

A microscopic image showing several Y-shaped antibody molecules in shades of purple and blue, set against a background of a complex network of fibers.

## BioArctic's antibodies

BioArctic is a pioneer in developing selective, specific antibodies against misfolded and aggregated proteins in the central nervous system. The company has built a pipeline of disease-modifying antibodies not only against amyloid-beta, which causes Alzheimer's disease, but also against TDP-43 – which can be linked to ALS – and alpha-synuclein, which is central to Parkinson's disease and other synucleinopathies. During the year, BioArctic also broadened its research portfolio to include Huntington's disease.





# Pioneer in developing antibodies against misfolded proteins

After developing the world's first disease-modifying drug for Alzheimer's disease, BioArctic has accrued unique expertise in developing antibodies against misfolded proteins in the central nervous system. This competence is now being used to continue driving progress forward, not only in Alzheimer's disease, but also in other neurodegenerative diseases.

BioArctic's first approved drug for Alzheimer's disease, Leqembi, is an antibody against misfolded aggregates of the protein amyloid-beta. The antibody was developed after BioArctic's co-founder, Lars Lannfelt, discovered what is known as the Arctic mutation in a group of patients with hereditary Alzheimer's disease. The discovery of this mutation led to the conclusion that it was soluble aggregates of these specific amyloid-beta proteins that drive the progress of the disease. Not only has this discovery led to a groundbreaking treatment for Alzheimer's disease, it has also led to BioArctic now having a pipeline with selective antibodies that could become disease-modifying treatments for several neurodegenerative diseases.

Neurodegenerative diseases that stem from misfolded proteins Alzheimer's disease, Parkinson's disease, Huntington's disease, Parkinson's disease dementia, Lewy body dementia, multiple system atrophy (MSA) and ALS are all caused by various proteins that, for various reasons, begin to misfold. This misfolding causes the proteins to clump together and form larger and larger accumulations, known as aggregates. At a certain size, these aggregates are called oligomers and protofibrils. At that size, they have not yet formed plaques, but are still soluble and biologically active, and can affect various functions in the neurons. This makes oligomers and protofibrils the most harmful forms of aggregate – which is why BioArctic's antibodies have been developed with the aim of eliminating these forms without affecting the monomeric forms, which have physiological functions.





### Developing selective antibodies

To slow or stop neurodegenerative diseases caused by misfolded proteins, the harmful accumulations must be removed and the production of new aggregates must be prevented.

BioArctic is developing antibodies that work by binding to misfolded proteins in the brain. For such an antibody treatment to be effective, it must be clear which misfolded protein causes the disease. Only when this is known, an antibody that is selective for that specific target can be developed, enabling

effective removal of the disease-causing protein without affecting the healthy form.

### A growing pipeline

Research into misfolded proteins in the central nervous system is developing rapidly, and it is becoming increasingly clear that the misfolding of a particular protein can underlie a number of different diseases. This is the case, for example, with the protein alpha-synuclein. Today, the term synucleinopathies is

used, which are a group of diseases – Parkinson's disease, Lewy body dementia and multiple system atrophy – that stem specifically from misfolded alpha-synuclein. Similarly, the misfolding of the TDP-43 protein appears to not only underlie ALS but also play a role in various dementias. BioArctic's researchers closely follow developments in the field to continuously identify new potential targets where the company's ability to develop innovative and selective antibodies can make a difference for patients with neurodegenerative diseases.



### This is a misfolded protein



A protein consists of a long chain of amino acids, whose sequence is determined by our DNA. Which amino acids are included, and the order in which they appear, determine the specific three-dimensional shape the protein takes. The shape is important for the protein's function in the body. If one amino acid is replaced, the three-dimensional form and function can change dramatically. A protein's shape can also change depending on the surrounding environment. Once this occurs, the protein may begin to misfold, which can result in it aggregating and becoming harmful, thus causing a disease.

