Gunilla Osswald – CEO, BioArctic, Sweden

Our broad innovative portfolio spanning from early discovery to Phase III, strong collaborations with strategic partners and universities combined with our solid financial situation make us a unique biopharma company, not only in Sweden but globally

14.08.2019

Tags: Sweden, Biotech, Bioarctic, CNS, Alzheimer's, Parkinson's

BioArctic is a Swedish biopharma company with the vision to become a world-leader in the research and development of disease-modifying treatments for patients with neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, and pioneering treatment methods for complete spinal cord injuries. Gunilla Osswald, CEO, explains how BioArctic is uniquely positioned to achieve this vision thanks to its innovative project portfolio, high scientific competence, strategic partnerships with Eisai and AbbVie, collaboration with leading academic research groups, and strong financial position.

BioArctic is often highlighted as one of the incredible success stories in Swedish life sciences. However, not all of our international readers will be familiar with the company. Could you start by introducing the story of BioArctic?

BioArctic is a unique research-intensive Swedish biopharma company focused on developing new treatments that address the causes of Central Nervous System (CNS) disorders. Today, the only options available for Alzheimer's disease (AD) and Parkinson's disease (PD) are symptomatic treatments. In contrast, the disease modifying treatments we are developing for both conditions affect the underlying disease pathology and have the potential to stop or significantly delay disease progression. If we succeed, it would represent a significant paradigm shift in the standard of care and address huge unmet medical needs.

BioArctic was originally founded in 2003 to develop breakthrough discoveries made by Professor Lars Lannfelt at Uppsala University. These discoveries, the Swedish mutation and the Arctic mutation, which the company is named after, explain the central role of amyloid-beta in AD. They have attracted much attention internationally and led to the development of new treatment strategies. Professor Lannfelt discovered that AD patients have increased levels of misfolded amyloid-beta oligomers and protofibrils in the brain. Together with Professor Pär Gellerfors, he founded BioArctic to create an antibody selectively targeting these toxic forms of misfolded amyloid-beta protofibrils and oligomers. These efforts led to the development of our lead compound BAN2401. Early-on, the Japanese pharma company Eisai came onboard as a strategic partner for the development and commercialization of BAN2401 in AD. In the collaboration, BioArctic focuses on early discovery and research, while Eisai is responsible for the clinical development, market approval and commercialization of the products for AD. BioArctic retains the rights to commercialize in the Nordics and the global rights to other indications beyond AD. The long-term collaboration with Eisai has been extremely successful. In March, Eisai announced that initiation of the global confirmatory Phase III study in early AD with BAN2401.

We follow the same approach for the development of PD treatments. In 2016, we started a research collaboration with AbbVie around targeting the toxic protofibril and oligomer forms of alpha-synuclein. At the end of last year, AbbVie decided to license the full rights to BioArctic’s alpha-synuclein antibody portfolio, including the lead compound ABBV-0805. In March, they initiated the Phase I study with ABBV-0805 in the US.

Thanks to these partnership agreements, and the regular progress made with our lead compounds, BioArctic has a solid financial situation for a biopharma company without a product yet on the market. Upfront and milestone payments received from our partners have allowed us to generate positive financial results every year for the last six years. In total, the deals with Eisai is valued at EUR 218 million in received and potential payments, in addition to royalties. The licensing deal with AbbVie is valued at USD 755 million in received and potential payments, in addition to royalties. Since AD and PD are both huge and growing markets, the royalties can also be significant. Moreover, our cash position is also very healthy with more than SEK 1 billion (about USD 100 million) in the bank.

In addition to our two lead antibodies in clinical development, we have several innovative programs with high potential being developed in close collaboration with research groups at universities and hospitals, which is one the keys to our success. For instance, in collaboration with the department of Neurosurgery at the Karolinska University Hospital, we are developing a potential treatment for

patients affected by complete Spinal Cord Injury for whom no treatment is currently available. Earlier this year, the program advanced into the second part of the on-going Phase I/II study.

Moreover, BioArctic and Uppsala University have joined forces to develop a new technology platform that facilitate the passage of antibodies across the blood-brain barrier with the aim to improve immunotherapy for brain disorders, including Alzheimer's and Parkinson's diseases.

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Sweden is known for its tradition of excellence in medical research embodied by the Nobel Prize in Physiology or Medicine awarded in Sweden. What do you see as the key strengths of the domestic life sciences ecosystem?

Swedish universities are extremely innovative. Many groundbreaking medical innovations used today were the result of research at Swedish universities such as the pacemaker and xylocaine. In PD specifically, research from Swedish scientists has led to a better understanding of the disease and improvements in treatment methods. Professor Arvid Carlsson from Gothenburg University won the Nobel Prize for his realization that PD is caused by dopamine deficiency in some parts of the brain, which led to the development Levodopa, an effective drug against this disease. More recently, Professors Sten-Magnus Aquilonius and Christer Nyström from Uppsala University developed Duodopa®, an improved method for the continuous delivery of Levodopa directly to the small intestine with the help of a pump and a specifically developed gel. This innovative drive has a lot to do with the so-called "teacher's exemption". Unlike in other countries, in Sweden, researchers retain the intellectual property rights to their inventions.

