NeuroVive PHARMACEUTICAL

Newsletter

December 2019

CEO Erik Kinnman sums up 2019

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A successful year

2019 has been a successful year for NeuroVive in many ways. Our projects for primary mitochondrial diseases, KL1333 and NV354, have made good progress during the year. KL1333 is currently in clinical trials and NV354 is being prepared for the clinical phase. In 2019, we also streamlined our strategy to make optimum use of our internal resources, and to optimize opportunities to deliver value to patients with major medical needs and to our shareholders.

Strategy based on two pillars

In brief, our strategy means internal resources in the form of capital and R&D capacity are concentrated to our projects for primary mitochondrial diseases.

This is one pillar of the strategy. The other, is active business development. Our business development efforts have two purposes:

- With respect to our projects for primary mitochondrial diseases, we are looking for business partners who can support us in various ways in our work to move these projects through clinical trials to market.
- For our other projects that are being developed for diseases with larger patient populations, we are looking for well-resourced partners who can move these through clinical trials to market.

This type of business development requires long-term and persistent efforts. Today, NeuroVive has positive relationships with several attractive potential partners who are following our projects and with whom we have a continuous dialogue. One important element in business development is participation in various international scientific conferences and partnering conferences, where new contacts are established with potential partners.

Orphan drug designation offers important benefits

Drugs being developed for rare disorders, which lack effective treatments, have a good chance of receiving orphan drug designation. KL1333 has received this designation in Europe and the US and we believe NV354 has excellent opportunities to receive the same designation.

Orphan drug designation offers substantial benefits. Briefly, these can be summarized as follows: development costs are lower compared with non-orphan drugs, development work can be carried out faster and orphan drug candidates have far greater opportunities to reach the market than ordinary drugs. Generally, the pricing of orphan drugs is also highly attractive, and marketing is focused on a limited number of specialist centers.

Taken together, this means NeuroVive can optimize its internal resources to move these projects through all stages of clinical development and thereby gradually build value in these projects.

Merry Christmas and a Happy New Year

I would like to take this opportunity to wish you all a Merry Christmas and a Happy New Year. 2019 was a good year for NeuroVive with significant advances in our projects for primary mitochondrial diseases. 2020 has the potential to be an even stronger year!

Erik Kinnman, CEO

Projects in primary mitochondrial diseases

KL1333
This project is being developed for the treatment of primary mitochondrial diseases such as MELAS, KSS, PEO, Pearson's syndrome and MERRF. The project is in a clinical Phase Ia/b study in the UK. The project has orphan drug designation in Europe and the US.

NV354
The objective of this project is to develop an alternative energy source for primary mitochondrial diseases, including Leigh syndrome and MELAS. The project is currently being prepared for clinical development.

Projects for further development through partnership

NeuroSTAT
This project is being developed for the treatment of traumatic brain injury (TBI). NeuroSTAT has orphan drug designation in both Europe and the US and IND approval for clinical development and Fast Track in the US. The project is prepared for clinical efficacy trials.

NV556
This project is being developed for the treatment of fatty liver (NASH) which is found in 20–25% of the global population and is a condition that can lead to cirrhosis of the liver or liver cancer (hepatocellular carcinoma). The project is in a preclinical phase.

The mitochondria produce energy. Our bodies are made up of trillions of cells and we need a lot of energy to make them work.

Interview with Dr. Amel Karaa

Dr Karaa is an internist and geneticist. She practices mitochondrial medicine at Massachusetts General Hospital in Boston, USA.

What are mitochondria?
"At the time when the world was ruled by single cells, an early primitive cell captured a proteobacterium. In exchange for protection and nutrition given by this early cell, the proteobacterium in turn enhanced the energy production of the cell through a process called aerobic respiration. This was at the origin of complex life and all living creatures on earth.

Two billion years later, these cells still coexist and the proteobacterium has become the mitochondrion that we know today. The mitochondrion has kept some of its proteobacterium characteristics by possessing its own DNA which is different from the DNA that we have in our nucleus".