### Sustainability facts



For BioArctic, patient benefit is a central part of creating a sustainable society. During the year, SEK 377 M was reinvested in research. The drug candidate Exidavnemab is being investigated for Parkinson's disease and multiple system atrophy (MSA) in EXIST, a Phase 2a trial. Furthermore, the BrainTransporter technology platform has demonstrated great potential to improve how treatments reach the brain, which has attracted significant external interest over the past two years and resulted in two new partnerships with world-leading pharmaceutical companies. BioArctic has also expanded its research portfolio to include Huntington's disease. Read more about BioArctic's sustainability work related to patient safety and health on page 167.



# BioArctic's antibodies remove misfolded proteins in the brain

**1**

## Neurons deteriorate

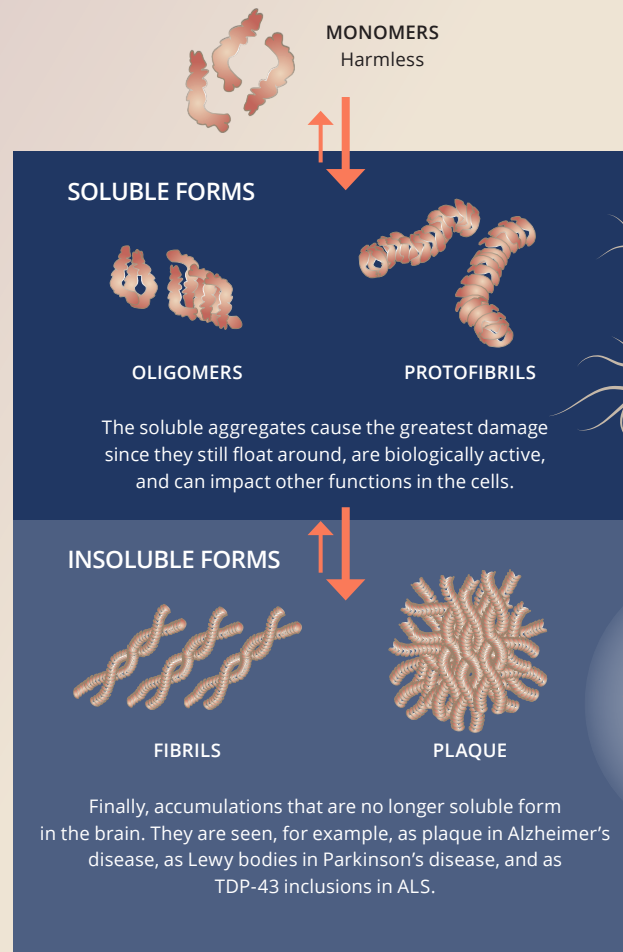
In neurodegenerative diseases, neurons deteriorate and gradually lose their function. For the person affected, this means impairment, or loss of cognitive ability or mobility – or both.



