Text: Henrik Möller / Photo: Mikael Wallerstedt

Better medicine against glioblastoma cancer

Glioblastoma cancer is an aggressive form of brain tumor with a poor survival prognosis for those afflicted. The Uppsala-based company Beactica is aiming to develop a substance that forces the tumor's stem cells to enter apoptosis – a programmed cell death.

Patients with the cancer form *Glioblastoma Multiforme* (GBM) live, on average, for 15 months after they have been diagnosed. The first counter-measure is usually to surgically remove the tumor, but it is difficult to get rid of all cancer cells. Further treatment with Temozolomid, the most common therapeutic agent for glioblastoma cancer, kills a large number of the cancer cells that remain after surgery, but resistent cells survive and most often lead to the tumor growing back. The substance that Beactica is developing into a drug, a modulator of the target protein LSD1, may be the solution to this problem. This substance has been tested on more than 50 cancer types and has proven to be particularly effective on glioblastoma cancer cells.

"It is specifically on resistant cancer stem cells – those with the ability to re-establish a more difficult-to-treat tumor – that our substance is most effective," explains Beactica's Chief Scientific Officer Ulf Bremberg.

"Beactica's LSD1 modulator forces the cancer stem cells to enter apoptosis, a programmed cell death."

The company's LSD1 modulator project, which began in 2013, has received support from Vinnova and the EU fund *SME Instrument* and is being conducted in collaboration with Uppsala University and SciLifeLab.

With extensive experience from the pharmaceutical industry, Ulf Bremberg knows that a lot of work remains on the road to an approved drug.

"I know that we have found something valuable, but it's hard to know if it will lead all the way to a drug. Either way, I'm convinced that these substances may be useful to treat cancers, and GBM is a pressing disease to begin with."

Developing a drug is a strictly regulated process that usually takes 10 to 12 years.

"Optimistically, I see a clinical trial on patients around 2019–2020, but a lot has to happen before then. We've seen what we can do with cultured tumor cells, but we also need to show that our substances can cure this kind of cancer in animals. The results from a very exciting glioblastoma study in mice are expected this autumn."

Beactica was founded in 2006 based on research at Uppsala University, and the company has developed a unique drug discovery platform based on measuring extremely weak interactions between target proteins and small fragments of drug-like molecules. By studying the binding of disease-relevant proteins and small pieces of molecule fragments, promising fragments can be identified, optimized and gradually transformed into drug candidates using medicinal chemistry.

"We can detect very weak protein-fragment interactions. Then we put the jigsaw pieces of fragments together to build complete drug molecules that then need to be adjusted many times to ultimately become an approved drug," says Ulf Bremberg.

It was when research on epigenetics gained speed in the early 2010s that Beactica began studying the target protein LSD1. Epigenetics relates to changes in gene expression that are independent of the DNA sequence and serves as a link between heredity and environment.

"Epigenetics is like a layer on top of DNA. Our substances that affect LSD1 disrupt the cancer cells' epigenetic machinery so that they die," Ulf Bremberg explains.

A future LSD1 modulator drug may be extra beneficial in combination with an immunological preparation of the type that has recently revolutionized cancer treatment by triggering the immune system to attack the cancer tumor. A synergistic effect with several factors that interact, according to Ulf Bremberg.

In the on-going work of developing

the drug, several factors are motivating.

"If this discovery can help thousands or millions of people who would otherwise die, it is very meaningful. It's also intellectually stimulating to be part of this journey. It literally stretches our researchers' capability and creativity to the limit of what we can achieve."

In the project, Beactica has collaborated with several facilities of SciLifeLab's infrastructure, including In Vitro and Systems Pharmacology which has been crucial to the project. Head of Facility Vendela Parrow has assisted the project by studying how the substances affect cell cultures from different tumors.

"Determining dose and time correlations is important in drug development. We provide several different methods to measure cell death as a function of time and we analyze changes in the gene expression of cells to understand how the substances work," she says.

Ulf Bremberg is pleased with the overall collaboration.

"The collaboration with SciLifeLab is very important to us. SciLifeLab has a critical mass of researchers with expertise and advanced equipment that can make a difference for Sweden as a whole – both industry and academia. We could not have done this without SciLifeLab."

Technology and service
In Vitro and Systems Pharmacology supported this project with studies of functional mechanisms and cellular effects. Cell Profiling and the former SciLifeLab facility Fluorescence Correlation Spectroscopy contributed with mechanistic analyses. The facilities Protein Expression and Characterization and Biophysical Screening and Characterization assisted with instruments.

Insight

Text: Lisa Thorsén / Photo: Adobe Stock

Deeper knowledge of new-found bacterium

Christine Wennerås and her colleagues were among the first in the world to discover the tick-borne bacterium *Candidatus Neoehrlichia mikurensis* in humans. These bacteria can cause severe difficulties, especially among people with impaired immune systems. The researchers have now got up to speed in the work of building up the actual bacterial chromosome.

Christine Wennerås is a doctor and researcher in infectious diseases and hematology at the Sahlgrenska Academy at the University of Gothenburg. It was in 2009 that she came across a case where an older man with an impaired immune system fell ill during a canoe outing. He had been struck by acute diarrhea and fever and had lost consciousness. Once at the hospital, it was also discovered that he had several blood clots. The patient sought emergency care numerous times during the following months, but despite suspicions of infection, no microbe was found. It was through PCR technology that Christine Wennerås' research team ultimately succeeded in discovering a large amount of bacterial DNA in the patient's blood. She was, however, puzzled. Here was a bacteria that she did not recognize. When the DNA was matched against a web-based gene bank, it turned out that the disease-causing agent had previously only been detected in ticks and rats, never in humans. The sensation was a fact – the man had been struck by a previously undiagnosed infectious disease. The causal bacteria, estimated to be present in approximately one tick in ten, can be effectively eliminated with the right antibiotic therapy.

"Since this discovery, we have managed to determine the sequences for six bacterial genes. But it has been hard to make further progress since so far the bacteria have been difficult to culture," explains Christine Wennerås.

What's more, the bacteria need to grow inside cells. So for the sequencing to be successful, the researchers need to have sufficient material and also be able to determine what DNA belongs to the bacterium and what doesn't.

Per Sikora at SciLifeLab's Clinical Genomics facility in Gothenburg has supported the project with bioinformatics expertise. Specifically, he has developed a method to identify and put together small amounts of bacterial DNA in the extensive amounts of data generated by next-generation sequencing, the new technology for DNA sequencing.

"One of the things we've done is to tag bits of DNA in new ways prior to sequencing, so that we know what DNA strand they come from. Then it's quite clear what belongs to the bacteria's DNA and what doesn't. We haven't heard of anyone else using this technique the way we are, so it feels exciting," he says.

Now the researchers are building the actual bacterial chromosome.

"We are incredibly happy that we can do this on site in Gothenburg and learn together. There's infinitely much more that we still don't know about this bacteria and it's fantastic to be able to study it in greater detail. I can compare this with putting together hundreds of thousands of jigsaw puzzle pieces. We now hope that we will be able to learn how the bacteria cause disease and to develop diagnostics to discover it," says Christine Wennerås.

Technology and service
Clinical Genomics provided bioinformatics support and customized equipment so that it could be applied to the study. The facility also prepared the DNA libraries and helped with sequencing and analysis.