

Summit 2022

Looking to the future:
The dementia landscape



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

From basic science to new treatments

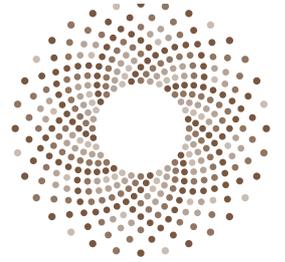
Transcript of a session from the
World Dementia Council summit
28 March 2022

Johnson & Johnson

**SCIENCE
FOR MINDS**

Lilly

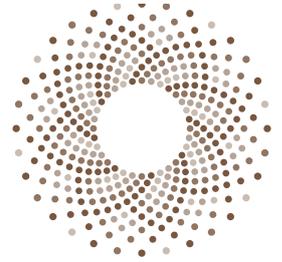
Chair



Howard Fillit

Howard Fillit, MD, Founding Executive Director and Chief Science Officer of the Alzheimer's Drug Discovery Foundation, is an internationally recognized geriatrician, neuroscientist, expert in Alzheimer's disease and an innovative philanthropy executive. The Alzheimer's Drug Discovery Foundation is a nonprofit whose mission is to rapidly accelerate the discovery and development of drugs to prevent and treat Alzheimer's disease. Dr Fillit has had a distinguished academic medicine career and is currently a clinical professor of geriatric medicine and palliative care, medicine and neurosciences at The Icahn School of Medicine at Mount Sinai in New York. Throughout his career, Dr Fillit has maintained a limited private practice in consultative geriatric medicine with a focus on Alzheimer's disease. Dr Fillit has received numerous awards and honors including the Rita Hayworth Award from the Alzheimer's Association, and has authored or co-authored more than 350 scientific and clinical publications.

Speakers



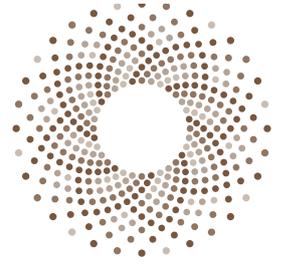
Maria Carrillo

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.



Bart De Strooper

Bart De Strooper, MD, PhD is director of the Dementia research Institute of the UK and professor of molecular medicine at the VIB Centre for Brain and Disease research University of Leuven and Professor at University College London. His scientific work is focused on the understanding of the fundamental mechanisms that underlie Alzheimer's and Parkinson's disease. His major finding is the identification of gamma-secretase and its role in the proteolysis of the amyloid precursor protein and in Notch signaling, for which he received the Brain Prize 2018 together with Hardy, Goedert and Haass. Recently he has reoriented his work to the understanding of the cellular phase of Alzheimer's disease. His aim is to understand the mechanisms of resilience that make that some people survive into very old age with the biochemical signs of Alzheimer's Disease but without the symptoms of dementia. He has published close to 400 papers with h-index of 121 and is recognized as highly cited researcher 2018, 2019 and 2020 (Clarivate, Web of Science Group). Expertscape considers him World Expert in Alzheimer's disease (no 8 worldwide), Presenilins (no1 worldwide) and Amyloid beta-Peptides (no 4 worldwide).



Colin Masters

Alzheimer's disease researcher University of Melbourne

In 1984, Beyreuther and Masters purified and sequenced the amyloid constituent of the plaque in Alzheimer's disease, and three years later, their group used this sequence to clone the gene encoding the A β amyloid peptide located on chromosome 21. These studies demonstrated that the A β amyloid was derived by proteolytic cleavage of a neuronal transmembrane receptor.

Subsequent studies by many groups has shown that a variety of A β -amyloid oligomers lie at the centre of AD pathogenesis, and these are now the validated primary targets for both diagnostic and therapeutic strategies. Masters and Beyreuther therefore defined the principal molecular and genetic pathways leading to the current A β amyloid theory of causation of Alzheimer's disease.

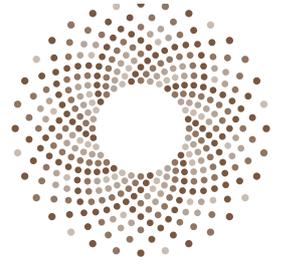
More recent studies from Masters and colleagues have also demonstrated the time-course over which the A β accumulates in the evolution of Alzheimer's disease, using molecular PET- A β imaging, allowing the preclinical and prodromal stages to be identified during life. They have also identified some of the genetic determinants which affect the rates of cognitive decline. These insights into the natural history of Alzheimer's disease will have a major impact on clinical trial design and provide prognostic information for subjects at risk.



Nadeem Sarwar

Nadeem's expertise stems from the intersection of genomics and data sciences with collaborative business models to drive therapeutic innovation. He was recently appointed as the Global Head, Genomic Strategies & Global Head, Digital Therapeutics (DTx) Strategies at Eisai, having previously served as Founder and President of the 100-scientist Eisai Center for Genetics Guided Dementia Discovery (G2D2). He has senior-level experience across academia (Cambridge), pharma (Pfizer, Eisai), and Biotech (G2D2); has successfully built and led organizations across the UK, US and Japan; and contributed to delivery of therapeutics into clinical trials for CVD, diabetes, renal, immunology, oncology, COVID-19 and dementia. His research has been published in leading journals (eg, NEJM, Lancet, JAMA), presented at international meetings (eg, American Diabetes Association, American Society of Human Genetics, Prix Galien Foundation) and profiled by international media (eg, BBC, Forbes, Nature). He has provided expert insights on therapeutic innovation for: The World Dementia Envoy; the UK Department of Health; UK Trades and Investment; the World Economic Forum; and the National Academies of Sciences.

Discussion transcript



Dr Howard Fillit
Co-founder and Chief Science Officer, ADDF



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FROM BASIC SCIENCE TO NEW TREATMENTS

Let me introduce the panel. We have Maria who I am sure you all know, Maria Carrillo from the Alzheimer's Association Chief Scientific Officer, Bart De Strooper from Dementia Research Institute here in the UK and Colin Masters of the Florey Institute in Melbourne Neurosciences and online we are going to have Nadeem Sarwar from Eisai.

OUR SCIENTIFIC STRATEGY:

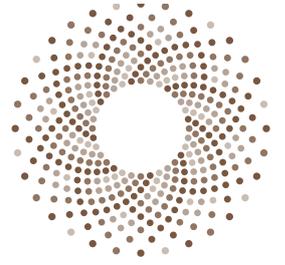
AGING IS THE
LEADING RISK
FACTOR FOR
ALZHEIMER'S
DISEASE



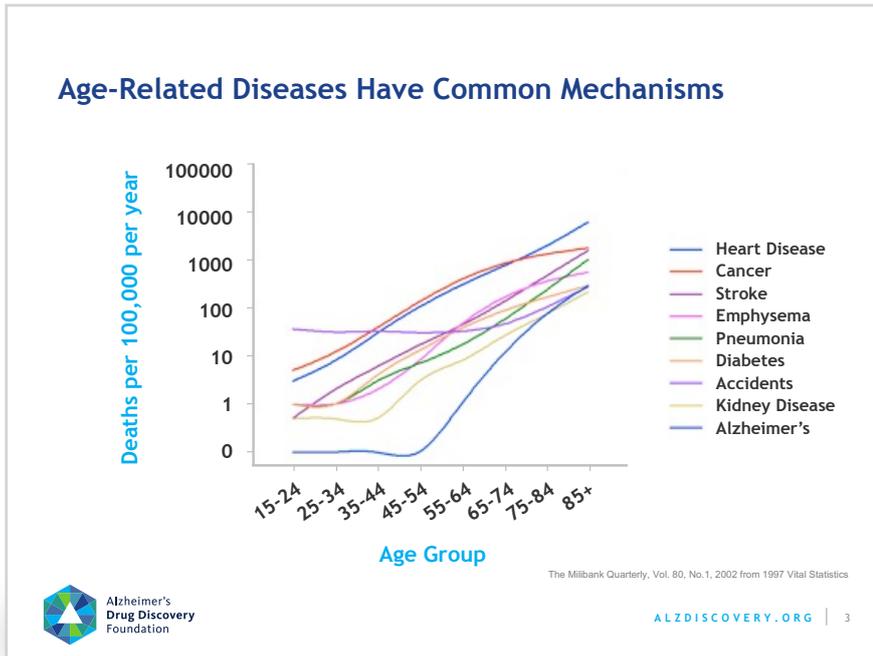
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Foundation