**2**

## Accumulation of misfolded proteins damages cells

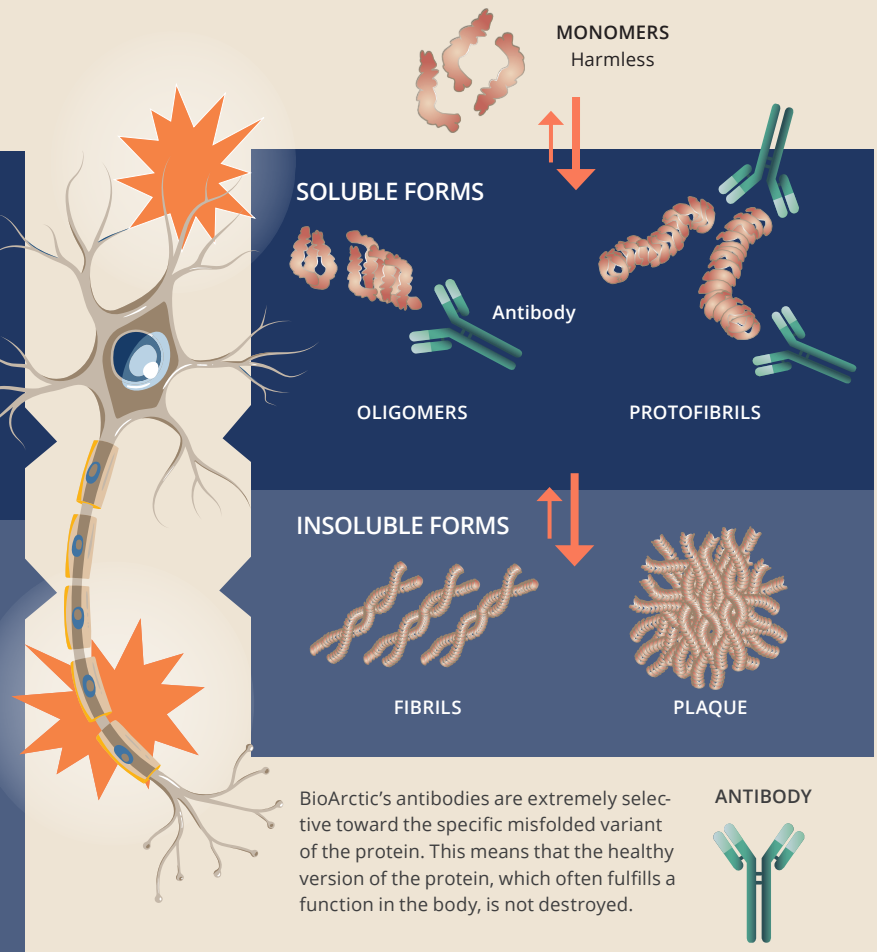
Proteins that misfold begin to clump together and form increasingly large accumulations, or aggregates.



**3**

## Antibodies remove the harmful forms of misfolded proteins

BioArctic is developing antibodies that bind to aggregated proteins, specifically identify the misfolded and harmful aggregates, and clear them out.





# BioArctic is developing the next generation disease-modifying antibodies against amyloid-beta

After contributing to the development of the first disease-modifying treatment for Alzheimer's disease, BioArctic is now continuing its work. The goal is to develop new antibody-based drugs that target different forms of amyloid-beta.

The soluble form of the protein amyloid-beta occurs naturally in the brains of healthy people, but in Alzheimer's disease, the misfolded forms of amyloid-beta cause the protein to aggregate, forming what are known as protofibrils, which damage

the neurons. By developing selective and specific antibodies against different misfolded forms of amyloid-beta, BioArctic hopes to offer patients even better treatments in the future.

## This is Alzheimer's disease



Alzheimer's disease is caused by the protein amyloid-beta misfolding and clumping together. When amyloid-beta circulates as individual molecules (monomers) in tissues, blood, and other bodily fluids, it is harmless. In Alzheimer's disease, however, the monomers begin to bind to each other and form larger aggregates. These aggregates – oligomers and protofibrils – damage nerve cells and drive the progression of the disease. Eventually, insoluble fibrils form, which cause plaques in the brain tissue.





### Antibodies are combined with BrainTransporter

Several of BioArctic's antibodies against amyloid-beta are developed both as single antibodies and in combination with BrainTransporter, the company's technology for transporting drugs across the blood-brain barrier. This platform technology utilizes the transferrin receptor, a protein that normally transports iron across the blood-brain barrier, to improve the uptake of antibodies, proteins and other substances in the brain, and could increase brain exposure to amyloid-beta antibodies by up to 70 times. This could potentially lead to better efficacy, fewer side effects and lower dosages compared with corresponding antibodies unaided by transporters.

BioArctic has several antibodies against Alzheimer's disease in its pipeline. One of them is BAN2802, which is combined with BioArctic's BrainTransporter technology. BAN2802 is being developed in partnership with Eisai, with the aim of delivering a new disease-modifying treatment.

### Antibodies against PyroGlu-A $\beta$

BioArctic has also developed antibodies that target PyroGlu-A $\beta$ , which is a truncated, more neurotoxic form of amyloid-beta. PyroGlu-A $\beta$  acts as a trigger for the aggregation of other A $\beta$  molecules, which means that the form is believed to play a key role in the formation of plaque and neurodegeneration in persons with Alzheimer's disease<sup>1)</sup>.

