NeuroVive PHARMACEUTICAL

Newsletter

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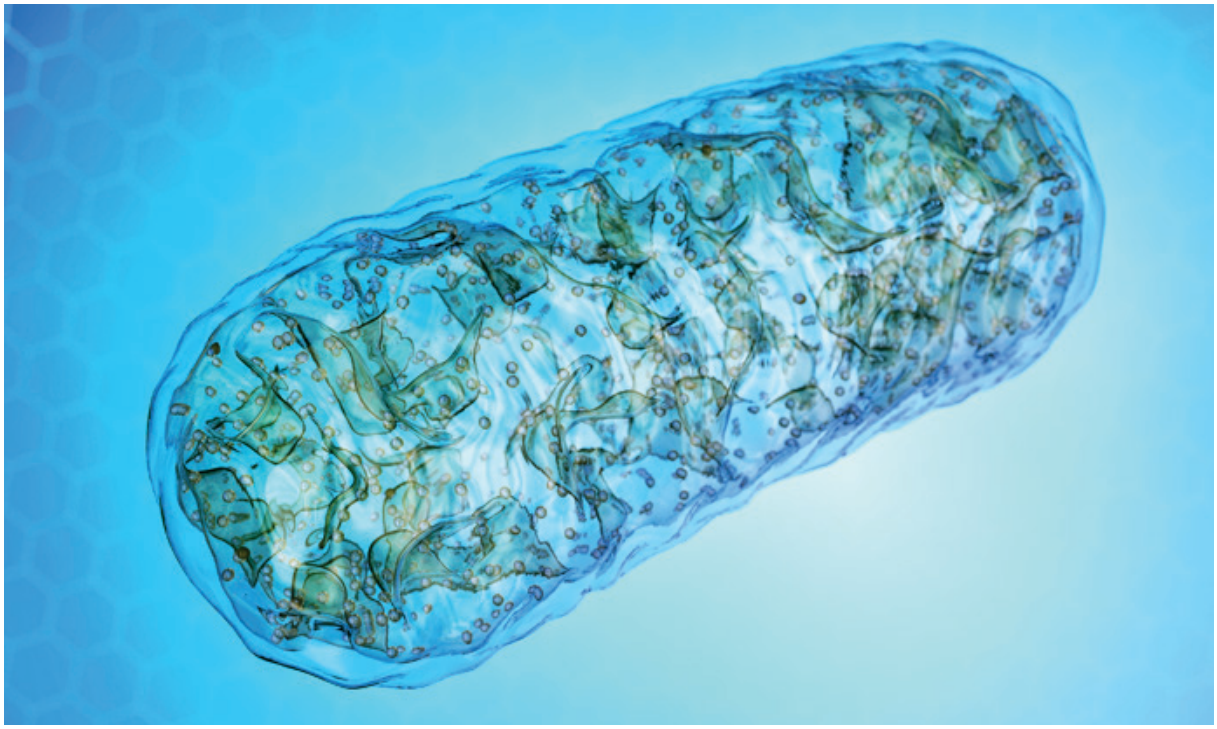

Breakthrough brings hope of treatments for muscle diseases

Recently, NeuroVive was able to report a breakthrough in the company's research on mitochondrial myopathy. In experimental studies conducted by NeuroVive's partner Karolinska Institutet under the leadership of Professor Håkan Westerblad, NeuroVive's model substance showed positive effects that could counteract the disease progression in mitochondrial myopathy and potentially other muscle diseases.

Mitochondrial myopathy

Mitochondrial myopathy is a group of genetic muscular diseases caused by congenital injuries to the cells' power plants, the mitochondria. Mitochondrial myopathy is manifested by muscle weakness, fatigue and exercise intolerance, and is often associated with other symptoms of genetic mitochondrial disease, such as heart failure and rhythm disturbances, dementia, agitation and periods of stroke, deafness, blindness, hanging eyelids, restricted eye movement, vomiting and cramps. The most common mitochondrial myopathies are KSS (Kearns-Sayre Syndrome), CPEO (Chronic Progressive External Ophthalmoplegia), MERRF syndrome (Myoclonic Epilepsy with Ragged Red Fibers) and MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes). The disease usually develops from general progressive muscle weakness to death, which, combined with few or no treatment options creates a significant medical need.

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NeuroVives research in genetic mitochondrial diseases

NeuroVive's NVP025 project is developed primarily for mitochondrial myopathy, which together with the KL1333 and NVP015 projects constitute the company's program for genetic mitochondrial diseases. While NVP015 focuses on the treatment of acute energy crises that may occur in mitochondrial diseases, KL1333 and NVP025 have long-term treatment profiles. KL1333 aims to increase energy production in the mitochondria and reduce the accumulation of lactic acid by stimulating the formation of new mitochondria. The NVP025 project is aimed at protecting the muscle cell mitochondria and preventing muscle weakness in mitochondrial myopathy but may potentially also be relevant to other muscular diseases, such as Duchenne muscle dystrophy.

