Johan Luthman – EVP & Head of R&D, Lundbeck

There is still a big role for symptomatic treatments in Alzheimer's. Until we have a cure or a preventative therapy, matched with very early detection, we need treatments that can improve patients' quality of life.

11.03.2025

Tags: Denmark, Lundbeck, Global, Alzheimer's, Neuroscience, Clinical Trials, R&D, Strategy

A seasoned neuroscience researcher with firsthand experience of both successes and failures in one of biomedicine's most challenging fields, Johan Luthman is better placed than most to comment on the past, present, and future of Alzheimer's disease. Luthman, who currently serves as EVP and Head of R&D at Danish neuroscience player Lundbeck, shares some of the key lessons from past clinical trial and launch failures in Alzheimer's and why - in the absence of a miracle cure - a focus on behavioural and psychiatric symptoms rather than cognitive decline is the most impactful approach for patients and caregivers.

Can you outline your experience as a researcher in the Alzheimer's field?

My work in Alzheimer's research started a long time ago as an academic associate professor at the Karolinska Institute, studying neurodegeneration and dying cells. That naturally led me to Alzheimer's disease, but it wasn't until I joined the industry in 1991 that I truly started focusing on this field. By 1992–93, I was deeply engaged in chronic neurodegenerative diseases research and drug discovery, including stroke, multiple sclerosis (MS), Alzheimer's disease, and Parkinson's disease.

My career has been largely in industry, but early on, I still had PhD students, mostly at the Karolinska Institute. One of them – Camilla Nilsberth – finished her thesis in 2002, on work she mainly did in our AstraZeneca laboratories. I advised her, together with Lars Lannfelt, then a

professor at the Department of Clinical Neuroscience, later a professor at Uppsala University. He led the team discovering the Arctic mutation (E693G), a genetic variant in the APP gene linked to abnormal amyloid-beta aggregation in Alzheimer's disease, while my team at AstraZeneca contributed to the understanding of the biochemistry of the mutation, studying aggregation propensities of the Arctic mutation amyloid-beta (Aβ) peptide, isolating various products of its aggregation, and other molecular factors.

Lars, Camilla, and I, together with other key contributors, co-authored the first publication on the Arctic mutation and its molecular properties. Later, Lars developed antibodies against the amyloid beta antigen which we had isolated, and co-founded the Swedish biotech company BioArctic, similarly to many other biotech and pharma companies at that time that generated antibodies against Aβ-peptide species; all encouraged by the pioneering work done by the late Dale Schenk on the Alzheimer's immunotherapy concept. Initially, BioArctic managed their program, but quite soon thereafter the pharma company Eisai stepped in, funding preclinical work, and fully in-licensing the product in 2007 and thereafter fully taking over the development of what eventually became the now-approved drug lecanemab.

What were some of the major challenges in Alzheimer's drug development you encountered at Merck and Eisai?

When I later worked at Merck Inc, we had several Alzheimer's programs focused on amyloid, tau, and neuroinflammation. At Merck, I helped bring three BACE inhibitors [drugs that block the BACE1 enzyme, which is involved in the production of Aβ peptides; an assumed key driver of Alzheimer's disease – ed.] to human trials. We eventually chose one for a major phase 3 trial, a drug target approach which turned out to be one of the more painful experiences of my career.

After leaving Merck, I joined Eisai in 2014, where we had our own BACE inhibitor, elenbecestat, meaning that I have been part of bringing two BACE inhibitors all the way from very early stages to phase 3 trials. During this time there were several major BACE inhibitor programs across the industry; however, the entire field collapsed due to problematic findings. BACE is a very promiscuous enzyme; it interacts with multiple pathways, making it difficult to target safely. Lowering Aβ peptides in cerebrospinal fluid (CSF) seemed like a promising biomarker strategy, but it did not translate to clinical benefit.

Why did so many early Alzheimer's drug trials fail, and what lessons were learned?

Back in the day, if a drug showed a PK/PD response – meaning a clear pharmacokinetic-pharmacodynamic effect – that was considered sufficient evidence to move forward. We measured Aβ peptides in CSF, confirmed the drug's potency, and jumped directly to large-scale trials.