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We're going to get started here. I am just going to present a point of view to try to tell you about not just our strategy at the Alzheimer's Drug Discovery Foundation, but also what I think is as a field a cross fertilisation that we could learn from a great deal. And the reason is

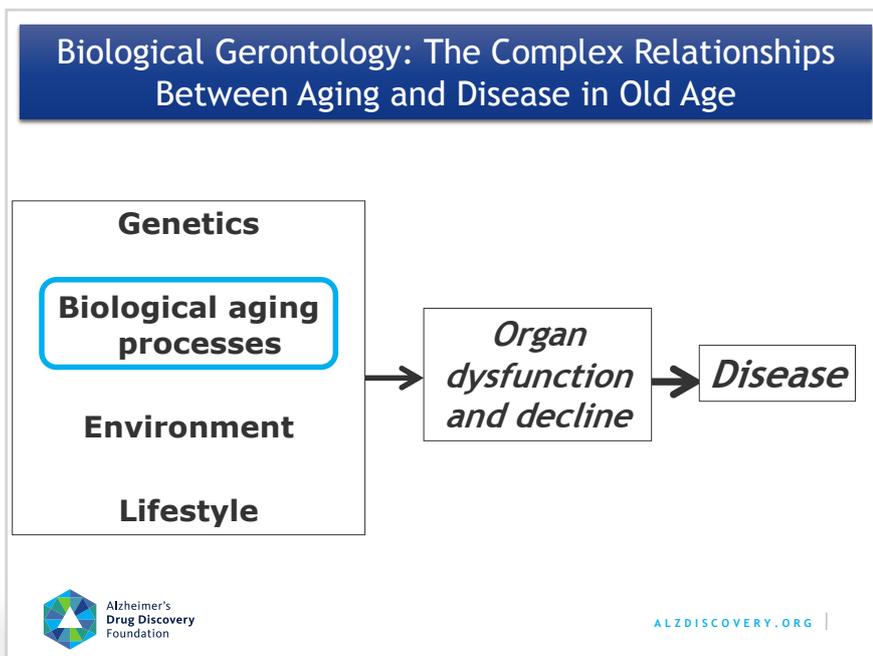


that while we talk a lot about risk factors, I think probably we would all agree that aging is the leading risk factor for Alzheimer's disease and, as a geriatrician and a gerontologist, this has always been my personal point of view.

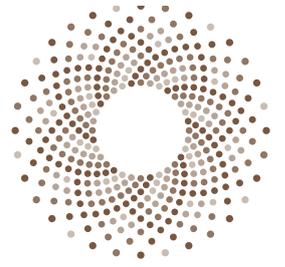


This is a slide that shows something that we all know, but maybe plays it out in some perspective. There's a number of aging related diseases and they all increase with age. There must be something fundamental about the way these processes go to lead to different organ involvement with aging, and indeed these are the processes of aging itself.

It's interesting that when this was published back about 20 years ago you see the line down at the bottom there is the Alzheimer's line. But I think we think about this differently now, that we know that Alzheimer's disease starts 20 to 30 years before their symptoms, and these are just mortality curves. But there is some underlying process here of aging that's related to all the comorbidities that most of us will suffer as we get older and frailer, I suppose.



The biology of aging certainly fits in, with other processes that put us at risk. We just heard about genetics as a risk factor in the previous session. Certainly, some of us will get Alzheimer's with aging and some of us won't and I think talking about resilience factors, that I think Bart you've written about, will also be interesting for us today when we talk about new targets. It's only environment and lifestyle report we have heard a lot about.



**Biogerontology has a long history of progress:
Elie Metchnikoff coined the term “Gerontology” in 1903**

Discovered macrophage and phagocytosis. Considered the father of innate immunity

1882

1903

1908

1946

Won Nobel Prize for work on immunology

Coined the term gerontology (study of aging). Considered one of the fathers of aging research

Journal of Gerontology



Alzheimer's Drug Discovery Foundation

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I just want to mention Elie Metchnikoff here as a kind of a fun point, because not only was he Ukrainian, but he is considered the father of innate immunity. When the modern microscope was developed in the late 19th century, he was the one who observed these cells engulfing bacteria and he called the process of phagocytosis and identified cells as phagocytes which were recognised later as macrophages. He won the Nobel Prize for his work on immunology in 1908. But in 1903 he actually coined the term gerontology and is considered the father, or one of the fathers and perhaps mothers, of modern gerontology. And the Journal of Gerontology, which is probably the most prominent journal of our field that made maybe many of you have never read or heard of, was established in 1946.

What I want to say here is there is a huge body of knowledge, Lenny talked about accumulation of knowledge, on gerontology, of biological gerontology, medical gerontology, social gerontology and psychological gerontology, those are the four pillars of gerontology, that's out there, that we can all learn from in the field, to understand the processes that lead to a neurodegeneration.

The Biology of Aging Reveals Numerous Processes Relevant to Alzheimer's Disease

Neurology®

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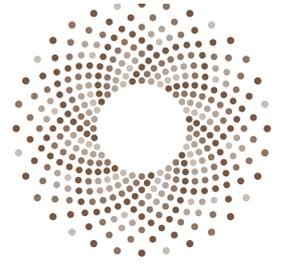
Translating the biology of aging into novel therapeutics for Alzheimer disease

Yuko Hara, PhD, Nicholas McKenzie, BS, and Howard M. Fink, MD
Neurology® 2015;49:84-93. doi:10.1212/WNL.0000000000000745

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HMF@alzdiscovery.org

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What we did in this paper back a few years ago was look at all of the programmes that were out there and categorise them according to the mechanisms of aging that had been identified in the field of gerontology. And the funnel that we see here, which I really don't have time to go through on a one-by-one basis, identifies the many processes that we all look at separately as processes that lead to neurodegeneration, including misfolded proteins, which is up there. But there's many misfolded proteins in the ageing brain. You all know that. We focused on amyloid and tau because these were pathological biomarkers that define the disease but now we think of mixed of pathological comorbidity. We know that 35% or so people come up alpha-synuclein and 15% TDP43. And who knows how many other misfolded proteins there are in the aging brain.

And so, we're going to need a broader perspective on what's going on here. Is it a failure of proteostasis for example? And if it's a generalised failure of proteostasis that would lead us to say that the more parsimonious approach to drug development and target identification would be to try to deal with failure of proteostasis with aging rather than focusing on monoclonal antibodies individually targeting one of these misfolded proteins. Certainly, it looks like the monoclonal antibodies to anti-amyloids are having an effect, but we're going to need to do more than that and look at new ways to do that.

I also would like to point out that systemic inflammation affects the brain enormously. We have known that for many years, and it actually primes microglia in the brain to become the inflammatory phenotype, and certainly the hallmark of aging is what has been called infla-aging or systemic inflammation. And so, we have this interaction between the brain and the body with aging that also needs to be considered. And managing medical comorbidities is part of that.

There is also mitochondrial metabolic dysfunction that we are all familiar with, insulin resistance in the brain, epigenetic dysregulation, vascular dysfunction and so on. All of which in an independent way, and probably in varying degrees of different individuals, affect the ultimate expression of Alzheimer's and dementia.