Collaboration with Karolinska Institutet

In the beginning of 2017, NeuroVive signed a collaboration agreement on mitochondrial myopathy with Karolinska Institutet and Professor Håkan Westerblad. Håkan Westerblad and his research group had demonstrated in previous studies that patients with mitochondrial myopathy have abnormally high levels of the substance Cyclofilin D, a protein that regulates the opening of pores in the internal membranes of mitochondria. Too much cyclophilin D causes the membrane to release an excess of calcium ions, which in turn can cause cell death. By inhibiting cyclophilin D using ciclosporin A, the researchers managed to counteract the muscle weakness of mitochondrial myopathy in experimental models.

However, ciclosporin has several undesirable side effects for myopathy patients in chronic treatment, including suppressing the immune system. Thus, the researchers at Karolinska Institutet have instead studied NeuroVive's new cyclophilin inhibitor, which is considered to have higher specificity and tolerability than ciclosporin. This, in turn, facilitates dosage and, in the long run, the prospect of developing a new drug.

The studies at Karolinska were conducted in an experimental animal model and, in January of 2018, researchers reported that the study was successful. At the end of the study's treatment period, survival was 94% in the treated group, compared to 50% in the control group. Also, the muscle function in the treated group was better than in the control group.

Next step and prospects

The results from Karolinska Insitutet are an important milestone in NeuroVive's NVP025 project, meaning that the company can now take the project to the next development phase. In that phase, NeuroVive will make further tests on the substances to select and optimize a drug candidate suitable for further development for patients with different types of muscle disease. The need for new treatments is significant and the positive results have generated a great interest, especially from relatives of patients with mitochondrial myopathy. Although the results of the studies at Karolinska are positive, and a prerequisite for the continuation of the project, clinical development and clinical studies are still a few years in the future. However, NeuroVive's drug development strategy, productive partnerships and strong mitochondrial disease programs provide good conditions for taking the project through the development phases to a highly anticipated drug.

Orphan drugs – advantages in developing therapies for rare diseases

Towards the end of 2017, NeuroVive announced that the European Commission had granted orphan drug designation for KL1333, a candidate drug for treating genetic mitochondrial diseases. Such diseases often have severe consequences for affected patients, but since the diseases are rare and the number of patients relatively few, the number of effective therapies is limited. By granting orphan drug designation, the medicinal products authorities in Europe and the United States can stimulate and facilitate the development of drugs for rare diseases. When orphan drugs are fully developed and have been granted marketing approval, they may be eligible for orphan drug status, which grants seven or ten years of market exclusivity in the United States and Europe respectively, providing more favorable conditions for commercial success.

More orphan drugs through new legislation

Thus far, NeuroVive has been granted orphan drug designation for NeuroSTAT in the United States and Europe, and for KL1333 in Europe. Other drug candidates in the company's project portfolio may qualify for orphan drug designation. The development of orphan drugs is supported economically in the United States through the Orphan Drug Act of 1983. It was so successful that similar provisions were adopted on other key markets, such as Japan (1993) and the European Union (2000). Over the years before the Orphan Drug Act, only 38 orphan drugs were approved, compared to over 900 in the 35 years since the law was introduced.

A rapidly growing market

Globally, an estimated 350 people suffer from rare types of cancer or infectious and neurological diseases. The global market for orphan drugs is currently growing at a faster rate than the total drug market and is estimated to have exceeded USD 120 billion by the end of 2017. In 2022, it is expected that the market for orphan drugs will have grown to USD 209 billion, at which time the value of orphan drugs under development will make up 55% of all drugs in development. Since both the number of patients and the available therapies are quite few, the price for orphan drugs is relatively high – often four times that of non-orphan drugs. The rapid growth and the possibility of favorable pricing has attracted major pharmaceutical companies to the field, for instance Celgene, Bristol-Meyers-Squibb, Novartis, Roche and Shire, which were the top five companies in orphan drug sales in 2016.[1)]

Stimulus and support for expanded development

Despite the rapid growth of orphan drugs, some 97% of all rare diseases still lack approved drugs. This is largely because drug development is a very expensive process. Yet the average cost of developing an orphan drug through a phase III program constitutes only about half of that of a non-orphan drug. Also, the access to regulatory advice and support is greater during the development process and the median time for applying for market approval with the FDA in the United States is on average three months shorter with an orphan drug compared to a non-orphan drug. In the European Union, development of orphan drugs is supported by lower application fees and access to regulatory and scientific advice, for instance concerning clinical study design. Furthermore, the documentation burden is lower and the scope of clinical studies smaller for orphan drugs compared to non-orphan drugs, which cost on average twice as much to develop through phase III. The European Union also supports orphan drug development by smaller companies such as NeuroVive through special provisions for what are called SME companies (micro, small and medium enterprise). These provisions contribute towards lower development and commercialization costs through lowering fees even further or in many cases eliminating them entirely.

