarkers that like QEG for example



Professor Claudia Suemoto

Linda, we also have seen a lot of mixed pathologies in the very old in our brain bank in Brazil (Brain Pathol. 2019 Nov;29(6):771-781. doi: 10.1111/bpa.12719), which certain brings challenges to therapeutics of this age group.



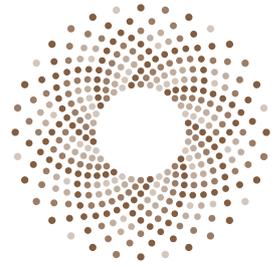
Professor Henrik Zetterberg

I really think a world-wide informed consent form would be wonderful, where study participants can mandate sharing of samples and data.



Professor Frank Gunn-Moore

Maria: have a conference in St Andrews, as you can see behind me the golf course is in sunshine...



or event-related potentials that have not been at the focus of interest in the recent years. And there is a surprising wealth of literature that points to at least points to the predictiveness. Yes, there are problems with standardization and so on, but in my mind it's relatively underutilized field which makes that important difference for those smaller companies that have enormous investor pressure to come up with some findings that maybe predictive to address the core phenotype.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Hans that's a good point. And I know that some companies are using evoked potentials and certainly early on, and maybe Eric, I think you've been involved of course in pharma for a very long time. So, I'm gonna call on Eric Siemers to see what he thinks about this. And I know that you're involved with companies now and, and in, in the interim between your tenure at Lilly and now, you've seen a lot of small companies. What are your thoughts about what Hans just referenced in terms of evoked potentials and the ability to use that as a quicker target, or at least a quicker mechanism and biomarker?



Dr Eric Siemers
Former distinguished medical fellow,
Eli Lilly and Company's Alzheimer's Disease Global Development Team

Well, yeah, so it's a great question. Hans could probably talk a lot more about the details of the electrophysiology than I can. But I think it is a good example of technology moving forward. And I can tell you, this was several years ago and it was actually while I was at Lilly, we sort of evaluated pharmaco-EEG, or quantitative EEG, whatever you want to call it. And it just wasn't quite ready for prime time in terms of clinical trials we thought. But that was about 10 years ago, let's say, technology really does improve. And it also depends a little bit the mechanism of the drug, right? Depending on what the drug is, you may or may not expect an electrophysiologic effects that would happen in a short duration. Two things. One, technology gets better. But the second thing is you have to match the biomarker with the drug and the mechanism because not every biomarker works with every mechanism, obviously.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yeah that is a very good point. I think that, you know, there are a lot of challenges, but I think if we work together and crosstalk, I think a lot of those messages can actually be shared and we can build upon them if we, I think the field, had more of these types of conversations, but thank you very much. Appreciate both of those comments, Ron. I see your hand up as well.



**Professor
Henrik
Zetterberg**

Or DEMAND sharing.



**Professor
Malú Tansey**

Yes, I'll come to St. Andrews :)



**Dr Maria
Carrillo**

Love that ! St Andrews it is! Let's do it. Science is stimulated by a fantastic environment.



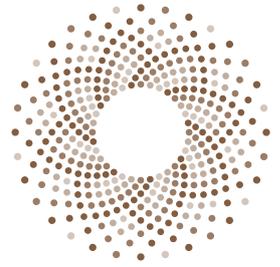
**Dr Jort
Vijverberg**

Data sharing very important; Big Pharma must join in this discussion.



**Dr
Christopher
Chen**

It may not be possible to bring all cohorts together but a coalition of the willing is feasible, particularly in federated partnerships with highly secure means of data analysis



Dr Ron Petersen

Professor of Neurology, the Cora Kanow Professor in Alzheimer's Disease Research, and a Distinguished Mayo Clinic Investigator

Yeah. Thanks Maria. Very interesting discussion. I think one thing that the field needs from an infrastructure perspective, are larger, more diverse clinical cohorts to be followed. Many of the questions we're asking now with regard to biomarkers, ageing issues, and all that really need to be addressed by following people longitudinally. And you know, some of us have them, but they really need to be much larger, cross-cultural and involving people who have medical comorbidities. Such that we'll be able to evaluate any of our biomarkers and interventions in that setting. So certainly, I mean the World Dementia Council is sort of poised to at least inventory what's going on internationally and what can be done about that. In particular, with regard to data sharing - what can be done across these different cohorts right now, taking into account privacy and all those types of issues.

