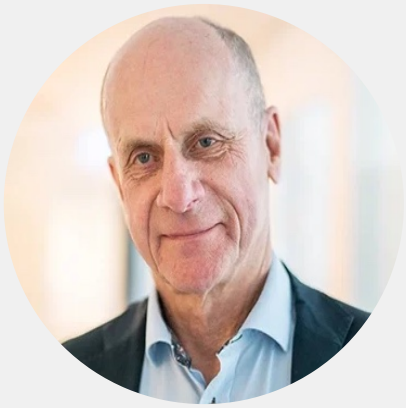
Lars Lannfelt – Co-Founder & Board Member, BioArctic



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Lars Lannfelt, co-founder and board member of BioArctic, shares the story behind the discovery of the Arctic mutation and how it helped reshape the scientific understanding of Alzheimer's disease. He reflects on the long journey toward the development and approval of lecanemab, BioArctic's groundbreaking treatment for early Alzheimer's, and explains what set the company's approach apart from past failures. Lannfelt also offers insights into BioArctic's current pipeline, promising areas of brain disease research, and his continued motivation to advance the field.

To begin, could you briefly explain what the Arctic mutation is, and how its discovery has contributed to advancing our understanding of Alzheimer's disease?

I first entered the field of Alzheimer's disease research in January 1992. Before that, during the 1980s, I had worked on a rare inherited disorder called acute intermittent porphyria, which is quite well studied in Sweden. Although it is a rare condition, that experience gave me a strong scientific foundation for my later work on Alzheimer's.

Very soon after I began working in this field, I discovered what later became known as the Swedish mutation. We published our findings in *Nature Genetics* in August of that year. The importance of this mutation was that it clearly showed an increase in amyloid beta (Aβ). Around six months earlier, a group in England had discovered another mutation—the London mutation—that also led to Alzheimer's, but at that time it was difficult to demonstrate the mechanism behind it. In

contrast, the Swedish mutation was very straightforward to interpret. Using a simple method like Western blotting, we could clearly see increased levels of Aβ. This provided strong evidence that amyloid beta was triggering the disease—at least in that family. However, the clinical and pathological features matched those of all Alzheimer's cases, so it was reasonable to believe that this mechanism applied more broadly.

A few years later, after studying hundreds of families, we discovered a new mutation in a family from northern Sweden. This mutation was located in the middle of the amyloid beta sequence, and we named it the Arctic mutation, since it came from the northern region. When we studied this mutation, we found that it caused amyloid beta to form large, soluble aggregates—what we called protofibrils. Protofibrils can also form in people with the normal, or wild-type, amyloid beta sequence, but the Arctic mutation made them much more likely to appear.

This gave me the idea, around 1999, that we should try to target these soluble aggregates using an antibody. My thinking was that amyloid beta monomers could not be toxic—they are produced in all cells, in both healthy individuals and Alzheimer's patients. The final, fibrous aggregates found in plaques also seemed metabolically inactive. So it was the soluble aggregates that were most likely to be toxic. That was my reasoning.

Inspired by the Arctic mutation, I set out to find an antibody that could preferentially bind to protofibrils. By that time, I had moved from the Karolinska Institute to Uppsala University, and although I had several ongoing projects, this one became a major focus. It was difficult work that took many years. We immunized mice, created hybridomas, and screened many clones. A key part of the process was a special two-step assay. In the first step, the antigen and antibody interacted in solution, mimicking the real-life situation when an antibody enters the brain and encounters a soluble aggregate. The second step transferred the interaction to a 96-well plate coated with amyloid beta. This solution-phase step was crucial to identifying the right antibody.

Eventually, we succeeded and found an antibody called mAb158. During this process, I also founded BioArctic, where I am now. I realized that in order to develop a drug for Alzheimer's disease, this work could not remain solely within the university—it needed a company behind it.

Could you share the story behind the founding of BioArctic and what inspired you to take this research forward through a company?

I had a colleague from Pharmacia, and we started this journey together. From early on, I understood that for a project of this scale—something that could cost over a billion dollars—it was essential to have clear ownership. Without that, no company would be willing to invest in the development. So, to make sure everything was both ethically and legally sound, we bought the patent rights from the PhD students and postdocs involved by offering them shares in BioArctic. That way, everyone's contributions were recognized, and the ownership structure was clear from the beginning.

In Sweden, we are fortunate to have the right to patent our own inventions, which made this possible. After setting up BioArctic, I remained at the university, but my colleagues at the company worked on further developing the antibody. They humanized mAb158, which became BAN2401 in clinical trials, and later lecanemab.

Early on in this journey we connected with Eisai, the Japanese pharmaceutical company. As a medical doctor, I was already familiar with Eisai because they developed one of the best cholinesterase inhibitors at the time, and I also knew they were serious about Alzheimer's disease. We went to London to meet with their commercial team, and I think the only word they understood during that first meeting was "immunotherapy," but the very next day we received a call from their headquarters in Tokyo. It turned out to be a very successful meeting and the beginning of our collaboration.

