NeuroVive PHARMACEUTICAL

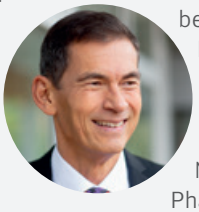
Newsletter

October 2019

Global Mitochondrial Disease Awareness Week

GLOBAL MITOCHONDRIAL DISEASE AWARENESS WEEK

A few words from NeuroVive's CEO, Erik Kinnman



On Wednesday, September 18, NeuroVive organized Mitochondria Day 2019 together with the Italian pharmaceutical company Chiesi to mark Global Mitochondrial Disease Awareness Week. Mitochondria Day is invaluable for NeuroVive because it gives us an opportunity to meet patients, family members, doctors and researchers. Gaining insight into the experience of patients and their family members is especially important, and I am very happy that so many family members and patients took the time to participate.

There is a huge unmet need for therapies to treat mitochondrial diseases. At present, there is only one approved drug for mitochondrial diseases – Raxone – for patients with the inherited optic nerve disease LHON. For other mitochondrial diseases, which can severely disable patients and be challenging for family members, no effective drugs are currently available. Dietary supplements, vitamins and so forth can help to relieve the symptoms, but not much more.

NeuroVive currently has one clinical project in Phase I and is planning to have one more project in a clinical phase next year. Much work remains to be done, but we are aiming to offer a drug in the near future that can significantly improve quality of life for patients worldwide.

Erik Kinnman, CEO

In this issue

Global Mitochondrial Disease Awareness Week

Hosted by International Mito Patients

International Mito Patients (IMP) is a network of national patient organizations for people living with mitochondrial disease. Originally an informal network, IMP was formally established in the Netherlands in 2011.

An estimated one in 5,000 people suffer from a mitochondrial disease today. In many countries, including Sweden, there is no active patient organization, and there is a great need to share best practices, information and knowledge in order to improve quality of life and care for those affected, and to accelerate long overdue drug development. Full IMP membership is open to large national patient organizations, while smaller groups and individuals who want to make a difference can become associated members. IMP currently represents 6,000-8,000 people with mitochondrial disease worldwide.

An active organization

The organization runs two major projects: developing and establishing an IMP worldwide patient register, and a IMP quality-of-life study, with a goal to gain more insight, knowledge and understanding of mitochondrial patients. The worldwide patient register is a non-clinical, patient-owned databank of mitochondrial patients all over the world. With permission from the patients, the data can be used by researchers to carry out further studies. It may also be possible to expand the study with a clinical trial, where treating physicians can also submit data about the disease progression. The quality of life (QOL) study was carried out as a pilot in Germany, and the results will soon be published. The outcomes of the study formed the basis for a further QOL study in the Netherlands, focused on other value-added aspects for patients.

A service that is highly appreciated by members is the list of drugs that are potentially harmful for mitochondrial patients that IMP publishes on its website. The list is updated on a regular basis in close collaboration with mitochondrial specialists.

IMP also provides ongoing support for grant applications for mitochondrial disease projects, helps to build networks between researchers, clinicians and patients by attending international meetings and conferences, supports national campaigns and participates in patient advocacy groups.

Global Mitochondrial Disease Awareness Week was initiated by IMP as part of its efforts to raise awareness of mitochondrial disease.

Read about “Light Up For Mito”, another initiative from IMP, on page 10.

Presenter: Alfons Heetjans

Alfons Heetjans is the father of two children affected by mitochondrial disorders. Alfons has become increasingly involved in various patient organizations since his children were diagnosed. He is currently Chairman of the Dutch Associations for Metabolic Disease and the Radboud Center for Mitochondrial Disease. NeuroVive invited Alfons, as a representative of International Mito Patients (IMP), to Mitochondria Day 2019 where he spoke about the organization and how it works to spread knowledge and raise awareness of mitochondrial disease around the world.

Leber's hereditary optic neuropathy (LHON) is a mitochondrial eye disease that leads to severe loss of central vision. There are approximately 200 LHON patients in Sweden.