At Merck, we skipped phase 2 entirely and went straight from phase 1 to phase 3. That was common practice in the Alzheimer's field at the time, because we didn't believe we could establish meaningful proof of concept in smaller populations.

I still remember knocking on the massive oak doors of Merck's headquarters in White Plains, entering a high-level executive meeting, and requesting over a billion US dollars to run a phase 3 program on our BACE inhibitor verubecestat, even though our estimated chance of success was just 10%. We didn't even have amyloid enrichment, meaning that maybe 50% of the trial patients might not have had true Alzheimer's disease. Despite that, we still moved forward with the trial as Ken Frazier, Merck's CEO at the time, was passionate about innovation and had a father with Alzheimer's.

This was before we had amyloid enrichment, PET (Positron Emission Tomography) tracers [radioactive substances used in PET scans to visualize biological processes in the body – ed.] and CSF diagnostic tools to use in larger trials. I was heavily involved in the development of PET tracers and CSF biomarkers, and I am proud to have contributed to bringing a companion diagnostic for Alzheimer's to the market.

What has made Alzheimer's drug development so uniquely challenging for the industry?

There were a few key factors. First, the psychology of the field: there was excessive optimism in academia. Every few years, people thought, "We've cracked it!," particularly around the amyloid hypothesis, which dominated and created a false sense of certainty.

Second, we made the same mistake as in stroke research. We thought we had solved stroke neuroprotection a decade earlier, while we actually did not understand it. We ran massive stroke neuroprotection trials, and nothing worked. But we never seemed to learn from those failures.

The high-risk, high-reward mindset played a big role too. The belief was, "Yes, it's risky, but if we succeed, it will be a blockbuster drug." Those expectations were not realistic: the Alzheimer's drugs that have been approved have not become the massive blockbusters we once envisioned.

This was supposed to be a multi-billion-dollar market, but it hasn't materialized yet in the way people expected.

Have recent regulatory approvals, especially lecanemab and donanemab, given new hope to the Alzheimer's field?

Yes, but I have an Alzheimer's drug discovery and development perspective spanning over a longer period, having been working on large-scale Alzheimer's programs since the early '90s. Initially, the focus was on symptomatic cognitive enhancement treatments, but we soon realized that cognitive impairment itself wasn't the biggest clinical issue, it was the behavioural and psychiatric symptoms.

For years, the industry focused on cognitive enhancers alongside amyloid-targeting drugs. People forget that Aduhelm (aducanumab) wasn't the first amyloid-targeting drug. There were several earlier programs, such as Janssen Alzheimer Immunotherapeutics, which was a joint venture between Elan, J&J, and Pfizer. Their antibody, bapineuzumab, may have worked, but the trials were designed before we had amyloid enrichment as a standard approach, and validated sufficiently to be used as a surrogate biomarker for accelerated approval.

What were some of the biggest early lessons learned with amyloid-targeting drugs?

One of the biggest lessons was about safety risks. We learned early on that anti-amyloid antibodies could cause ARIA-E (Amyloid-Related Imaging Abnormalities–Edema) and ARIA-H (Amyloid-Related Imaging Abnormalities–Hemosiderin), side effects which, in severe cases, can even be fatal. That created a lot of caution when it came to dosing up amyloid removal to a level that can provide clinical benefits.

There are two fundamental principles in drug development; ensuring the drug actually works – solid proof of concept – and finding the right dose. A classic example of failing to get this right was Roche's gantenerumab. Roche had two competing internal programs, crenezumab (from a collaboration) and gantenerumab; both programs were pushed into phase 3 too quickly. Gantenerumab probably works, but lingered eight years in phase 3 trying to find the right dose. That's a terrible position to be in – wasting money, time, and credibility.

Who was responsible for taking a different approach to clinical trials?

There is no doubt that one of the most seminal figures in the Alzheimer's drug development field is Andrew Satlin, then at Eisai. He recognized early on that Alzheimer's trials were being done wrong. At the time, Eisai had lecanemab entering into phase 1, but Satlin knew Eisai couldn't afford a massive phase 3 trial, at least not without first establishing a solid proof of concept with proper dose evaluation. Instead of taking the traditional approach, committing to large trials from the start, Satlin, together with Barry Consultants, helped develop an innovative approach based on Bayesian-adaptive trial methodology that allowed the testing of multiple doses simultaneously, adjusting the trial in real time based on early results.