But you mentioned earlier, and several of the speakers have commented on it, the aging process in and of itself and how it interacts. As you know, we're doing some stuff in senescent indistinct cells, well, that's just one aspect of it, but it may very well be a modifiable aspect. If you get in into these systems with some senoanalytics indistinct, that actually have an impact on some of the aging process that may have a secondary impact on disease process as well. So, I think the clinical cohort infrastructure really needs to be all improved.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Yeah, that's right. That's a great point. Thank you, Ron. I think that is but one of the things that certainly is the case is that when we do augment clinical cohorts, and I think that NIA has done a lot in terms of being able to do that at the, at least in the United States level, we also have a global problem. So how do we get him back to the sort of Stacy's challenge originally how do we really work together? Certainly, data sharing is something that a lot of us try to be involved in. I think that Tetsu, I don't know if he's still on, but they're working through this ADDI consortium to try to do that. We've worked a lot on that through GAANN and, and c-path has been working on that in the United States as well with the sponsors of drugs and FDA collaborations. But how do we go further?

Certainly, sharing of samples would be great, but we've talked about GDPR and how there are challenges to this. And so, I think that is a really good point and in the US we need to do more. But this is a global problem, and we've got people here representing leadership from around the globe including Latin America, Europe, Australia, Asia, what can we do? Tough question no answers for that one?



**Professor
Henrik
Zetterberg**

Agree!!



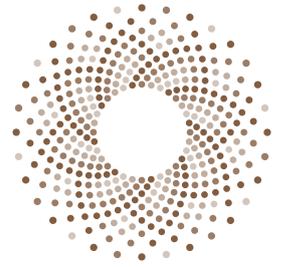
**Dr Mathew
Varghese**

Wonder whether the answers would come from very early prevention studies. What exogenous or endogenous agents cause inflammation or immune changes. And what are they? What is the systems biology to explain that?



**Dr Elisabetta
Vaudano**

Thank you.



Professor Malú Tansey

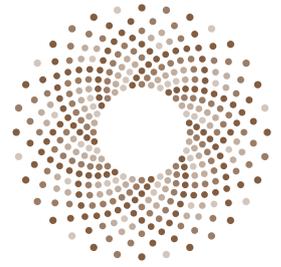
Norman and Susan Fixel Professor of Neuroscience and Neurology, Co-Director Center for Translational Research in Neurodegenerative Disease and the Parkinson's Foundation Research Center.

So, Maria, let me mention something that Allan brought up in the chat. I think we can't do that. We can't really harmonize and get enough numbers unless we get more patients and controls to participate in trials. And I think that is super key. And I think Allan said something about changing the culture.

One of the things that was really helpful when I was at Emory is these Lunch and Learn's that Allan's group devised for their ADRC and their neurology patients. We did it for Parkinson's. We did it for Alzheimer's. These were when the community just comes and learns about what's going on. And wow. You know, it changes everything because all of a sudden, we had all sorts of people showing up for our trials and enrolling and telling their friends. I think that's going to be key, especially if we want to compare and contrast diseases.

And many of us already work in different areas. Certainly, those of us that work on inflammation and immunity, because there are so many underlying mechanisms that are common. The other thing is if you study co-pathologies, you will quickly find that some of the things that tie these co-pathologies together is some of the inflammatory mechanisms that are happening. And I think that's trying to tell us something. So, I think we need to figure out a way to increase patient participation, subject participation, not just patient, but we need a lot of controls to understand what is normal, what is not, and household controls for the environmental component, because you can't just compare, you know, someone that doesn't live in the house with a different person because of the immune component.