What do the mitochondria do?
"They are best known for producing energy. Our bodies are made up of trillions of cells and you need a lot of energy to make them work. The mitochondria do that by converting the food we eat into a biochemical energy called ATP. ATP is distributed within the cell so that each cell, tissue and organ can function properly. The way the mitochondria make the ATP is through a complex process. The mitochondrion has an outer membrane that separates it from the rest of the cell, an inner membrane and an intermembrane space in between. It's

Dr. Amel Karaa

within that intermembrane space where all that energy is made, through a very complex set of proteins called Complex I, II, III, IV and V. This complex pathway has evolved and became very efficient over time. Over billions of years the mitochondria also evolved into doing many other things:

- It's the major organelle in the cell that contributes to programmed cell death. One might think that cell death is a bad thing, but if your cells are being attacked by viruses or bacteria or too old and need to be changed, the best thing is to destroy them. Mitochondria do that, to keep the rest of your body healthy.
- Mitochondria also produce free radicals, as byproducts of its normal function. Free radicals are like little mines that target areas of the body and cause destruction but can also serve as messenger molecules. Over time, with age or if mitochondria are not functioning properly, more free radicals are produced and can accumulate causing harm to the body and disease. These free radicals are what causes the apple to rot when you leave it on the counter, or your skin and body to age over time.
- But most importantly, mitochondria are associated with so many other biochemical pathways, like processing of proteins and fat, synthesis of steroids, iron homeostasis and calcium as well as hormone signaling.

The more we know about mitochondria the more we realize how they really are at the heart of many medical conditions that we know of as of today. We also continue to discover new pathways and functions regularly".

How have the mitochondria become so complex and efficient over the years?
"That's partly related to its unique ancestral origin. The mitochondrion has kept its own mitochondrial DNA, its bacterial ancestral DNA. Over time it also developed connections with the nuclear DNA. The difference between the nuclear and the mitochondrial DNA is that we have a

lot more nuclear DNA than mitochondrial DNA. When tapping into the nuclear DNA, the mitochondria are able to acquire and perform many of the body's biochemical processes. There are hundreds of different genes in the nuclear DNA that are involved in the normal function of the mitochondria. There are 37 genes in the mitochondrial DNA. Together they make sure that our mitochondria function properly. When there is a change or a misspelling in that DNA (a mutation), disease might arise.

The nuclear DNA can be transmitted from both parents, whereas mitochondrial DNA is only transmitted from mothers to all of her children. It is estimated that on average one in 4,300 adults carry a mutation in the nuclear or mitochondrial DNA. Another study has found that one in 200 people might be born with a mitochondrial DNA mutation which may or may not evolve into a disease state. We think that people with mitochondrial diseases related to a mitochondrial DNA problem are underdiagnosed and underrecognized because they often have symptoms like diabetes, heart failure or hearing loss, which may be more commonly seen in the general population and which doctors don't necessarily relate to mitochondrial disease".

What happens when there is a problem in the mitochondria?
"The mitochondria become less efficient in making energy. Instead of having a fully charged battery, you have less and less energy. This means that your cells, tissues and organs are now not able to function properly, optimally. Also, your mitochondria are making more of the free radicals, which in turn are attacking the mitochondria's own compartments. So, on top of not delivering enough energy, your mitochondria are also destroying different components of your body. Patients start developing symptoms and organs start to shut down.

What we see in the clinic is that mitochondrial disease can present with any symptom, in any organ and in any person at any age from birth to death and can have any mode of inheritance".

What symptoms can a patient develop?
"Mitochondria are present everywhere in our body at hundreds and hundreds of copies in a single cell. The organs that require the most energy are the first to malfunction or shut down. Your brain, your eye, your muscles, your bone marrow, your gut and your heart would be the first organs to show symptoms.

In children we mostly see brain, nerve disease, because of the developing brain and nervous system but also bone marrow and gut problems. If the disease presents later in life, we mostly see muscle problems, gut problems, diabetes, hearing loss, kidney and heart disease. A patient with mitochondrial disease can have about 16 symptoms at the same time".

How is mitochondrial disease managed and treated?
"Right now, we do not have a cure. We treat the symptoms as they come. It's like putting band aids on big issues. We try to minimize the energy loss and to maximize the energy gain e.g through nutrition, exercise, adequate rest and through avoiding stressors".

What is being done within the research community?
"One very positive thing is that the number of scientific publications within the scientific research community has increased tremendously over the past 20 years and mitochondrial research represents today the bulk of medical publication. People have recognized that if you can treat primary mitochondrial disease, you can potentially also treat millions of people having more common diseases, since mitochondria are involved in so many processes in the body.

People have been trying to repurpose already existing drugs to treat mitochondrial disease, developing new molecules as treatments, and also potential gene therapies. But only one drug has so far been approved for mitochondrial disease, with limited efficacy, specifically for an eye disorder called Leber hereditary optic neuropathy (LHON). So, there is a long way to go before we can find a cure for every mitochondrial disease.