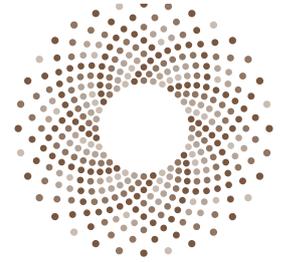
Aging Related Processes Implicated in Alzheimer's Disease Are Also Drug Targets

- Genetics & Epigenetics
- Inflammation
- Misfolded Proteins
- Mitochondrial & Metabolic Dysfunction
- Oxidation
- Vascular Disease
- Senolytics
- Synaptic Activity & Neurotransmitters

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And so, to summarise from a target point of view which is the discussion that are going to have today, I laid out on this slide eight of the most common kind approaches that are non-amyloid approaches and non-traditional approaches that we're starting to see as new areas of clinical development even in clinical trials.

On this slide, the one that I think is the newest, and maybe not traditional, but it's finally coming of age, is senolytics and how senescence cells in the brain can in themselves be causing inflammation in the brain. We are actually supporting the trial of senolytic in Alzheimer's disease dasatinib plus quercetin for Alzheimer's disease. So this this is moving forward.



Entering A New Era: Majority of New Drugs in Development Explore Novel Targets

77%
of disease-modifying trials across all phases have novel targets other than amyloid and tau approaches

ADDF Clinical Trials Report 2021
<https://www.alzdiscovery.org/research-and-grants/clinical-trials-report>

118
Potential Treatments Being Tested to Treat Alzheimer's*

TYPE OF TARGET

- Misfolded Proteins / 27
- Neuroprotection / 24
- Synaptic Activity & Neurotransmitters / 23
- Inflammation / 17
- Mitochondria & Metabolic Function / 14
- Genetics & Epigenetics / 5
- Vascular / 4
- Other / 4

* Including Alzheimer's dementia and mild cognitive impairment

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And the proof of what I've tried to say here briefly is that for the first time the majority of clinical trials are non-amyloid non tau programmes. I think for all of us that have been looking at the clinical trial landscape for Alzheimer's disease over time this is a first. In our clinical trials report from about a year ago 77% of the clinical trials today in Alzheimer's disease are in those categories on the right that parallel the eight categories that I mentioned on the previous slide, which is really exciting given we're going to need combination therapy and we're going to need precision medicine.

A Rationale Approach: Repurposed Drugs For Age-Related Diseases

Age-related chronic diseases have similar pathophysiology

Repurposing is a rationale approach to new drug development for Alzheimer's disease

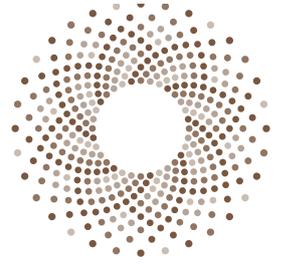
PHASE 1: 32% Repurposed

PHASE 2: 27% Repurposed

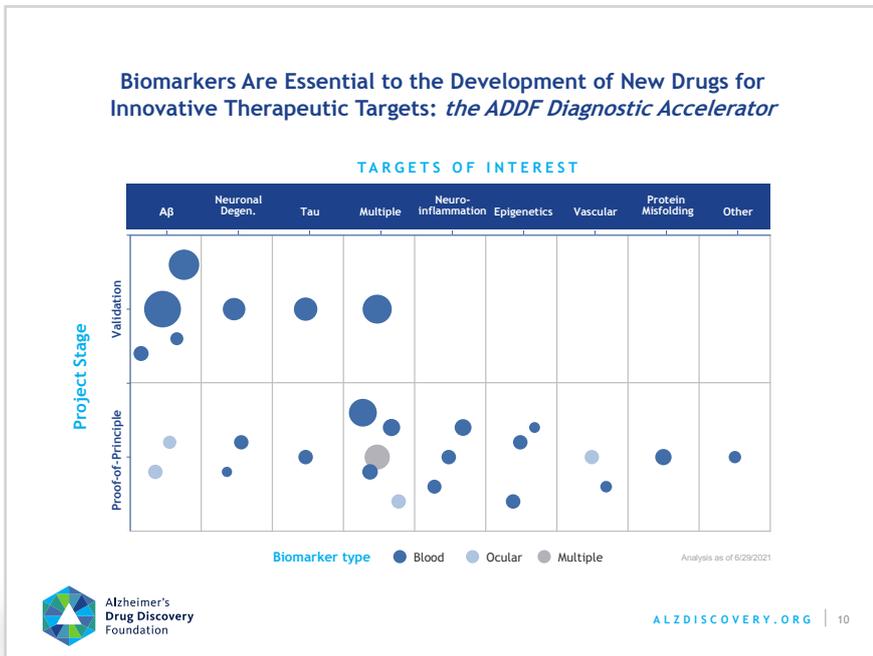
PHASE 3: 21% Repurposed

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One more point that I'd like to make is how we talk a lot about re-purposing, and I think from the perspective of aging and multifactorial mechanisms, and learning from other diseases of aging, re-purposing makes a lot of sense. We have drugs for hypertension, diabetes, Parkinson's disease and so on, where they're on the market, we know their safety profiles and there's a good rational mechanism of action that could be applied. And we have a large portfolio of re-purposed drugs that we have been putting through exploratory studies in phase 2A.



I think it's a rational approach to not only bringing drugs for other mechanisms on non-amyloid non-tau mechanisms to patients, but also to learn from these drugs and eventually develop new chemical entities with new intellectual property that can help market access for drugs and new indications for these drugs and I think based on that, it's a rational approach to new product development.

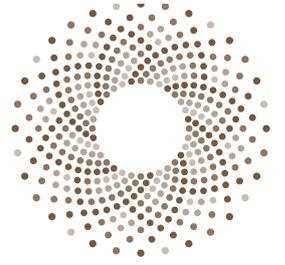


Then finally from the point of view of biomarkers as we view this new world of multiple targets that are non-amyloid and non-tau targets, we are going to need biomarkers. As many of you know, we have partnered with Gates Ventures to have this ADDF Diagnostics Accelerator which was originally a \$50 million programme that's grown quite a bit since. Across the bar at the top what you're seeing is basically the eight categories of targets that I mentioned, and the circles are investments that we've made – over forty investments to date – in the last three years in various non-amyloid, non-tau targets, that hopefully will be used to accelerate drug development in these new emerging fields of drug development.

A Parsimonious Approach to New Drug Development for Alzheimer's Disease

- Alzheimer's is a **multifactorial disease**
- The multiple pathways of **neurobiological aging** provides insights into potential new drug targets
- Anti-amyloid approaches are a beginning, but there is a need for **pleiotropic drugs** and **combination therapy**

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And so, with that that really excited about our panel today, I will just conclude by saying that Alzheimer's is a multifactorial disease and probably varies in each individual. And we're going to need precision medicine and combination therapy, which is all of our mantras. And lastly that I think there's much to learn from gerontology here to apply to Alzheimer's disease.

From Basic Science to New Treatments

Where is the new treatment pipeline going? What are the emerging trends in research?
How do we innovate and fund drug discovery and development?

CHAIR



Howard Fillit, MD
Co-Founder and Chief Science Officer
Alzheimer's Drug Discovery Foundation (ADDF)

PANELISTS



Maria Carrillo, PhD
Chief Science Officer
Alzheimer's Association



Bart De Strooper, PhD
Director
UK Dementia Research Institute



Nadeem Sarwar, MD, PhD
Global Head, Genomic Strategies &
Global Head, Digital Therapeutics (DTx)
Strategies



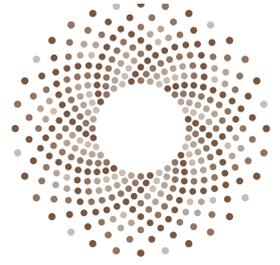
Colin Masters, MD
Laureate Professor of Dementia Research and
Head of the Neurodegeneration Division at
The Florey Institute, The University of Melbourne
and consultant at the Royal Melbourne Hospital



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Just some pictures of our panel. But you can see them in real life here. And we've introduced them briefly. So, I'd like to hand to our next speaker who will be Maria. I know Maria chaired a session here not too long ago back in October and that was a lot about aging. I read the transcript, so maybe it's a good segue.