Moreover, in order to be successful, biopharmaceutical companies not only need innovative researchers and scientists but also experts in drug development and regulatory affairs. In the past, this expertise was concentrated in two companies, Astra and Pharmacia. In the 2000s, the Swedish life sciences ecosystem experienced a dramatic shift after Astra merged with Zeneca and Pharmacia was acquired by Pfizer. AstraZeneca closed down its R&D sites in Lund and Södertälje. This shift led to the emergence of life science hubs with many small innovative biotech companies that benefit from the research and development expertise accumulated at AstraZeneca and Pharmacia. For instance, while 900 people used to work at AstraZeneca's R&D site in Lund, there are now 1,600 people working in the life sciences hub in Lund. The Stockholm-Uppsala region is

also a booming hub. Moreover, AstraZeneca still has an extensive R&D footprint in Sweden with its hub in Mölndal, and still drives the ecosystem. The company opened the BioVentureHub in its facilities in Gothenburg giving emerging life sciences companies and academic groups a unique opportunity to co-locate and interact with Big Pharma. It is a completely new way of working compared to ten or twenty years ago. When I worked at the AstraZeneca site in Södertälje, we were 1,300 people together with support staff. At BioArctic, we are a team of 50 people! It is simply amazing what you can accomplish with a small agile biotech company working hand in hand with Big Pharma companies.

The Swedish government seems committed to the development of the domestic life sciences sector. To what extent has this support helped make BioArctic a success locally and internationally?

Support from public authorities has been a decisive factor in BioArctic's success. We have received several non-dilutive grants from Vinnova, the Swedish innovation agency. Although the amounts were relatively small, they came at critical times in the company's development. For instance, we submitted a grant application in 2014 as we needed funding to start process development of our Parkinson's program, which is costly for a small company. We were awarded about SEK 5 million (about USD 500,000), a relatively small amount but which allowed us to take the next step and initiate the partnering process in 2015. In the end, we entered into a strategic partnership with AbbVie which brought in USD 80 million when the deal was signed, and an additional USD 50 million when AbbVie purchased the full licensing rights. In other words, this small grant has generated a huge return on investment for both BioArctic. Recently, in April, Vinnova gave BioArctic and Uppsala University a grant of SEK 10 million (about USD 1 million) to help us further the development of our innovative blood-brain barrier technology platform.

In addition to the much-needed support from Vinnova, we have also received three grants from the EU Horizon 2020 program, including one totaling €6.4M for our potential treatment for Spinal Cord Injury, which has allowed us to fund its clinical development.

We are incredibly grateful for the amazing support from both Swedish and European authorities which acknowledges the quality of our work and encourages us to keep going.

When we met with Jonas Ekstrand and Helena Strigard from SwedenBIO, they mentioned the need for the Swedish life sciences sector to attract more capital from abroad as investment sources remain mainly local. How do you convince foreign investors to take on the risk of investing in a small biopharma company far from their shores?

Even though BioArctic is a rather small company, we are among the world leaders in the development of potential therapies for central nervous systems disorders. Our programs are based on solid scientific grounds, and we have a track record of saying what we are going to deliver and delivering what we say. This creates credibility. As a result, during our IPO in 2017, we attracted institutional investors from Europe and the US supporting our core Swedish investors.

As mentioned, BioArctic's lead candidate in Alzheimer's disease BAN2401 is based on amyloid theory. So far, many drugs that prevent or clear amyloid have failed to improve cognition in even early Alzheimer's patients. Earlier this year, Biogen and Eisai discontinued Phase III trials of aducanumab, and so did Roche for its candidate crenezumab. What makes your candidate different?

It is an excellent question. In order to understand what makes our candidate different, we should first explain the amyloid hypothesis in more detail. Every healthy person produces amyloid-beta monomers which are non-toxic. Professor Lars Lannfelt observed that in patients with the Arctic mutation, these monomers start to misfold and aggregate to form soluble types of neurotoxic oligomers and protofibrils. If they continue to aggregate, they form amyloid plaques that are insoluble and inert. His idea was to develop an antibody that selectively targets, binds to and eliminates the toxic species of oligomers and protofibrils before they start to form plaques.

Other antibodies have different targets and different binding profiles. Every antibody is unique and needs to stand on its own merits. BAN2401 has a specific binding profile that selectively targets neurotoxic formation of oligomers and protofibrils and eliminates them, offering a potentially significant advantage in terms of both efficacy and safety.

The Phase 2b-study with BAN2401 is, to date, the first and only study in late clinical phase to have demonstrated a potential disease modifying effect on three different cognitive endpoints. It has also shown clearance of amyloid-beta in the brain, and a decrease in nerve degeneration as shown by four different neurodegenerative biomarkers. In addition, BAN2401 has shown a good tolerability profile. In March, Eisai announced the initiation of a global Phase III trial to confirm the

positive Phase IIb results. These are exciting times.