Alzheimer's disease affects over

# 30 million

people worldwide and is characterized by a gradual deterioration of memory, cognitive and motor skills as well as intellectual capacity due to the death of brain cells.



At the end of 2024, BioArctic signed an agreement with the US pharmaceutical company Bristol Myers Squibb for an exclusive global license for BioArctic's antibody program targeting PyroGlu-A $\beta$ . The program includes BAN1503 and BAN2803, the latter of which incorporates BioArctic's BrainTransporter technology (read more about the agreement on page 34).

### Key breakthrough in diagnosis of Alzheimer's disease

The development of diagnostics for Alzheimer's disease has been a priority in recent decades. After several years of intensive research and development efforts, the first blood-based biomarker, p-tau, was approved for use in routine medical care. The test, developed by the Japanese company Fujirebio Diagnostics, measures levels of phosphorylated tau (p-tau217), which plays a key role in the progression of the disease by forming tangles that accumulate in the neurons of the brain. High levels of p-tau217 in the blood are closely linked to both an increased risk of developing Alzheimer's disease and the presence of the disease itself. What makes p-tau unique is that it differentiates between Alzheimer's disease and other types of dementia, while also reflecting the degree of neurodegeneration in patients with Alzheimer's disease<sup>2</sup>. Measuring the biomarkers with a simple blood test rather than spinal fluid provides medical care with a more accessible and clinically manageable tool for diagnosing and monitoring disease progression in Alzheimer's patients. For BioArctic, these advances mean that the right patients will be identified at an earlier stage, which creates better conditions for treatment of patients as well as design of future clinical studies and market introductions.

1. Bayer, T.A. Pyroglutamate A $\beta$  cascade as drug target in Alzheimer's disease. *Mol Psychiatry* 27, 1880–1885 (2022). <https://doi.org/10.1038/s41380-021-01409-2>

2. Gonzalez-Ortiz, F. et al. Brain-derived tau: a novel blood-based biomarker for Alzheimer's disease-type neurodegeneration. *Brain*, Volume 146, Issue 3, March 2023, Pages 1152–1165. <https://doi.org/10.1093/brain/awac407>

## Martin Larhammar

*researcher in Alzheimer's disease at BioArctic*



### What is happening in your research area, antibodies against amyloid-beta?

“The first generation of disease-modifying medicines for Alzheimer's disease has now obtained market approval. These drugs are therapeutic antibodies administered intravenously and work by clearing aggregated amyloid-beta. Recently, subcutaneous dosing of lecanemab was also approved, which significantly simplifies treatment for both patients and healthcare professionals.

The next step now is to develop second-generation

immunotherapies with improved efficacy and safety. In the project that I am responsible for, we have developed a unique bispecific antibody that binds to a pathological form of amyloid-beta (PyroGlu-A $\beta$ ), in combination with BioArctic's BrainTransporter technology. We recently entered into a license agreement with Bristol Myers Squibb for further development of this antibody toward the clinical stage. To sum up – we are in an extremely exciting time in research and drug development for Alzheimer's disease.”



# Antibodies against alpha-synuclein being tested in Parkinson's disease and multiple system atrophy

BioArctic's antibodies for misfolded alpha-synuclein have the potential to become effective, disease-modifying treatments for various synucleinopathies such as Parkinson's disease, multiple system atrophy and Lewy body dementia. The antibody at the most advanced stage, exidavnemab, is currently being evaluated in a clinical Phase 2a study.



Synucleinopathies are caused by misfolding of the protein alpha-synuclein, which forms soluble aggregates in the form of oligomers and protofibrils. In the next stage, insoluble aggregates – known as Lewy bodies – form, accumulating in neurons and glial cells. Research indicates that it is the soluble aggregates that are most harmful to the neurons, by causing inflammation of the nerves and driving progression of the disease. These soluble forms can also move among the neurons, spreading the misfolded proteins to neighboring cells, which could explain how the disease spreads throughout different parts of the brain<sup>1</sup>.