Dr Maria Carrillo
Chief Scientific Officer, Alzheimer's Association

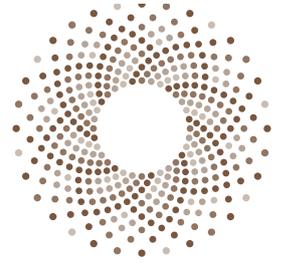
Thank you Howard. It is great to be here with all of you. I do not have slides. I am just going to talk a little bit about my thought on basic science and where we are and where this is going to take us. I am a basic scientist myself by training, a behavioural neuroscientist, but have become a jack of all trades at the Alzheimer's Association as you can all imagine.

The conversation that Howard referred to just now was a conversation with the World Dementia Council that took place in October. The official title of it was something like “non-amyloid treatments and where are we” and it was a fantastic discussion with over 100 people taking part. Of course, back then it was virtual. But we really talked a lot about ageing and the underlying contribution of ageing and how important it was to understand it in the context of all of the mechanisms that we are starting to uncover and understand more deeply. We know they are complex, and we know we are only scratching the surface through basic science. But the more we see basic science coming to fruition, to publication, to presentation, the more we understand the complexities we are facing.



And I think one of those important contributions is that we continuously talk about that diversity and the approaches we need to follow. I was really pleased to see this taking place at the recent AD/PD meeting. Now part of it may have been that I hadn't been at a large face-to-face conference that was like 70/80% focussed on basic science for some time! As you all know AAIC is a bit broader in mandate. But it was fantastic to see at AD/PD we really saw all these mechanisms coming together in terms of discussion. That was fantastic. I learnt how amyloid can modulate, can influence, not only tau but inflammation. How tau can modulate and influence inflammation and amyloid. How inflammation can influence, modulate, stimulate, amyloid-beta species and tau. And add on pick your protein! And on top of this you have the vascular contribution, and we saw a fantastic video, it is a lot of fun to watch those videos from Art Toga, earlier today that links that. And I am not even mentioning alpha-synuclein and TDP43 and so on. Again, pick your proteins!

What I took away the most is that we no longer have one causal pathway, one cascade. It is really so many. It is actually all of them. First it can be daunting. How do you proceed? But on the other side it makes sense. It makes sense to me and perhaps to all of you how one pathway that we have pursued that has taken us from the basic lab to human and trying to replicate and recapitulate everything that not only happens in the petri dish and animal models may not always give us the home run. Because it is much more complicated than just following one causal pathway.



And on top of this of course we know blood tests are telling us these things are intersecting. We are measuring tau to understand actually we are measuring underlying amyloid and tau. There is just no doubt that these single pathway cascades are of the last decade. We need to move on. We need to turn that page. Mechanistically this gives me a lot of hope. And it tells me that all of these things working together can in fact be pursued. So how do we do this? In our conversation in October, I know it was Reisa Sperling who talked about through the practical nature of clinical trials we must follow one protein's change and implication on the system at a time. At least at this point in time. Howard talked about combination therapies. Absolutely. We need to get there as soon as we can. But following one at a time. And as soon as we start to see that window cracking open, that hint of progress, that in my opinion we are seeing now with the monoclonal antibodies, that is what we have to expand upon, and expand upon with combination therapies, but doubling down on what we are doing.

I was really pleased to see at AD/PD Prothena actually proposed a vaccine against amyloid and tau and that they are currently working on it in an animal model. So, this is how you are starting to see that people are bringing all of their theories together and trying to implement them within one system and certainly doing that in humans as again, you've heard Howard talk about.

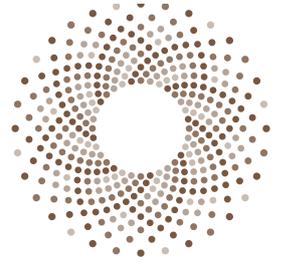
Where are we and what does this mean for translation? Well, first off, we are at a time which is I would say a pivotal moment because we have more money. Certainly, in the United States there is \$3.5 billion dedicated to Alzheimer's. In Europe, in other countries, other countries here represented by the World Dementia Council, we are seeing additional funding and commitments. That's fantastic. So, this is our moment. We've had moments for cancer, we've had moments for HIV, this is our moment.

On top of that, we do know money is absolutely critical, but translating that money, how does that work? Well, we have to start putting more money into those novel ideas. We've heard some here today, actually, to be able to take them out of the lab and into the human condition. And that's what's happening now, but we must continue to do more. We have to double down on all of that because I think that pivotal moment where we can either maybe slow or actually take off. And the latter is what certainly we all want to see.

We know that today the first readouts for monoclonal antibodies have been out there and whether you agree or not with what you've seen out of Biogen makes no difference because the other programmes are showing those hints. And that again, the agreement around among the community, maybe it's not crucial, but the agreement that we have to actually move forward in a positive way and seize that hope for what can come next. It would be, in my view, a missed opportunity if we didn't at least voice that as a community, and I know that in the United States we've had some harder times doing that recently. I don't know about other countries. But we must push forward because that hope that you've heard about that you've heard discussed from this morning from Arthena Caston our first speaker today, that hope is what we have to continue to provide. It would be in my view irresponsible of us as a scientific community to in anyway, stifle that hope.

Now, last thing I want to say is that blood tests are absolutely on the horizon. We do have to be very careful in terms of how we interpret and when we push them out into clinical practice. But in research, they're already making a huge contribution and impact. And that I think is also accelerating us into this next era.

We may not all agree on our causes and on our pet theory on our pet protein. But at this point we can agree that it is a system that is interconnected and interdependent. And that system must be ultimately tested in that way. And we can also all agree that we must do more, we must do it better, and we must do it faster. So, with that, I will leave you and have over to Bart De Stropper.



Professor Bart De Strooper
Director, UK Dementia Research Institute

World Dementia Council

Bart De Strooper Director
UK Dementia Research Institute



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It is difficult to talk after Maria. I am largely agreeing with most of what she said, and part of my talk will be to re-iterate what she said. I am agreeing as a scientist on the optimism but when we look about the organization and funding of the field, and I will share some numbers with you, I am much less sure we are on the right track.

I am Bart De Strooper I am the Director of the Dementia Research Institute. This was established by the UK government in 2008 when the G8 came together here in London and decided it needed to do something about the major global health challenge.