As no single test detects AD with 100 percent accuracy, diagnosing it remains a challenge. What is BioArctic doing to address this issue?

Today, there are a few methods used to diagnose AD. For instance, during the Phase IIb trial of BAN2401, we used an amyloid PET scan to observe amyloid deposits in the brains of patients. Another method consists in taking a sample of cerebrospinal fluid (CSF) to look at a signature of the amyloid-beta and tau proteins.

Together with Uppsala University, we are trying to develop an improved and more sensitive imaging diagnostic tool to specifically measure the accumulation of the toxic forms of proteins, which are too small to be measured accurately today. Together with scientists at Gothenburg University, we are developing more sensitive biochemical diagnostics to diagnose central nervous system disorders with blood and CSF samples.

For disease modifying treatments to be effective, it is crucial to start treating before neurodegeneration becomes advanced. For this reason, it is important to find tools that can identify the patients at an early stage as well as follow the disease progression.

In late 2018, BioArctic out licensed its portfolio of antibodies for PD to AbbVie. What makes this candidate so exciting that AbbVie decided to take on the full risk of clinical development?

Similarly to AD, PD is caused by the accumulation of toxic misfolded protofibrils and oligomers of a protein called alpha-synuclein. Just like our AD treatment, our antibody for PD (ABBV-0805) has a unique binding profile, selectively targeting those toxic soluble misfolded aggregated forms of alpha-synuclein. We presented very strong preclinical proof of concept results which impressed AbbVie. We showed a 65 percent reduction in neurotoxic alpha-synuclein protofibrils and oligomers compared to placebo in animal models. We also showed a significant delay in disease progression leading to a doubling of the lifespan in animal models. We started collaboration with AbbVie in September 2016 and earlier in 2019 the US FDA approved the IND application for the lead antibody, ABBV-0805. In March, AbbVie initiated Phase I clinical trials. AbbVie will now drive and finance clinical development going forward whereas we focus on the preclinical development of other compounds.

BioArctic is also developing a new treatment concept for patients affected by complete Spinal Cord Injury (SCI), which has received funding from the EU Horizon 2020. What promise does this treatment hold for these patients and the healthcare system?

Complete spinal cord injuries are more common among younger persons, more often males, as a result of road accidents or sports injuries for instance. For these patients they often have complete paralysis and suffer many other significant quality of life issues that come with the paralysis. Those patients are thus in a desperate situation since no effective treatment is available. Moreover, patients with complete SCI require life-long therapy and care, which means high costs for the health care system. A treatment that could even partially reduce the paralysis or improve some function would be a significant step forward, not only for the patients and their families, but also for society from a cost perspective.

We are developing SC0806, a therapy combining a biodegradable device with a growth factor which has received orphan drug designation in the US and EU. The therapy requires taking the patient’s own nerves from the leg and implanting them in the spinal cord to use as a growth medium. Our preclinical model showed extremely promising results with nerve regeneration, restored electrophysiology and improved motor function. Based on these strong results, we applied for the EU Horizon 2020 grant. Thanks to the funds, we were able to initiate Phase I studies in collaboration with the Neurosurgery Department at the Karolinska University Hospital. Our treatment was combined with a robotic rehabilitation system for 18 months after the surgery. Earlier this spring we performed an interim safety analysis and saw that it was safe to progress to Phase II, which has now been initiated. As this is a pioneering treatment method requiring an invasive procedure, we are deliberately being very careful, taking one step at a time for the safety of patients. We are planning to perform an interim analysis concerning efficacy and safety within the first half of 2020.

What makes you a partner of choice?

It is a combination of great science, great projects and great people. Our research and development projects are among the best in the world in their respective areas. We have highly qualified staff with a proven track record in drug development at Big Pharma and biotech companies. 75 percent of our employees are in our core research organization, including two professors, associate professors and three MDs. We most recently welcomed Dr. Per-Ola Freskgård,

a world-leading expert in blood-brain barrier technology who was previously Vice Director and Group Head Neurovascular Biology at the Roche Innovation Center in Basel. Personally, I have worked 28 years with Astra and AstraZeneca where I was involved in acquiring and licensing compounds and projects, so I understand the expectations of Big Pharma companies. Now I am sitting on the other side of the table. Taken together, these strengths make BioArctic uniquely positioned to succeed.

What do you hope to achieve in the next three to five years?

My driving force is to help patients. With the start of Phase III, BAN2401 has the possibility to be the first disease modifying treatment for AD on the market. We also have three early programs for AD that we are driving ourselves, each with a different mechanism of action, each different from BAN2401. Additionally, I am very excited about our blood brain barrier technology platform and its potential. Big Pharma companies have already communicated their interest in many of our early programs. However, now that we have a solid enough financial situation, we wish to drive them further in the development process in order to maximize their value before we enter partnering discussions. In the future, we also hope to commercialize products in the Nordic market. The company started as a research company, now it is a research and development company and, when the time comes, we hope to also be a marketing and sales company in the Nordic market.

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