And lastly, I just want to say on biomarkers, it's going to be super challenging if you don't do longitudinal measures within each person and how they're changing pre and post intervention. Because the biomarkers are not static, right? And so cross-sectional comparisons are super difficult. We published a study with a 24-hour sampling that Fox ran on PD versus controls, where there's so many things going on with different cytokines in the CSF that, some that just happened to be diurnal and changing throughout the day. Some do, some don't and the CSF doesn't reflect the plasma at all. There's only one marker that I've ever seen CRP that is linearly related in plasma and CSF, but the magnitudes are very different. So, I think that what Soyoon said about deep immunophenotyping of the cells that you get from the periphery and how they're dysregulated, although more expensive, it's going to be really useful. And I think when I was at Emory, I convinced Allan and his team that that was an important process, and the Emory Vaccine Center has been doing it for a hundred years. I think we need to maybe think about that and not just the fluid biomarkers.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yeah. Very good points. I think we have a lot of work ahead of us that's for sure. Eric, I think you were going to chime in, on this topic as well.



Dr Eric Siemers
Former distinguished medical fellow,
Eli Lilly and Company's Alzheimer's Disease Global Development Team

Right? Yeah. I just want her to come back and comment on your comment about data sharing and Stacy brought it up too. And I think Tetsu may have dropped off he had a meeting. I just full disclosure, I've done some work with Gates Ventures and the Gates folks. And so, I've been sort of involved with those conversations. And I think I can tell this group that, you know, there's a certain amount of people being territorial with their data and with their samples.

And in, in a lot of ways that's understandable. I mean, people have spent their whole career putting together a lot of data and a lot of samples and you know, why should I give these up to somebody else? Just so the other person can write a better grant and I'm going to lose my grant funding. That school of thought is, I mean, nobody likes to talk about it, but it's one of the challenges.

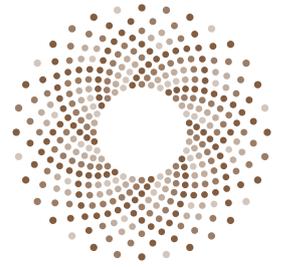
But I think the mentality of this has to be we all share with each other. And so, a rising tide is going to float all ships. And so, it's not like, oh somebody else gets my data. And now they're kind of ahead of me in the competition. If everybody can just open up their data, and samples, we're just going to make the next step of this. Then you get into a situation where a rising tide floats all ships. But it's psychologically a little challenging to get people to shift their thinking.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

It is challenging. There's no doubt. I know the NIH is trying to make inroads into requiring that as well. We certainly already have, if you get funding from us, we have a requirement. I see Laurie putting that in the chat. Thank you, Laurie. So, finding places to do that, maybe in a federated way where you're not giving data away, that's what GAAIN is trying to do, right? It's just federated, that's represented there. Some people how to find it and how to ask for it. So that you can create those collaborations instead of just saying, oh I'm just giving it away to anybody. And somebody's going to scoop me. It is not like that. You know, in this sense there are ways to get this done.

But I also want to go back to your comment about deep phenotyping and Henrik and Malu are having a conversation in the chat about being able to do that actually in the



CSF. So Henrik, maybe you can comment on that? Because I think if we can do that and share that type of information more broadly. It's not blood samples, because Serge Gauthier also put in the chat, but you know, DIAN is sharing data globally, successfully. It is a global trial. But I'll tell you, that as one of the major funders of that trial, we worked very closely with Randy Bateman, along with the NIA and others, and they're having a very difficult time right now trying to figure out how to share that data across these countries. It is actually not easy, even though it is a global trial that is trying to do that. They are experiencing extraordinary challenges with GDPR.

But Henrik, I think I want to go back to your comment that you and Malu were sharing about the deep phenotyping. And perhaps if we have this fluid, now, maybe that is something that can be done because there are stores all over the world of CSF.



Professor Henrik Zetterberg

Professor of Neurochemistry, University of Gothenburg

We should also look into the cell pellet of spun CSF. Mononuclear immune cells exist in the CSF, but most often you spin the sample and throw away the cell pellet. And that cell pellet is interesting because it contains mononuclear cells that survey the brain, it seems. It would be very interesting to explore them in regard to their expression profile. And Tony Wyss-Coray has done pioneering work on this and gotten quite exciting findings on a T-cell clonality that seems to relate to inflammatory processes in association with amyloid in the brain. I believe there is much more to learn on this topic.