Building vital capacity at the UK DRI

7
Research centres & HQ form the multidisciplinary institute

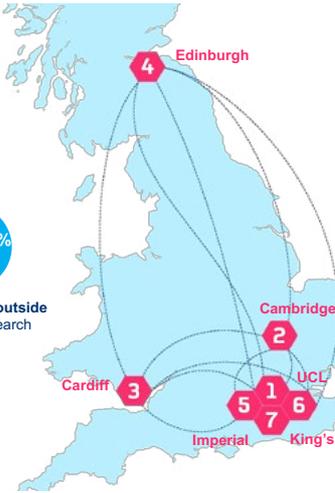
750+
Researchers, support staff & students

61
Group Leaders recruited

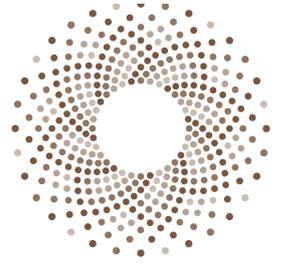
Established first independent laboratory

Recruited from outside dementia research

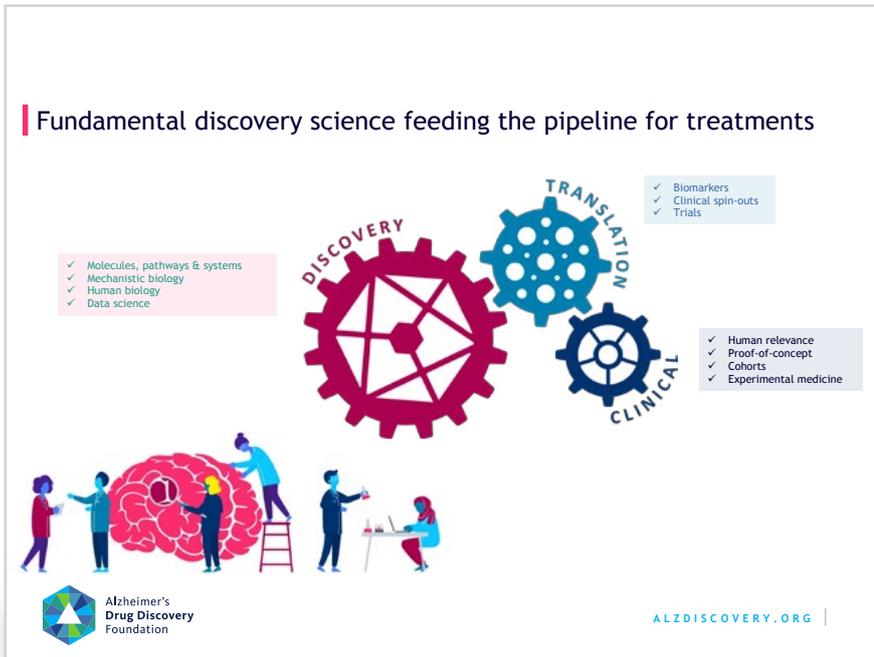
Recruited from prestigious overseas laboratories



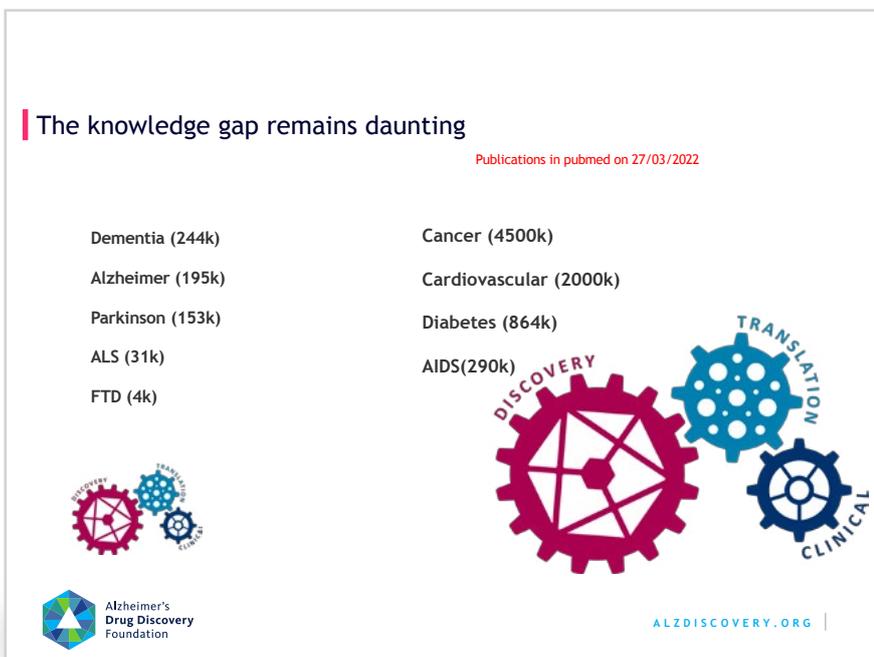
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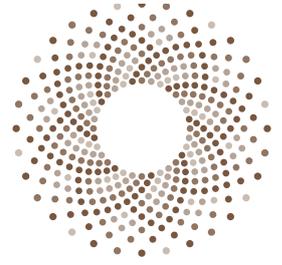


Five years later we have started to implement the Institute. I am very proud to say we have achieved this now. We have an Institute of seven centres across the country in the best universities in the UK. These bring together a group of really top scientists. And we have been able to attract a couple of young scientists which were from other fields and getting interested in what happens in our field. This is really important because sometimes I have a feeling we are a bit old fashioned in this field and very traditional and internationally running behind what happens in the biology world. But we try to work in that direction.



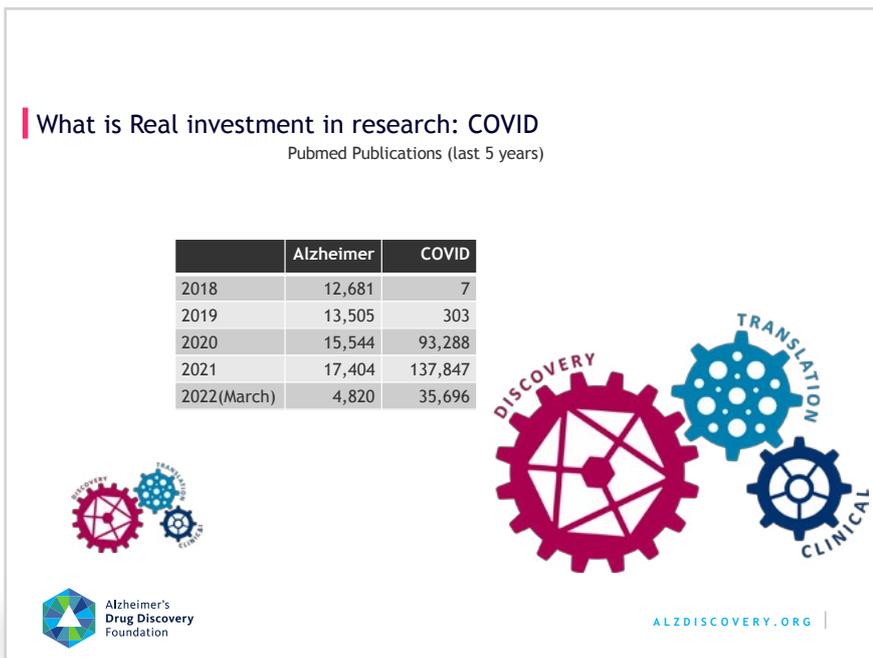
In the Institute there are three wheels, as shown on this slide, that are essential for our work. The biggest wheel is discovery and even at the conference here I feel disappointed. I am not disappointed about how much people are talking about translation and clinical, but I am disappointed by how little attention is given to discovery. I will show you numbers why this is really a problem. Translational and clinical research will not exist if we do not have good discovery. So, discovery is the main thing we do in the Institute.





