The Amyloid Obsession

Baroness Susan Greenfield, Founder and CEO of Neuro-Bio Ltd, shared her insights on the challenges of developing Alzheimer's disease treatments, and the fundamental flaw with approaches to date

***EBR*: What are the current limitations of Alzheimer's disease treatment?**

Susan Greenfield: The current limitations are that no one has come up with a convincing narrative for how Alzheimer's actually develops. Until you do that, it's going to make the task of intercepting it successfully – or, indeed, of deriving a biomarker that would be a faithful index of the condition – very hard.

The reasons that no one has come up with a convincing narrative are several. One is the love affair with amyloid which has been going on for a long time – I don't need to rehearse the disenchantment now of, for example, the FDA. We would argue that amyloid is part of the picture but it's a downstream part. It's something that will be related to later stage Alzheimer's, but it's not central to the story. Targeting it may be slightly effective in certain respects, but it's not going to be the answer. That's the first problem.

The second problem is that you'd only have the symptom of cognitive impairment 10 to 20 years after the degeneration process has started. That means any drug will be closing the door after the horse has bolted. It also means that, for the moment, the only way of evaluating a drug or evaluating efficacy is by cognitive tests; cognitive tests are by definition subjective, they're individual, and no two individuals are the same – they'll have different rates of progress anywhere in life regarding their mental development or deterioration. Therefore, evaluating whether a drug versus placebo has been effective is going to be difficult to take a large sample, and so on.

Also, no one has really focused on what we started with, which is the really interesting fact that the primary cells that degenerate in Alzheimer's – the first ones to go – are not the hippocampus or cortex. Traditionally, these two areas, which are associated with cognitive powers, have been targeted because they contain amyloid. However, the key cells, the primary vulnerable ones, are deep down in the brain – they're not part of the hippocampus or cortex at all. They're much more primitive than that; they are a hub of cells in the brain. This was pointed out by Rosser in 1981, and there was a brilliant review in 2015. Since then, there's been significant evidence and data showing how, before you have degeneration in the cortex, it's these cells that show pathology first. It's not amyloid, it's tau pathology. That, to me, is the final coup de grâce on the amyloid hypothesis, that the primary cells don't ever have amyloid. That's another reason.

The current limitations are: looking too much at tweaking the amyloid hypothesis; not enough attention to the clues that the pathology is giving you, which is often used to have Alzheimer's and Parkinson's code appearing; and not having any explanation for the time lag, which we can explain immediately. These very primitive cells have a high degree of redundancy – the cells lost in Parkinson's are adjacent to the ones lost in Alzheimer's, so you could imagine the damage if you had both.

With Parkinson's, 80% of the relevant cells have to be lost before you see motor symptoms, because they're very primitive cells. They're all entangled with each other, hence the term isodendritic cells, meaning of equal dendrites – the processes and branches all tangled up together. They're very basic cells that could compensate for each other. This is what we believe occurs, and the damage in these cells will only spread 10 or 20 years later. That's why you don't see cognitive impairments when it goes to the more sophisticated areas.

What have been the flaws of the approach towards Alzheimer's drug development?

The flaws of the approach have been several. One is the 'me too' approach of just looking at variants of amyloid, even in the face of increasing evidence and cynicism – it's just not effective. The flaw has also been to try and find something to bring and target it rather than stand back and come up with an explanation for the mechanism, and that has been the main issue, whereas I'd like to think that we have come up with the mechanism.

What's really interesting from reading the literature, is that these very primitive cells are the primary vulnerable ones, where we can explain things like the co-pathology and the time lag. Astonishingly – this was my lightbulb moment – there was a review showing that they come from a different part of the embryo. They come from the basal

plate, not the alar plate. So even at four weeks' gestation, they're different. The lady who wrote this review is called Nancy Wolf. I know her very well, and when I found out I immediately said, "don't you realise the soul roots that you're showing come from a different part of the embryo and are the very ones that are lost in Alzheimer's and Parkinson's?" It was astonishing. She wasn't a clinician, so she hadn't actually put this in her review, but it was a lightbulb moment that the cells are the same.