But hope is on the way, with increasing number of ongoing and planned clinical trials, more disease foundations and consortia supporting the research, and international efforts in mitochondrial research, clinical care and drug development".

Challenges in treating mitochondrial diseases

Mitochondrial diseases are difficult to recognize
- There are hundreds of different disorders within the broader mitochondrial disease label
- There are different symptoms between the different mitochondrial disorders and syndromes
- Many genes can cause the same disorder presentation
- The same gene can cause many different disorders or syndromes

Mitochondrial diseases are difficult to predict and manage
- Progressive
- Unrelenting
- Deteriorating with stress

Mitochondrial diseases are difficult to diagnose
- No perfect diagnostic method (molecular testing is positive in 25-55% of the cases at best)

Mitochondrial diseases are difficult to treat
- Multiple organ systems involved
- Symptoms severity varies (lethal to mild)
- No specific treatment available

Nobel Prize and mitochondria

William G. Kaelin, Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza will today receive the Nobel Prize in Physiology or Medicine from King Carl XVI Gustaf at Konserthuset in Stockholm. They will receive the prize for their discovery of how cells sense and adapt to oxygen availability, and have provided the research community with insight into how this impacts the body in health and when sick.

During physical training, the available oxygen is quickly used by muscles, which leads to a reduction in oxygen levels. This in turn stimulates muscles to be better prepared for the next training session e.g. by creating more blood vessels. Spending time at high altitudes in air with lower oxygen levels than the body is accustomed to, stimulates the creation of new red blood cells, which in turn enhances the efficiency of oxygen supply to cells in vital organs. Moreover, cancer cells utilize the effects of low oxygen levels to stimulate the growth of blood vessels in tumors in order to grow and spread. All of this uses the HIF-1 (Hypoxia Inducing Factor) protein, the levels of which increase in a long-term low oxygen environment and creates a defense mechanism to help the body adapt.

Oxygen is also key for mitochondria. Together with nutrients in the food we eat, it is converted in the mitochondrion to the vital chemical energy that enables us to function properly. At low oxygen levels, the mitochondria become less active and other cellular processes less dependent on oxygen (anaerobic) step up to ensure energy production (for example, in the process where lactic acid is formed). Many researchers have demonstrated that when oxygen levels decrease and mitochondrial activity falls, a signal is also sent via HIF-1 from the mitochondria, which enhances the adaptive measures in the body. HIF-1 has also been shown to prevent the creation of harmful substances in mitochondria when oxygen is less available.

Access to oxygen is not a problem in primary mitochondrial diseases. However, oxygen is processed less efficiently in mitochondria and harmful by-products can form, which leads to low energy levels and tissue damage without starting the adaptive defense mechanism. Researchers have, in experimental models of the severe mitochondrial disease Leigh syndrome, demonstrated that a reduction in oxygen levels over long periods can improve life expectancy and health, but the mechanisms behind this are not completely understood. NeuroVive's drug candidates for the treatment of primary mitochondrial diseases work by enhancing the efficiency of oxygen use and KL1333 also triggers the creation of healthy mitochondria, which improves the cells' total ability to create energy.

Spreading the word

NeuroVive is continuously engaged in the vibrant mitochondrial science community as well as the world of investors and potential partners. Over the past few months alone, NeuroVive has attended and presented at conferences in Sweden and Germany.

BioStock Life Science Summit: Lund, Sweden, on 23 October 2019

This meeting gathered several companies, investment banks and financial experts in the field to exchange knowledge and experiences. **Erik Kinnman**, CEO, presented the company's focused strategy. See the presentation here: https://youtu.be/2lAYD0wEqO0.

The 25th Annual International Partnering Conference, BIO-Europe: Hamburg, Germany, on 11-13 November 2019

Mark Farmery, VP Business Development, and **Erik Kinnman**, CEO, participated at the meeting – Europe's largest Life Science partnering conference. See BioStock's on site interview here: https://youtu.be/qGewwqEjd5E.

Redeye Life Science Day: Stockholm, Sweden, on 19 November 2019

Erik Kinnman, CEO, presented a short overview of the company's key projects and short-term milestones. See the presentation here: https://www.redeye.se/events#/videos/dex1xyf7.

Stora Aktiedagen: Stockholm, Sweden, on 25 November 2019

Stora Aktiedagen gathered 64 listed Swedish companies for a full day of presentations and interviews. **Erik Kinnman**, CEO, presented NeuroVive's strategy, portfolio and future prospects. See the presentation here: https://youtu.be/RnoijF126pA

Further reading at www.neurovive.com

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