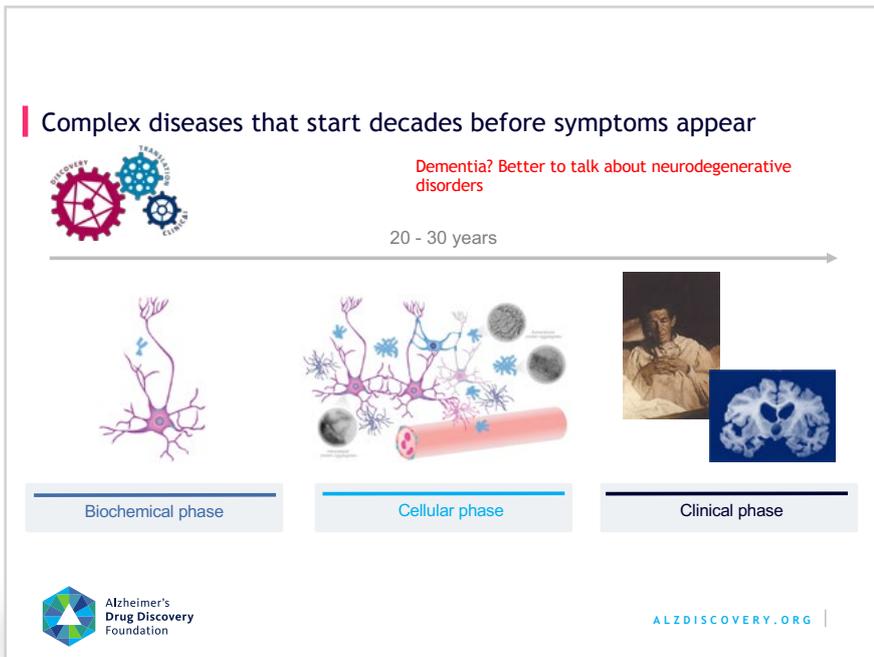
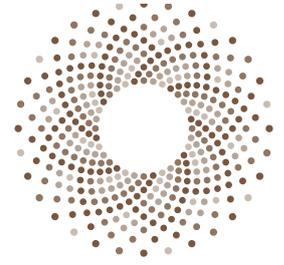
This is something I have shown and shown but I get the feeling I have not shown it enough. This is the number of papers available in Pubmed for different fields of research. I am going to cite one number dementia, which is a big collection of different diseases, 250,000 papers. It is a lot. But for cancer, a collection of different disorders, 4.5 million papers. Think of this disparity in the database, this lack of information, when you want to implement a clinical trial, when you talk about filling the pipeline. Everyone is talking about translation and bringing drugs to the clinic, but we don't have enough knowledge and drug targets in the pipeline compared to cancer. And the same is true if you look at cardiovascular diseases where there are 2.5 million papers. And the problem is even bigger when we want to interpret the results from failed trials: we do not have the knowledge to understand why they went wrong.

So, we have a problem. I realise sometimes people say there are so many papers published and many are of poor quality, so what does this actually reflect? Well, it reflects, basically, the activity in a field and investment in a field and how much you know in a field.



Covid has been a really interesting experiment in that regard, for me at least. I did the same exercise with Covid and Alzheimer's. And what I show on this slide is two machines. The left one is the Alzheimer's one and the right one is the Covid one. And the Covid machine started four years ago, and the Alzheimer's machine started 100 years ago.

Look to the papers. In 2018 there were 12,000 in Alzheimer's and 7 in Covid. In 2021 there were 17,000 in Alzheimer's, that is a positive increase. But there are 137,000 in Covid. That is what getting serious about a disease looks like. This reflects what the field has done in three years! They have as many papers as the whole Alzheimer's field has built up over 100 years. So, when people say trials fail, or the field doesn't move forward, what do you expect? The science is not supported in the way it should be supported.



Now I am going to largely agree with Maria. We have made a lot of progress. We have finally understood that this is not a simple disorder. I think the most important thing that we have understood, and this is why the World Dementia Council is a very bad name for the problem we are talking about right now, is that these are complex diseases which start long before dementia is present. Dementia is an end phase. I don't think it is really stimulating to define our research as about solving dementia. It is about understanding these disorders. The ten or twenty years that it take to move from the initial accumulation of amyloid peptides to dementia. I called this the cellular phase of Alzheimer to reflect on the complexity of this disease. And we have made some progress but not enough.

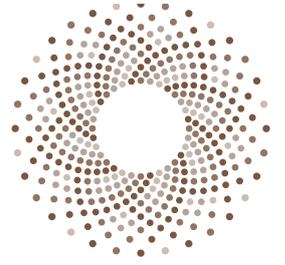
So back to clinical trials and diagnostics. We need to find the clinical signs of the cellular phase. We need to know what is going on in the brain before the start of dementia. Dementia is an end stage, not much to be done anymore. There are subtle changes in the cellular phase, likely reversible. There is a way to identify those. To create diagnostics that detect these very early changes: think about cardiovascular disease where you cycle to see how your heart is doing; think about cancer where you have preventative interventions. Everybody agree in these chronic conditions that people are already sick before they have clinical symptoms. We need a similar approach to the dementias.

Despite being slow, because of underfunding, we have made good progress as a field

- Small molecules
- Gene therapy
- Oligonucleotides
- Antibodies, nanobodies,
- Cell therapy
- Deep brain stimulation, brain supporting devices
- Technologies to support people

Of note: anti-amyloid therapies
Karran and De Strooper, Nature reviews Drug Discovery, 2022

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So, despite being slow we have made a lot of progress. I didn't make a big slide about all the progress but here is a summary list. We are working to find drugs, but we are too slow and work with too little scientific background.

I have put here of note anti-amyloid therapies. I am not going to have the discussion here. But I hear so many stupid things about anti or pro amyloid! And I am thinking if you were to talk about drug targets in the cancer field in the way we talk about amyloid we would look ridiculous. We don't know what AB peptide is doing we don't know if there is a biological difference between AB40 and AB42. We don't know these basic things and we are all talking about lowering it or increasing it. So, if there are side effects or it doesn't work like you want it is maybe not such a surprise. We need to give these drugs a serious chance and go for the patients where these amyloid peptides are the upstream cause of the dementia. We are now treating a lot of patients that have dementia because of other causes or where many causes are playing. No surprise that anti-amyloid drugs do not work there. More work should be done to identify the correct patient population and to think carefully about the therapeutic hypothesis etc. I refer to a recent review that Eric Karran and me published in nature reviews drug discovery.

Breaking silos between pre-clinical and clinical research

- Engaging / building capacity of clinical scientists and health professionals
- Biomarkers
- Proof-of-principle studies
Move faster in human
Focus on early markers of disease
- Link to healthcare systems



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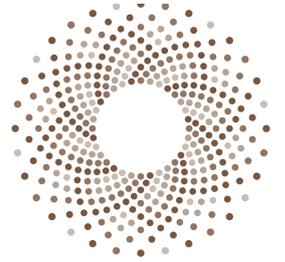
Anyhow! The other point I want to make is we need to break silos. I have presented it on this slide here but won't dwell on it. We all agree on it.

Accelerate translation to treatments:

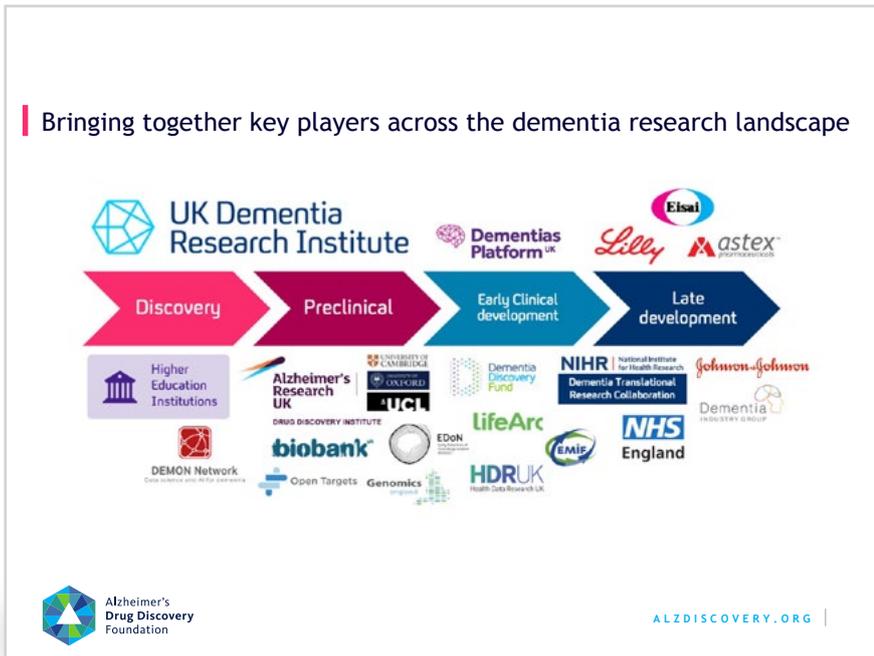
trust and empower science and scientists



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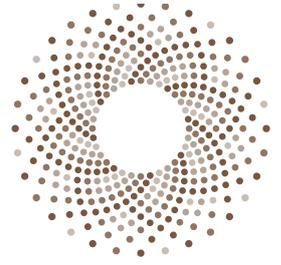
We need to accelerate translation – despite what I was saying! But I think we should do that by trusting and empowering the scientists much more. I have seen that in other Institutes where they have invested in the researcher. You need to help your researchers think in a translational way. That is what we do in the UK DRI.