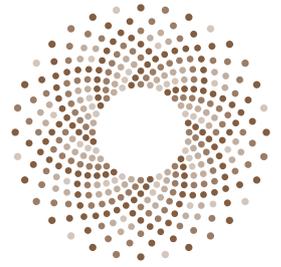


Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Yeah, absolutely. And I'm hopeful that some of us as even funders can get together to figure out how to act. Maybe also create conversations that go beyond this. This is great that we have these conversations, but we are, you are all in an elite category of, and we have a few early career researchers here to help bring fresh ideas as well. So that's great. But how do we really broaden this discussion? I think that's something that we can challenge Lenny and Philip with as leadership at the World Dementia Council, to make sure that these conversations can actually then stimulate other conversations that many of us can perhaps host and think creatively on how to carry them out so that they're not just sort of, you know, death by PowerPoint, in isolation of each different topic. But really trying to work together on a problem that requires a systems approach because all of these conversations we've had today, this conversation is a system approach to it because each of us is bringing in these ideas. That's so critical, I think, to the success of the future of the dementia research broadly, but even aging.

Well, thank you very much for the conversation. It's been fantastic and I've, I've really enjoyed it. I hope you have too, Dr Scheltens.



Professor Philip Scheltens

Professor of cognitive neurology and director,
Alzheimer Center, Amsterdam University Medical Centers
and member of the WDC

Thank you very much, Maria. Yes, it was a very exciting discussion from sort of the topic was actually non amyloid targets. And we went from that to biomarkers of course, if you have Henrik in your audience, you can't miss it. And also, to I would say data sharing, which is important. And, for sure, it's on the topic list also for the December 6th meeting. We did host already a conversation on it, and it was put in the chat actually where you can find the written report on it.

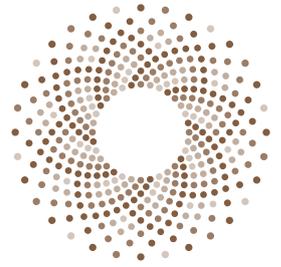
So, there are many of these elements and the most striking for me is any anytime again, when we have the discussions with the whole field, it comes back again to oncology. What can we learn from that field? How did they do this? What things happened 10, 15 years ago in oncology are happening now here in this particular field? And we should learn from that. And many of the elements how we can learn from that were already mentioned, of course, collaboration and thinking more broadly, not on specific perhaps disease types, but on neurodegeneration for instance, as a field has a lot of commonalities with oncology. And how can we do this together. Perhaps also discusses with oncology basic scientists, for instance, get them into the groups and get them into the discussion.

And also on the clinical part. I mean Serge made a comment very dear to my heart as well, that also in looking at patients, engaging patients in research in clinical trials, we have to learn from that field as well. I mean, every patient basically should be put into research into clinical trials, otherwise we will never ever, ever solve this whole problem. So, it's an attitude it's really an attitude change.

And I think that the World Dementia Council could also address this attitude and address the way how we, how we change this attitude. And for me personally, that's a very important point that I will take home with me and discuss with Lenny and the World Dementia Council.

So, I thank all of you very much for all the comments. And please do come to December 6th. And if you can't please join us virtually because we will continue this discussion and all the main elements of the discussion have been mentioned, and we have to do better, and we are able to do better because we are such a good group of people together. And we are all collaborators but in essence, that we need to do a little bit more.

So, thank you very much, Maria. Thanks all the group and I will shift over to Lenny to give you some concluding remarks.



Lenny Shallcross

Executive director, World Dementia Council

Thank you very much. So, I'll just briefly say thank you to everyone. As I mentioned at the top, we are actually publishing a collection of essays next month on data sharing and with some of the regulatory barriers and what was also talked about kind of cultural and professional barriers to data sharing Tetsu has written for that. And Heather has actually as well with Art Toga.

And as I mentioned, Bill Gates is also doing a piece and I should have said, as I note to say on the call that Dr. Petersen will be doing a piece for us as well as more reflective on where the research fields is.

And as Philip said, we have sent her some information about some the December 6th meeting but do reach out to Josh if you want anything more on that.

So let me conclude as it's now half past the hour by saying good morning and good evening, have great days or evenings wherever you are. Thanks very much for joining us. Goodbye.

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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