Overall, this creates conditions under which even small companies such as NeuroVive can guide a drug from discovery to preclinical development and clinical studies, and finally to the market, all on its own. For patients with rare diseases, this provides hope for new and more effective therapies.

1) EvaluatePharma Oprhan Drug Report 2017 (http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf)

Interview with Ramin Massoumi of Lund University's division of translational cancer research

Ramin Massoumi and his research team, together with NeuroVive, have been awarded funding from the Swedish Foundation for Strategic Research (SSF) for studies of liver cancer. The research grant provides funding for an industrial PhD student.

Photo: Åsa Hansdotter

What can you tell us about your research?
Today's medical cancer treatments need to be improved so that the tumor cells can be fought more effectively while minimizing the side effects. To succeed at this, we need more customized and individually adapted treatments. The purpose of our research is to study new molecules that can inhibit the spread and growth of tumor cells.

How is liver cancer currently treated?
Primary liver cancer can be treated with surgery, if the tumor is sufficiently small and has not spread, and in some cases with a liver transplant. Local treatment – destroying the tumor with heat or chemical substances, chemotherapy or radiation therapy – can also be considered. There are also specific drugs that act as inhibitors of the tumor cells' and blood vessels' signaling systems for growth. Sorafenib (Nexavar) is one example. A similar drug has also recently been registered: regorafenib (Stivarga), which is intended for those who do not respond to sorafenib.

Is there a need for new and improved therapies for liver cancer?
Absolutely. In cases where the tumor cannot be completely removed, there are no curative therapies, only therapies which may slow the progress of the disease. There are adverse side effects associated with current drugs that increase median survival by a few months. There is thus a great need for new treatment methods for liver cancer as well as for other tumor-related illnesses. The trend is to use combinations of drugs with different mechanisms of action and to pre-examine which drugs a tumor is sensitive to.

What are the most important topics in the PhD student program that SSF will support?
The proposed research program aims at understanding in detail the mechanisms behind the effects of drug candidates by confirming these effects in relevant models and in tissue samples from actual liver cancer patients. We want to find out in greater detail how the class of drugs called sanglifehrins inhibit tumor growth. Sanglifehrins are exciting molecules that can block the activity of specific target proteins in the cell, including proteins known as cyclophilins. Another topic will be further investigating which other drug substances are appropriate for combination therapies with sanglifehrins in order to achieve the greatest possible anti-tumor effect.

What is known about cyclophilins, the proteins that the research project is dealing with? Have they previously been shown to play a role in cancer?
Cyclophilins are a type of protein that ensures that newly synthesized proteins have the correct structure. The best known are Cyclophilin A and Cyclophilin B, which have been shown in experimental studies to be important in influencing the proliferation and survival of cancer cells. The mechanism itself is not known, but both proteins often occur in large quantities in liver and other cancers. In some cases, it has also been possible to link high levels of cyclophilins with impaired survival prognosis in cancer patients.

What opportunities (and possible difficulties) do you see in a collaborative project like this between a company and the university?
I think that the best opportunity to develop new promising therapies is found in combining the broad knowledge of cancer biology found at institutions such as Lund University and the innovative power of companies like NeuroVive. That being said, it is always exciting and challenging when academia and industry meet to create opportunities to industrialize innovative discoveries. We have previously collaborated with pharmaceutical companies on projects in cancer diagnosis and treatment. In every case, these collaborations have resulted in important discoveries.

ABOUT NEUROVIVE

NeuroVive Pharmaceutical AB is a leader in mitochondrial medicine, with one project in clinical phase II development for the prevention of moderate to severe traumatic brain injury (NeuroSTAT®) and one project in clinical phase I (KL1333). The R&D portfolio consists of several late stage research programs in areas ranging from genetic mitochondrial disorders to cancer and metabolic diseases such as NASH. The company's strategy is to advance drugs for rare diseases through clinical development and into the market. The strategy for projects within larger indications outside the core focus area is out-licensing in the preclinical phase. NeuroVive is listed on Nasdaq Stockholm, Sweden (ticker: NVP). The share is also traded on the OTCQX Best Market in the US (OTC: NEVPF).

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