And the last things I would like to say is I like the investment done in the US, which Maria mentioned, but the rest of the world is far behind. The European Union mentioned dementia once in their future plans for investment over the next seven years. Here in the UK, there is a lot of effort but as this slide shows it is a very splintered landscape. What I would say is that we need some leadership in this landscape and so I offer it for free at the UK Dementia Research Institute if anybody want to listen!

Thank you very much.





Professor Colin Masters
Professor in Dementia Research, University of Melbourne

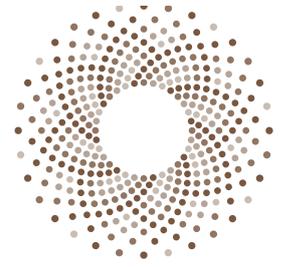
Thank you for a great spirited talk my friend. A polemic. It is a great pleasure to be here at short notice. I am delighted to fill in for one of my colleagues who is unfortunately ill with covid. I have got serious arguments with most of my fellow presenters, but this is not the forum to debate them! I am Colin Masters of the Florey Institute, University of Melbourne. I don't have slides.

I just want to say a few words. I know there are some amyloid sceptics in the room. I won't say amyloid deniers. But I would say the amyloid story is now a comprehensive theory. I see John Hardy at the back somewhere there. I prefer amyloid theory over hypothesis, sorry John. It is because ABeta amyloid is the proximate cause of Alzheimer's disease. I know that will upset some people. Particularly those that have already expressed the view that it is multifactorial, and it is complicated. But I think we should celebrate the fact today we know where in the brain it starts and when it starts. We can tell you that. We can go through all of those details with you. This is a major revolution in the field for me to be able to get up and make those two clear statements.

However, I have been told by my Chair that I am not to talk about amyloid today I have got to talk about non-ABeta targets. I just want to have a slight dig at the industry – I am looking at one of my colleagues from industry here – and say, as Bart has said, big pharma made a big mistake with inhibitors of BACE1 and gamma-secretase when they used them in such high doses that they all produced adverse events. They have to go back and redo it again at much, much, lower doses. So that is all I have to say on Beta amyloid.

So, taking seriously my instructions, I am now going to say a few words about non-amyloid targets. My favourite non-amyloid target is of course the major genetic risk factor for late onset Alzheimer's disease which happens to be APOE4. It is like the elephant in the room. It is there in front of us. It is the major non-amyloid drug target I believe. There are other genetic risk factors. None as big as APOE4: APOJ, TREM2, CD33 and sixty others that John Hardy knows much more about than I do. And Howard, I am so happy you introduced Elie Metchnikoff because most of these genes fall into the innate immune pathways. And so that is where we should be looking very carefully about where there are therapeutic opportunities.





I just want to have another little crack at the genetic people. There is great confusion in the field at the moment between the genetics of onset versus the genetics of progression. All the genes I have just mentioned, APOE4 and the others, are age-at-onset genes. But what about the genes that regulate the rates of progression? You can talk about that in terms of resilience or vulnerability. My view at this point is that there is only one major confirmed resilience factor for the rate of progression and that is the allelic state of BDNF (brain derived neurotrophic factor) gene. I would put that up high along with APOE as the other major therapeutic target. If your brain is not making enough BDNF, you go downhill very quickly once you go into the prodromal phase of Alzheimer's disease. We have got to understand that and figure out ways to lift the amounts of BDNF in the brain. It is all under genetic control. It is doable!

Now, of course, I want to say something about other non-amyloid targets, and put the genes to the side for one moment, and that is the environment. Miia and Kaarin spoke about this earlier today. There are three major environmental factors that I think one could argue do play into the Alzheimer's pathway. I am not talking about non-AD dementia. These are diet, exercise and sleep. Those are the three areas that I see at the moment as having some possibility of affecting the rate of amyloid accumulation in the brain. And from that we could seriously talk about non-pharmacological interventions.

Talking about lifestyle leads into my final point which is the co-morbidities. Everyone is getting confused about the major co-morbidities about Alzheimer's disease. And they conflate them. In most of the discussions I hear at scientific meetings, and even at a meeting like this, everyone mixes up the confluence of vascular disease together with the new entity which we are beginning to understand, and that is frontal temporal dementia (FTD) marked by hippocampal sclerosis (HS) and the aggregation of TDP43. So, if you continue to mix up the co-morbidities of cerebral vascular disease – both of small vessels and large vessels – and conflate that with the underlying causation of the frontal temporal dementias and mix all that up with Alzheimer's disease. It gets complicated. Very complicated! Thank you.



Dr Howard Fillit
Co-founder and Chief Science Officer, ADDF

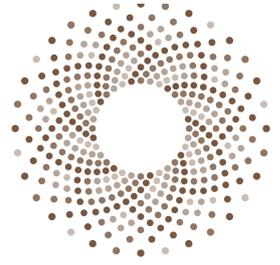
Our last speaker is Nadeem Sarwar from Eisai who we need to get up on the screen. So, a quick question while we do.



Professor Joachim Schultze
Director System Medicine, DZNE

Thank you very much to the panel. My name is Joachim Schultze I am trained as an immunologist in oncology and now I am directing Systems Medicine at the DZNE in Bonn in Germany. I was very interested in listening to this debate and hearing what comes up because I am a newcomer to the field. But I can tell you something about cancer first. We have P53 that is your 'a beta' in Alzheimer. P53 is extremely important in cancer, but it is not all.

In 2001 Weinberg and Hanahan had a review in Cell, it is cited thousands of times. There was not even the immune system in the review, not even vascular. In 2011 they were invited to write an update and four new areas came into this review. So, the cancer field is also learning slowly. But it is very clear that cancer is a multi-modal disease and there are many things that we have to better understand. It is multi-factorial, and I think we can learn a lot from that the successes in the cancer field. And what Bart (de Strooper) said is absolutely critical. Cancer gets at least ten times the money. Forget about progress without that. We have to lobby for more money but also, as Bart said, attract people from other fields into the dementia field to get new ideas. And I am very happy to be here because it is absolutely mind boggling how much we can do here. That's why I left cancer and I hope we can contribute. Thank you.



Dr Howard Fillit
Co-founder and Chief Science Officer, ADDF

In all fairness to our field, cancer is way ahead of us but I would like to note the Imperial Cancer Trust was established here in the UK in 1903, the National Institute on Ageing wasn't started until 1975. When my mentor Bob Butler became the founding director, he did a survey of the NIH at a time when they were spending billions of dollars on heart disease and cancer and we as a country spent \$600k dollars on research on twelve grants, mostly on caregiving.