Patient and physician perspectives on LHON

Leber's hereditary optic neuropathy (LHON) is a mitochondrial eye disease that leads to severe loss of central vision. There are approximately 200 LHON patients in Sweden. One of them is Fredrik Lindemark Guzmán, who is also Chairman of the LHON Eye Society. Fredrik spoke about his disease at NeuroVive's Mitochondria Day.

"I was 14," says Fredrik, "when I walked into the kitchen one day and discovered that I couldn't see the timer on the stove, even though it was right in front of me. At first I thought it was related to my migraine, and that my vision would soon come back."

But it didn't. Instead, his entire central vision disappeared within two weeks, and marked the beginning of a long patient journey. There were many possible explanations for his loss of vision, including a brain tumor and stroke.

"When your doctor can't say what the problem is and turns to his colleagues for advice – that's one of the scariest things you can ever experience. I met a lot of doctors and went through a lot of tests. The longer I went without a diagnosis, the more afraid I became."

Fredrik finally met pediatric neurologist Karin Naess at the Huddinge hospital, who could confirm that Fredrik suffered from the rare eye disease LHON.

"It might sound really strange, but the day I found out that I had LHON was one of the best days of my life – I thought I was going to die," says Fredrik, who now lives an active life. He runs, cycles and exudes an unrelenting zest for life.

"It's important to remember that my story is just one of many," says Fredrik. "LHON can present in many different ways." When asked how he manages to ride a bike despite his impaired vision, he laughs and says he is good at reacting quickly.

Opthalmologist Lena Jacobson, also took part in Mitochondria Day and spoke about LHON from a physician's perspective. LHON is so rare that not many ophthalmologists ever encounter the disease. It is also a condition that is hard to diagnose because there could be many explanations for the symptoms. There are also major individual differences in how much vision is affected, but most patients experience no loss of function in their peripheral visual field.

It is known that LHON typically affects young adult men. Because of the knowledge, and the fact that LHON is difficult to diagnose immediately, there is a risk that women of any age and children with the disease may not receive an accurate diagnosis. However, new technologies have made the diagnostic process must easier and more reliable, and an important task now is to raise awareness of LHON among Sweden's ophthalmologists.

Mitochondrial diseases – a healthcare perspective.

An interview with Karin Naess and Martin Engvall.

Karin Naess is a pediatric neurologist and Martin Engvall is an adult neurologist at Centrum för medfödda metabola sjukdomar (CMMS), a diagnostic laboratory at the Karolinska University Hospital in Stockholm. Martin is mainly focused on research, while Karin also meets patients and their family members.

What are mitochondria, where do they come from, and what do they do?
"Mitochondria are small cellular structures with double membranes – one permeable outer membrane, and one relatively dense and pleated inner membrane. A number of chemical reactions take place both inside and between the membranes. The widely accepted hypothesis is that mitochondria are derived from aerobic bacteria, i.e. bacteria that require oxygen to grow. The primary functions of mitochondria are to produce energy and to detoxify and take advantage of oxygen.

ATP, an energy-carrying molecule that is used by all of the body's organs, is produced by the various chemical reactions that take place in the cells and mitochondria, where nutrients and oxygen are broken down."

How do primary mitochondrial diseases arise?
"There are two types of genomes (genetic material, DNA) in a cell that can cause mitochondrial disease – the nuclear genome and the mitochondrial genome. The nuclear DNA is packaged into chromosomes in the nucleus of each cell and contains more than 20,000 genes. The mitochondria, remnants of ancient bacteria, contain their own circular DNA – mitochondrial DNA, which contain only 37 genes. The mitochondrial genome is much more vulnerable to mutation. Mitochondrial function depends on interactions between the nuclear and mitochondrial genomes. Enzymes, factors and other mitochondrial proteins are derived from both nuclear and mitochondrial DNA.

The mitochondria, and therefore mitochondrial DNA, are passed from mother to offspring. Both egg cells and sperm contain mitochondria, but sperm contains significantly fewer. After fertilization, sperm mitochondria are destroyed by a mechanism that is not yet completely clear."