This essentially reinvented phase 2 trials for Alzheimer's disease. The biggest advantage was that Eisai, following that innovative trial, only needed one phase 3 trial instead of two, which meant substantial overall program cost savings. If you look at the lecanemab program as a whole, it was quite ingenious – whether that was by design or luck, it worked. This approach demonstrated a breakthrough in how potential disease modifying treatments can be evaluated in chronic neurodegenerative disease. I've since copied it at Lundbeck, but many today still do not appreciate the tremendous value of this type of program design.

Has this approach changed how other companies conduct trials?

Some companies have learned from it. Take Eli Lilly, for example. They initially spent huge sums of money pushing drugs from phase 1 straight into phase 3, and it backfired spectacularly – solanezumab should never have made it to phase 3.

However, Lilly learned their lesson. They conducted a proper phase 2 trial for donanemab, and it paid off. The real turning point came when technology finally caught up. With PET imaging and biomarkers, we could track early disease progression much better. For years, the science, trial design, and technology weren't aligned. Once those three things finally came together, we started seeing real progress.

However, this came at a huge cost, and it took billions of dollars in failures before we figured this out. Some companies were ahead of the game – lecanemab and later donanemab were done right. In the donanemab program they didn't use a Bayesian-adaptive phase 2, but they still conducted a highly informative phase 2 program, before committing to phase 3.

These new drugs are not miracle cures – they work, but they have challenging safety profiles. You have to handle them carefully. It's like lung cancer treatments in the early days – patients may not be cured, but at least we have something to offer.

What do you see as the aspects of the Alzheimer's experience that are most challenging for patients and caregivers?

When people talk about Alzheimer's, they often focus on cognitive decline, but among the main challenges – especially for caregivers – are the behavioural and psychiatric symptoms. I have a personal connection to this. My mother died of Alzheimer's. My grandmother died of it. It seems to run on the female side of my family, and I have two daughters, and two granddaughters.

When you're a caregiver, as I was, you quickly realize that what makes the disease unbearable isn't just the memory loss – it's the behavioural changes. Yes, it's devastating when your loved one no longer recognizes you, but what often forces caregivers to make the painful decision to move someone into a nursing home are the agitation, aggression, and psychosis symptoms.

My mother, for example, had severe psychosis. She would look into a mirror and not recognize herself – she thought another woman was staring at her. It terrified her. She covered all the mirrors, the oven door, anything reflective, because she was convinced there was a stranger in the house. These behaviours are incredibly distressing for both patients and caregivers.

Of course, we'd love to preserve cognition, but the disease is often too advanced still today by the time of diagnosis to do much about it. What truly breaks caregivers is when their loved one becomes unmanageable – that's when they give up. A general awareness of the disease, early screening, and recognition that one can detect the disease at very early stages are fundamental for future successes in treatment and care.

How is your current company tackling these behavioural symptoms?

Lundbeck and Otsuka's brexpiprazole is the first-ever FDA-approved therapy for behavioural and psychiatric symptoms in Alzheimer's disease; indicated for the treatment of agitation symptoms associated with dementia due to Alzheimer's disease. Generally, such symptoms are very troublesome for caregivers. If one can reduce agitation and aggression symptoms, make the patients calmer, it can lessen the burden of the care, and, hopefully, patients will become more

engaged. When brexpiprazole was approved in May 2023, it was the first new drug entity to get full FDA approval in Alzheimer's in 20 years.

Meanwhile, lecanemab was granted accelerated approval in January 2023 based on amyloid reduction. Before then, aducanumab was the first drug that received accelerated approval, already in June 2021, also for amyloid reduction, but that drug approval did not play out well. Eisai, however, navigated the challenges much more carefully. That said, lecanemab treatment requires a complex infrastructure, such as an IV infusion, and, crucially, a slowing of decline is not easily experienced. The clinical data with amyloid antibodies show maybe up to 30-40% delay in progression after treatment, but for an individual patient, that's hard to perceive.

That's why I believe the concept of disease modification has been somewhat misunderstood – many assume it means patients will get noticeably better, but in reality it is not an obvious effect. It is also important to note that the concept of disease modifying treatments, is a theoretical concept that is not a regulatory term. In fact, even if you think your effect may modify the pathophysiology of the disease, it is only the trial design, e.g. longer-term treatment period in trials and the use of some supportive pathophysiology-linked biomarkers that differ, while the main clinical outcome measures are the same across drug entity modalities.