Most of us here remember a time in our professional lifetime when we knew almost nothing about the disease. In 1980 we knew nothing but in thirty or forty years since we have got to a point where we are clearly seeing disease modifying treatments coming to the clinic. I once saw a metric that it takes 35 years to go from basic research discovery to getting a drug to market and maybe 12-15 years of actually developing the drug but maybe many years of basic research. I like to think we're right on time actually. We are just historically way behind cancer and heart disease, but we are right on time for our own timeline.

Nadeem at this point can I bring you in?



Dr Nadeem Sarwar
Global Head for Genomic Strategies, Eisai

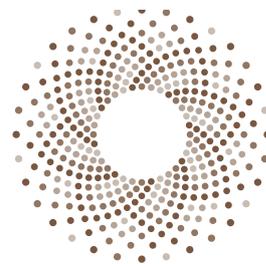
Thank you Howard and thank you to the organizers for accommodating my switch at such short notice from in-person to joining remotely. I really appreciate it. And shows we can do things quickly when we put our minds to it!

I would like to take issue with two things. First asking me to talk after Maria, Bart and Colin. Really! I am not sure what I can add either scientifically or in terms of passion. And secondly, I would like to take issue with the title. There is nothing basic about the science that we do. It is a very un-sexy title to give us especially with a two-track competitive process! Perhaps next time we can call it sci-fi science. But with that, I thought I would start with other diseases like others have done and see where we put ourselves in that context.

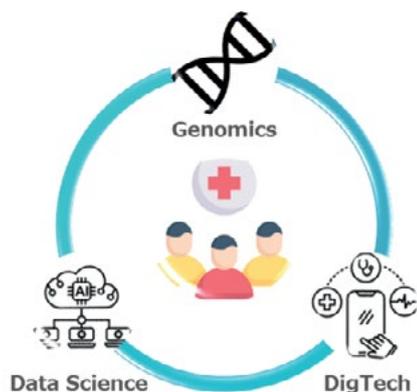
I grew up in the 90s and 2000s reading about remarkable innovations and breakthroughs in cardiovascular disease especially in the prediction and prevention field. This was illustrated by the remarkable development and deployment at scale, and globally, of risk prediction scores underpinned by data from the Framingham heart study. This enabled the targeted use of statins and other preventative life extending therapeutics. So, in the 90s and 2000s cardiovascular intervention really took off.

In 2000s and 2010s we have all been hearing about the remarkable innovations and breakthroughs in cancer, especially in mechanism-based precision medicine. This is illustrated by medicines that were matched to genomic and pathogenic trajectories of the disease and novel mechanisms of action and modality like immunotherapies and their combinations. So again, 2000s and 2010s cancer pretty much took those.

As I will argue over the next five minutes and hopefully convince you, 2020s and 2030s is our time. We are the generation of medicine makers that will change the game for dementia patients, their families and their caregivers. And that is because of the reasons that Maria, Bart and others have illustrated. The confluence of science and knowledge and I think now desire to do something is there. And I think we are able to deliver things that were truly sci-fi, unimaginable, even a decade ago.



So, the drivers of therapeutic innovation that I think we will see over the next decade, that will realise that this is our time, is the triangulation of: (i) genomics and human biology; (ii) data science and advanced analytics, and (iii) pharmacological and digital modalities. And I will speak briefly to each of those.

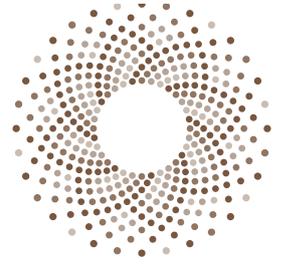


Genomics and human biology provide us with a remarkable arsenal now to understanding the causal pathogenic mechanisms that drive disease and in fact may allow us to change the way we even think about the disease. My hope is that within my lifetime as a medicine maker I won't make medicine for Alzheimer's or Parkinson's or other defined disease states. Instead, I would rather make medicine for causal mechanism X or causal mechanism Y and match medicines to the patient whose disease is driven by that mechanism irrespective of what clinical label we happen to put on it. That is what has happened in cancer and there is no reason why we cannot do that in neurodegeneration. I believe we now have the underpinnings needed to realise truly mechanism driven precision medicine, plus we now have the tools and ability to modulate causal molecular mechanisms in the right way.

Coming down to the bottom left of my triangle on the slide, data science and advanced analytics, our ability to study human biology in particular is delivering data at a scale and a speed and a quality that was again sci-fi a few years ago. We are able to generate vast amounts of data and there are vast amounts of knowledge that can come from that data. But being able to coordinate, integrate, harmonize, analyse, interpret and apply that data in a smart and meaningful way is a current bottleneck to the scale of our ambition. And I was really pleased to hear the last person speak switching to us from oncology. First, welcome. I hope many others will do that to. We are now competing not only with other life science sectors but also other sectors beyond for the best talent. What we hope is that the next genius in data science doesn't want to make apps but instead wants to make medicines because we need those people to help us make sense of the vast amounts of data we are generating.

I will talk briefly about modalities, pharmacological and non-pharmacological. So again, with the plethora of chemical tools at our disposal I am no longer concerned about druggability. This was a phrase I was first introduced to when I joined the pharmaceutical sector from academia over a decade ago. My understanding of the word druggability was something that was non-druggable, something that cannot be drugged. I have now learnt that what chemists mean by non-druggable is that I can't drug it yet, but I will. And I think that is really the opportunity we now have with not only small molecules and antibodies but the whole host of other modalities we now are able to use to moderate causal mechanisms in the right way and at the right time. Be that cell therapies, gene therapies, antibody conjugates, anti-sense oligonucleotides, RNA therapeutics, vaccines. There is a whole world of chemical modalities that have been opened for us. We can use again genomics and other insights to match that to the right people. And finally digital modality present remarkable opportunities to not only measure and quantify the disease process as it progresses, something we need to do, but perhaps also to intervene at a scale and cost that is globally manageable.

So, I would strongly echo the passion that Maria and Bart and others provided. This intersection of genomics and human biology, data science and advanced analytics, and pharmacological and digital modalities has put us at a point where we can drive true breakthroughs and prove to everyone that this is our time. Thank you very much.



Dr Howard Fillit
Co-founder and Chief Science Officer, ADDF

Thank you. As we bring the session to an end, I don't want to keep everyone from lunch, but I think we have time for one question. Yes sir?



Question from audience

I would just like to pick up on Maria's point about translation. How does the panel think we improve the transition from discovery to translation?



Professor Bart De Strooper
Director, UK Dementia Research Institute

I don't think that is the biggest problem to be honest. I think that goes reasonably well. Pharma is very ready to test good, validated drug targets. We see that happening the whole time at the DRI. The real problem is having a sufficient number of novel targets.

But the second problem is lack of understanding of the disease. We may already have drugs for specific dementias or for Alzheimer's. But the way we have used these drugs has in a way showed the ignorance of underlying science. I had something in my slides about that but didn't have the time to talk about it. We need to retest drugs that have shown some promise but were abandoned. I think the most dramatic example is the gamma secretase which is the best genetically validated target. But it is given up because there were side effects that weren't understood. The trials did not take into account that there were four different enzymes, that the inhibitors were non-specific, that the kinetics of the drugs were so that they optimized side effects and decreased efficacy. This is all knowledge that accumulated much too slowly because the trials were going and the research was only slowly progressing. And the trials were done. And the decision about gamma secretase was done. And in the meantime, we accumulated the research to understand why it failed. But for big pharma the time was over. We throw away the few good targets that we have. I believe that the problem is indeed upstream and that once we bring better targets with good mechanistic hypothesis and good biomarkers, pharma will be certainly interested to take it from there.



Dr Howard Fillit
Co-founder and Chief Science Officer, ADDF

Well, we are right on time for lunch so thank you very much everybody.

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.

worlddementiacouncil.org

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