Now, what was exciting about the different features they have from other brain cells – and it sounds like a good thing – is that actually they have retained their sensitivity to growth factors. They've retained the ability to grow again, unlike mature cells in the rest of the brain. That might sound like a great thing, but the problem is that a growth factor, if it lets in too much calcium (which is always the final trigger), can actually go from being trophic to killing. There's a spectrum from trophic to toxic – it's a bit like Jekyll and Hyde. It depends on the context; if you have too much, it'll result in death, not growth. But Eimerl and Schramm showed age could make a difference in 1994. Whilst a young embryo cell will mobilise calcium for growth, a mature one won't do that, and the calcium instead will disrupt the electron transport chain, cause leakage of free radicals, and then kill the cell. So, we came up with this theory that neurodegeneration is an inappropriate form of development. You can imagine if most cells in the brain are damaged for whatever reason, you'll get recovery of partial function, but if this hub of cells is damaged, unlike all the other cells they will try and grow again, and they will do so by mobilising their ability to grow by their developmental mechanism. That's the very

worst thing they could do. Then the question is: "What is the signalling molecule? What is the molecule that drives this inappropriate activation of growth?" The answer is the peptide T14.

The reason we got to that is adulthood. It's cleaved of a very familiar enzyme called acetylcholinesterase, which I've worked on all my life. All my research career has been working on the heretical idea of this enzyme not being an enzyme, as well as breaking down a transmitter called acetylcholine. Since the 60s, people have been finding it in places where its normal substrate is absent. I can't claim originality for that, but for my doctorate I showed that it could be released as a signalling molecule and have actions, independent of being an enzyme. We found that the bit at the end was the active component. We can actually give a narrative of how it happens now.

Can you elaborate further on the role of T14 in the development of Alzheimer's disease?

Braak staging is the gold standard for describing the severity of Alzheimer's disease; they go from one through six, starting with one and with severe dementia at six. These are based on tau pathology looking at post mortem brains. At Braak stage two, we showed in our paper that already in the brain, T14 was massively elevated over the control stage. And yet, interestingly enough, at Braak stage two, there are no symptoms of Alzheimer's. We're excited as this shows that this is a very early response to the early stages, and it also suggests that we might be on the track of getting a biomarker, because if we could now reproduce that profile in blood tests, even before you have symptoms, that would be an early diagnosis. The reason we haven't got a biomarker yet is that you need to know the basic mechanism.

If you don't know the basic mechanism, the biomarkers that people look for are amyloid, but then if amyloid is not present in the primary vulnerable cells, there's no way you can use it as a biomarker to detect pre-symptomatic Alzheimer's. So, you might be able to use it for something afterwards, or people use more generic things like ageing or pathological markers, but they're not specific to Alzheimer's. And then you want to intersect it, because obviously you want to block it. We identified the receptor, which is the most powerful calcium ionophore in the brain. And then we needed to block it. The way we blocked it as a normal agent, is actually T14 itself, but bent into a circle, so-called 'cyclated'. It's simply the inert and inactivated form. That's all it is, because you have to fight like with like. The reasons other drugs have failed, is that they haven't realised that the site is occupied by T14 in Alzheimer's. And that's a naturally occurring, extremely tenacious thing. In order to dislodge it, some separate synthetic thing isn't going to stand as much chance as the peptide itself in pushing it out of the way.

Why is it so important to diagnose Alzheimer's as early as possible?

I'd refer you to the speech I gave in the House of Lords earlier this year in response to the Queen's speech. I have to give credit to the Alzheimer's Research UK and the Alzheimer's Society, because they helped me significantly with all the facts and figures. They said, there's a backlog of diagnosis and early diagnosis. One of the most obvious reasons to diagnose Alzheimer's early is that you can put people into clinical trials – there are 150 trials around the world needing participants. Also, even existing medication, if given early, would surely be better than later. The person could also be looked after and given help with memory issues earlier. There's every sign, certainly from those two charities that know a lot about it, that early diagnosis, even though there's no effective treatment, would be hugely beneficial to the patient.

Where would you like to see Alzheimer's treatment in 10 years' time?

To have a blood test or something even more simple, like taking your macro cholesterol, to determine whether it's aberrant. This suggests that, although you may feel fine, you've already got the indications that neurodegeneration is underway – it's not a probability or possibility, this is definitely the case. It's an indication – you're pre-symptomatic, but you've already got a neurodegenerative process underway. Our dream is the coupling of a biomarker with a treatment that stops any more cells dying.

Baroness Susan Greenfield, Founder and CEO of **Neuro-Bio Ltd**, is a neuroscientist, writer, and broadcaster. She has published over 200 papers in peer-reviewed journals, based mainly at Oxford University but has held research fellowships at the College de France Paris, France, NYU Medical Centre New York, US, and Melbourne University, Australia.

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