Is this why Alzheimer's drugs have struggled to gain widespread adoption?

Yes. To truly have impact, a drug would need to stop or even reverse the disease, not just slow it down. But there's another problem – if a drug is complex to administer, has risks, and doesn't provide visible benefits, it's a hard sell.

There's also a perception issue – why do we treat Alzheimer's differently than lung cancer? Both are fatal diseases, but lung cancer progresses much faster, and patients remain mentally intact.

With Alzheimer's, you're dealing with a chronic, slowly progressing disease that mainly affects the older adults, and society has different expectations for treatment. That's part of why the big dream of a blockbuster Alzheimer's drug has turned out to be such a challenge.

Lundbeck doesn't have any new Alzheimer's drugs in development – why is that?

When I joined Lundbeck six years ago, we had a vaccine program against Aβ peptides for Alzheimer's – which I shut down immediately. Developing a vaccine for Alzheimer's is one of the

hardest things you can do. We made a similar decision when I was at Merck.

We also had a tau antibody at Lundbeck, but I wasn't convinced that it would deliver strong results. And, frankly, we couldn't afford to run a large-scale program with a drug with assumed disease modifying effects. These programs are very costly, and that's not feasible for a company our size, at least not without a partner.

How do you see the Alzheimer's R&D landscape evolving in the coming years and what role can a mid-sized European company like Lundbeck play?

There is still a big role for symptomatic treatments in Alzheimer's. Until we have a cure or a preventative therapy, matched with very early detection, we need treatments that can improve patients' quality of life.

Beyond symptomatic treatments, the field is moving toward segmentation, where Alzheimer's will eventually be divided into smaller subtypes. Right now, the disease is still treated too broadly, but there are rare forms of Alzheimer's caused by dominant genetic mutations that could be classified as ultra-rare diseases – and those might be more targetable for precision therapies.

Another exciting area is brain shuttle technology. These are drug delivery systems designed to transport therapeutic molecules across the blood-brain barrier (BBB) using receptor-mediated transcytosis. Roche's BBB shuttle-enabled anti-amyloid beta antibody trontinemab looks particularly promising. If you believe amyloid is the key target, then brain shuttles could be a game changer by delivering drugs more effectively while reducing side effects.

Lundbeck is also working in this area. Of course, we have a brain shuttle, too – everyone needs one. But we may use it differently than our competitors.

Right now, Lundbeck is focusing on smaller, rare neurodegenerative diseases rather than launching massive Alzheimer's trials. For example, we have an alpha-synuclein antibody targeting multiple system atrophy (MSA) – an aggressive movement disorder where patients die within seven to nine years. It's an overlooked disease, but it's the kind of program we can run on our own without needing a partner, if we match it with innovative trial designs and statistics, i.e., learn from the Alzheimer's field experiences.

Do you have any concluding thoughts on the future of Alzheimer's?

Beyond Alzheimer’s, I believe that neuroscience is the future. For years, people questioned why companies were in neuroscience, saying it was too difficult and too unpredictable. But suddenly, the field is hot again and all the big companies are bringing neuroscience programs back, including through acquisitions and rehiring staff.

The occurrence of new treatments coming in from other fields happens a lot, some of the best MS drugs actually originate from immunology and oncology, not neuroscience. Even in stroke, where I spent years working unsuccessfully on neuroprotective therapy approaches, the real breakthroughs came from cardiovascular preventive medicine.

Neuroscience is interconnected with many fields, and I think the next decade will be very exciting. Just look at GLP-1 drugs – people think of them as diabetes and obesity products, but they actually work in the brain and there are now ongoing trials investigating whether they can treat Alzheimer’s disease. Although the GLP-1 approach is a very high-risk enterprise, I generally think we may see more interesting mechanisms addressing critical life-style risk factors of the disease, such as diabetes and vascular/cerebrovascular drugs coming into Alzheimer’s drug development. I also hope we learned our lessons and that future drug programs in Alzheimer’s will include well-designed, smaller, but decisive, clinical proof of concept trials.

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