In partnership with researchers at Uppsala University, BioArctic has developed antibodies that selectively bind to the toxic and soluble aggregates of alpha-synuclein. The company is currently conducting two development projects with antibodies that target alpha-synuclein: exidavnemab, which is being evaluated in a Phase 2a clinical study, and BAN2238, which is in the preclinical phase. Both antibodies activate the body's immune system to detect and eliminate the harmful protein aggregates.

## Exidavnemab being evaluated in Phase 2a study

Exidavnemab is currently being evaluated in the Exidavnemab Synucleinopathy Trial (EXIST), a randomized, double-blind, placebo-controlled Phase 2a clinical study conducted to evaluate its safety and tolerability. The study, which is being conducted at clinics in Spain and Poland, initially included

1. Emin, D et al. (2022). Small soluble  $\alpha$ -synuclein aggregates are the toxic species in Parkinson's disease. *Nat Commun.* 2022 Sep 20;13(1):5512. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9489799/>



24 participants with mild to moderate Parkinson's disease. In July 2025, BioArctic obtained regulatory approval to expand the study to also include patients with multiple system atrophy (MSA), and recruitment of an additional cohort with MSA commenced. In addition to the primary endpoints of safety

and tolerability, a broad spectrum of biomarkers in both plasma and cerebrospinal fluid (CSF) is also being evaluated. Alongside digital measurements and questionnaires, the goal is to identify which patient populations and symptoms are most relevant for the continued development of this drug candidate.

## This is alpha-synucleinopathy



Synucleinopathies are degenerative neurological diseases characterized by abnormal aggregations of misfolded forms of the protein alpha-synuclein. These diseases overlap clinically, but differ in terms of which regions of the brain and which cell types are most severely affected. The most common synucleinopathy is Parkinson's disease (PD), which is caused by dopamine-producing neurons ceasing to function. The initial symptoms are often impaired sleep, mild tremors in one hand, or a decreased sense of smell. As the disease progresses, the tremors worsen, movements become slower and the body's muscles stiffen. Current treatments only alleviate the symptoms and are often most efficacious in the early stages of the disease.

Multiple system atrophy, or MSA, is a rare and fatal disease that progresses rapidly and affects the central and autonomic nervous system. This impacts balance, mobility, and the autonomic nervous system, which controls vital functions such as breathing, digestion, and bladder control. MSA is a disease with a highly significant medical need and a poor prognosis. Currently, there is no treatment that can slow the progression of the disease.

### Examples of synucleinopathies

- Parkinson's disease
- Lewy body dementia
- Multiple system atrophy
- Bradbury-Eggleston syndrome (Pure autonomic failure)

BioArctic is exploring possibilities for partnerships in parallel with the company's plans to carry the project further into clinical Phase 2b/Phase 3. In 2025, exidavnemab received orphan drug designation in the US and in the EU for the treatment of MSA.



### High degree of selectivity for aggregated alpha-synuclein

Preclinical data show that exidavnemab has a unique and targeted binding profile and is highly selective for pathological forms of aggregated alpha-synuclein. Moreover, the results show that exidavnemab reduces the amount of neurotoxic alpha-synuclein oligomers and delays the build-up of protofibrils, which could slow disease progression. A Phase 1 study conducted by BioArctic's former partner, AbbVie, indicated a favorable pharmacokinetics and safety profile for the drug candidate<sup>1</sup>.

BioArctic is also developing BAN2238, which combines a highly selective alpha-synuclein antibody with BioArctic's BrainTransporter technology, increasing the antibody's exposure in the brain.