With lecanemab having received regulatory approval after many years of development, what are your reflections on this journey and how do you view the broader impact of this scientific achievement?

After all these years, it is still a journey, and there is further to go. Lecanemab has been approved in the United States for two years now, and in many other countries. We are still waiting for approval or pricing agreements in Europe. It is a slow process.

When we talk about effectiveness, we need to remember that Alzheimer's disease often progresses silently for 15 to 20 years before symptoms appear. Even when we say we are treating it early, it is not truly early. Clinical trials typically run for 18 months, which is a very short window compared to how long the disease has been developing. I believe this will require lifelong treatment, likely starting with an initial higher dose for the first 12 to 18 months, followed by a lower maintenance dose. Over time, we will learn how to manage this in the best way.

What we can already see in the data from the Phase 3 trials is that if treatment starts early enough, some patients actually improve. That is fascinating. I have a personal friend, a woman slightly younger than me under treatment and who knows I am the inventor of lecanemab. She and her husband are very thankful, and I meet them several times a year. She has improved, and seeing that makes me very happy. It matches what we see in the data—there is real potential for improvement if treatment begins early enough.

With today's diagnostic tools, doctors are better able to identify the disease earlier which I believe is key to effective treatment. We are also working, like Roche, on brain shuttle technology to improve drug delivery across the blood-brain barrier. The research from Roche looks promising. Although one of their assets failed in Phase 3, the brain shuttle technology itself shows great potential for deeper and more effective delivery into the brain.

Even though the development of these treatments takes time, there are many capable people continuing to push the field forward. I believe that lecanemab, BioArctic, and others dedicated to this area will keep innovating, learning, and improving—ultimately leading to better outcomes for patients with Alzheimer's.

Considering the long history of setbacks in Alzheimer's drug development over the past two decades, what do you believe BioArctic and its clinical development partner Eisai did differently to succeed where many others did not?

Those who failed in the past mostly did it the wrong way, which is something we have published on. Most of the antibodies developed and brought into clinical trials were strong fibril binders. When antibodies bind strongly to fibrils, they also tend to cause a higher rate of a side effect known as ARIA-E. That was a major problem.

My thinking was different. I believed we should target what is likely the most toxic form of amyloid beta—namely, the soluble aggregates, or protofibrils. There have been many failures in this field, but I have always been confident because the genetics are very clear: amyloid beta is what initiates the disease. So we focused on the form of amyloid beta that causes the most harm. I believe it is now demonstrated that this approach works.

Another important factor is patient selection. In the early trials, there was a very mixed population of participants. Later, it became clear that you need to confirm that the patient actually has amyloid beta in the brain. With today's plasma biomarkers, we will likely be able to diagnose

patients even earlier.

I believe we are moving toward a future where Alzheimer’s disease can be almost completely stopped—if we catch it very early. That is my vision.

Now that lecanemab is on the market, what are the current areas of focus for BioArctic? Could you highlight any ongoing or upcoming projects?

We are focusing on several other projects. One of them is our work in Parkinson’s disease, where we are targeting alpha-synuclein in a similar way to how we approached amyloid beta. The goal is to target the soluble aggregates, while avoiding the monomers and fibrils.

We are also working on amyotrophic lateral sclerosis (ALS), specifically targeting the TDP-43 protein. Another area of focus is Gaucher disease, which is a rare condition caused by a dysfunctional enzyme. In this case, we are developing an enzyme replacement therapy. Interestingly, there are also links between Gaucher disease and Parkinson’s, so this work connects to our broader neurodegenerative research.

Finally, a very important project for us is the brain transporter program. It is not yet in the clinical stage, but we expect to have data soon and aim to move into clinical trials.

Given your longstanding contribution to Alzheimer’s research, what current scientific approaches or emerging projects in the field do you find most promising today?

The rapid development of diagnostics is, of course, very promising. When I entered the field in 1992, there was almost nothing available. Later, cerebrospinal fluid (CSF) biomarkers were introduced, and Sweden—especially the group in Gothenburg led by Kaj Blennow—was very early in adopting them. We began performing lumbar punctures, which significantly improved the diagnostic process.

However, the challenge is that you cannot perform lumbar punctures on every patient, especially not on an 85-year-old with back problems. This is why the advancement of plasma biomarkers is so important. They have the potential to make diagnosis much more accessible and less invasive, which could transform how we detect and treat Alzheimer’s disease in the future.

On a personal level, you have dedicated your career to advancing Alzheimer's research. What continues to motivate you to remain active in the field and serve as a board member at BioArctic?

I think it is enjoyable to work here, and we have many talented young researchers, which keeps the environment vibrant. I am 75, so I could retire, of course, but I still find the science deeply fascinating and remain passionate about the potential impact it can have on people's lives.

Earlier this year, Eisai invited me to Tokyo to give a lecture about the background of lecanemab to 700 Japanese medical doctors. I accepted, even though I was terribly jet-lagged the following week! Still, it was absolutely worth it to continue engaging with the people who will help in fighting against Alzheimer's.

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