Parkinson's disease affects more than

# 10 million

people around the world, and most of those affected are of working age when they fall ill.<sup>2</sup>

1. Boström, E. et al. (2024) Safety, Tolerability, and Pharmacokinetics of Single Doses of exidavnemab (BAN0805), an Anti- $\alpha$ -Synuclein Antibody, in Healthy Western, Caucasian, Japanese, and Han Chinese Adults. *J Clin Pharm*, 64: 1432-1442. <https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.6103>

2. Parkinson's Foundation - Understanding Parkinson's, Statistics 2020

**Malin Johannesson**  
*researcher in  
alfa-synucleinopathies  
at BioArctic*



**How far do you think research on drugs targeting misfolded proteins will have come in ten years, and what are the biggest challenges?**

“In ten years, I think we will be able to identify patients at risk of developing Alzheimer's disease to a greater extent, which would enable early treatment with Leqembi or other antibodies that will be available in the market. For synucleinopathies, such as Parkinson's disease and multiple system atrophy, I think that some of the antibodies that are now being evaluated in the clinical phase will have demonstrated good efficacy, and

that research into biomarkers for early identification and evaluation of clinical efficacy will have made significant progress. A paper was recently published by researchers at BioArctic showing that exidavnemab binds to aggregated a-synuclein in several therapeutic areas such as Parkinson's disease, Parkinson's disease dementia, Lewy body dementia and multiple system atrophy. In ALS, where misfolded TDP-43 may be a cause, I hope that research and drug development will have made progress that can provide hope to sufferers and their families.”



# Two antibodies targeting misfolded protein TDP-43 under development for ALS

Misfolded TDP-43 protein occurs in several different diseases with neurodegenerative impacts. The protein is therefore of interest both in developing new diagnostic biomarkers, and as a target for future antibody-based treatments against neurodegeneration. The link to ALS is particularly clear. BioArctic has two different antibody projects against TDP-43.

Misfolded TDP-43 (TAR DNA-binding protein 43) plays a key role in several neurodegenerative diseases. This condition is characterized by TDP-43 losing its normal location in the nucleus and instead accumulating in the cytoplasm of the cell, where it forms toxic aggregates that not only interfere with the normal function of TDP-43 but also disrupt various cellular processes, leading to the death of neurons.

## Clear link between TDP-43 and ALS

ALS emerges in the motor neurons of the brain, the brain stem, and the spinal cord, which control the body's movements. As with many other degenerative neurological diseases, the impact of ALS on the motor neurons is linked to an inflammation in the neurons. Despite decades of intensive research, the process that leads to the disease is not yet fully understood. What is known, however, is that misfolded forms of TDP-43 play a key role in the development of the disease. Abnormal accumulations of misfolded TDP-43 – called inclusions – are found in the brains of patients with ALS, and increasing amounts of data show a clear link between these misfolded forms of the protein and the degeneration of motor neurons. It is estimated that around 97 percent of all patients with non-hereditary ALS have protein accumulations containing misfolded TDP-43 in the brain<sup>1</sup>.

## Two antibody projects against TDP-43

BioArctic's aim in its BAN3014 project is to develop a unique antibody treatment that targets accumulations of TDP-43.





Antibodies make it easier to detect and eliminate the toxic aggregates of misfolded protein, which will hopefully have a slowing effect on the progression of degenerative diseases. Similar to BioArctic's drug candidates for Alzheimer's disease and Parkinson's disease, the antibodies in the BAN3014 project target soluble aggregates of misfolded TDP-43 – oligomers and protofibrils – since these forms are assumed to be the most harmful to the neurons.

BioArctic is also pursuing the ND-BT3814 project, in which an antibody against TDP-43 is being tested in combination with BrainTransporter, the company's technology that facilitates the passage of antibodies across the blood-brain

barrier. The BAN3014 project is in the preclinical phase, and ND-BT3814 is in the research phase.

**Growing market for antibodies against TDP-43**

The market for TDP-43 antibodies is expected to continue to grow between 2025 and 2033, driven by increased research into neurodegenerative diseases and the development of improved detection and therapeutic formats with higher specificity and sensitivity<sup>2</sup>. In parallel with the development of antibodies, intensive efforts to develop biomarkers for TDP-43 are also underway in the research field.<sup>3</sup>

The number of people with ALS is expected to exceed

# 375,000

globally by 2040\*

\* Arthur, K. et al. (2016) Projected increase in amyotrophic lateral sclerosis from 2015 to 2040.



About ALS



ALS is classified as a rare disease which means that drugs to treat the disease are developed as orphan drugs. However, a certain increase in incidence has been observed over the past few years<sup>1</sup>. A number of the patients affected are in midlife and of working age when they fall ill, which means great suffering for them and their relatives, as well as major costs to society. In the US, the cost of ALS is estimated to exceed USD 1 billion per year<sup>2</sup>. The costs in connection with ALS are higher than for other neurological diseases, which underscores the need for medical advances in the field.

1) Longinetti E, Fang F. (2019) Epidemiology of amyotrophic lateral sclerosis: an update of recent literature.

2) Berry, J. D. et al. (2023) Epidemiology and economic burden of amyotrophic lateral sclerosis in the United States: a literature review.



## Examples of diseases linked to misfolded TDP-43



Disease	Comments
Amyotrophic lateral sclerosis	Up to 97 percent of all patients with sporadic ALS have TDP-43-positive inclusions <sup>1</sup>
Frontotemporal dementia (FTD)	Approximately 45 percent of patients with FTD have TDP-43 aggregate <sup>4</sup> .
Alzheimer's disease	Around 30-50 percent of Alzheimer's patients have TDP-43 inclusions in the brain, which are associated with faster cognitive decline <sup>5</sup> .
Lewy body dementia	TDP-43 inclusions are indicated in 20 to 30 percent of cases, and is closely linked to cognitive impairment <sup>6</sup> .
Parkinson's disease	TDP-43 inclusions occur in 7 to 19 percent of cases, and are closely linked to cognitive impairment <sup>7</sup> .

- 1) Versluys L et al. (2022) Expanding the TDP-43 Proteinopathy Pathway From Neurons to Muscle: Physiological and Pathophysiological Functions. *Front. Neurosci.* 16:815765. <https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.815765/full>
- 2) TDP43 Antibody 2025-2033 Trends and Competitor Dynamics: Unlocking Growth Opportunities <https://www.datainsightsmarket.com/reports/tdp43-antibody-580501>
- 3) Zeng J et al. Decoding TDP-43: the molecular chameleon of neurodegenerative diseases. *Acta Neuropathol Commun.* 2024 Dec 31;12(1):205. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11687198/>
- 4) Ling, S-C, Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis. *Neuron*, 79 (2013), pp. 416-438. <https://www.sciencedirect.com/science/article/pii/S0896627313006570>
- 5) de Boer EMJ et al. TDP-43 proteinopathies: a new wave of neurodegenerative diseases. *J Neurol Neurosurg Psychiatry.* 2020 Nov 11;92(11):86-95. <https://pubmed.ncbi.nlm.nih.gov/33177049/>
- 6) Versluys L et al. (2022) Expanding the TDP-43 Proteinopathy Pathway From Neurons to Muscle: Physiological and Pathophysiological Functions. *Front. Neurosci.* 16:815765. <https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.815765/full>
- 7) Cook C et al TDP-43 in neurodegenerative disorders. *Expert Opin Biol Ther.* 2008 Jul;8(7):969-78. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2855963/>

## Jessica Sigvardson researcher in ALS at BioArctic



### What makes BioArctic a good place to work?

“I get to work on research aimed at developing medicines that can help patients with extremely serious diseases, and I get to do so alongside skilled and dedicated colleagues. Our project-team approach, where everyone contributes with different expertise and works together toward a common goal, creates a stimulating and motivating work environment. I have worked on the ALS project since the beginning and it is truly wonderful

to have been involved from Day One and follow developments going forward. We often talk about the ‘BioArctic spirit’, and to me that means asking and helping one another even if you are not on the same project team or in the same division.

We also have health-promoting activities such as wellness allowance, a fitness hour, various cultural events, as well as joint Thursday coffee breaks that promote social cohesion.