Where do the mnutations occur?
In mitochondrial DNA mutations, the mutation is not normally present in all mitochondria within a cell (heteroplasmy). Therefore, patients may have varying

degrees of mutation in different body tissues, with varying degrees of severity. The threshold for mutation detection can be relatively high. A person with 85% defective mitochondria might feel significantly better than a relative with 95% defective mitochondria.

In mutations, there are about 1,500 genes in the nuclear DNA that could be responsible for mitochondrial diseases. These mutations are the most common cause of the diseases. About 75% of children with mitochondrial disease have mutations in their nuclear DNA."

What diseases are there and what are the symptoms?
"Mitochondrial diseases can present at any stage of life and cause symptoms in almost any organ of the body – just one, or several at the same time. The symptoms tend to occur in organs with the highest energy demands, such as the brain or muscles. They range from movement disorders, epilepsy and spasticity to developmental delays and difficulty breathing and swallowing. Children typically experience a neurological decline with progressive loss of motor skills. The most common manifestation in adults is muscle weakness.

Many mitochondrial syndromes are known by acronym abbreviations. Leber's hereditary optic neuropathy (LHON) is the most common mitochondrial syndrome. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is relatively common and caused by mutations in the mitochondrial DNA. Most syndromes are very rare, and patients can often experience symptoms that are not entirely consistent with the syndrome. Children with mitochondrial syndromes are much harder to define, and their mutations are often referred to as 'mitochondrial disease.' The most common disorder in children is Leigh syndrome, with two to three cases per year in Sweden. This neurodegenerative disease typically presents before the age of one and may be marked by developmental delays and loss of motor skills, muscle weakness, epilepsy and symptoms that originate from the heart, liver and other organs. Mutations in nuclear DNA account for approximately two-thirds of patients, while mutations in mitochondrial DNA accounts for the remaining third."

How is primary mitochondrial disease diagnosed and what treatments are there?
"The single most important diagnostic procedure is a muscle biopsy. This will reveal the function of the various mitochondrial protein complexes, and you can also examine muscle tissue microscopically and perform sequence analysis. In addition to a muscle biopsy, blood and urine testing can be carried out to determine lactate levels and muscle enzymes, for example, while any signs of liver damage can provide important information. Imaging studies of the brain and/or muscles, such as MRI scans, are also important in the diagnostic process.

In cases of suspected mitochondrial disease, genetic testing is generally performed to verify the condition. We usually use the whole-genome shotgun (WGS) method now. This method enables complete sequencing of both nuclear and mitochondrial genomes, and the detection of various mutations.

Treatment consists of relieving the actual symptoms and avoiding any harmful effects from, for example, inappropriate drugs. In patients with epileptic seizures, which consume a lot of energy in the brain, you try to treat their epilepsy. Various types of cardiac effects can also be treated. Deficiency of, or increased need for, endogenous substances can also be corrected with dietary supplements. Drugs can also be used to lower lactic acid levels in the blood. Patients should avoid fasting, and keep moving and exercising if possible. While physical activity cannot fully compensate the muscle weakness caused by the disease, there are many indications that exercise can increase the ability to produce energy and spur the production of more mitochondria."

What's happening in drug development?

Magnus Hansson from NeuroVive gives an overview

Functional and dysfunctional mitochondria

The main function of mitochondria is to convert food and oxygen into energy that can be used by the body's cells. Energy production takes place in the electron transport chain via protein complexes inside the mitochondria. Functional mitochondria convert energy into molecules such as ATP, often using the NADH molecule, which is shuttled into the electron transport chain and converted into NAD^+. Mitochondrial dysfunction occurs when the ability to produce ATP decreases due to loss of function or instability in certain protein complexes. When this ability is impaired, NADH cannot work as it should, which leads to a relative loss in NAD^+ availability. Furthermore, electrons passing through the electron transport chain cannot be used properly. The electrons then react with oxygen and form harmful free radicals. In combination, these defects may cause further disruptions in global mitochondrial function.

Compounds in drug development

Formal drug development is divided into various phases: discovery, preclinical, clinical (Phase I, Phase II, Phase III) and regulatory approval. In the development of drugs for mitochondrial diseases, only one drug has been granted regulatory approval (in Europe and Israel) – idebenone, for the treatment of LHON, an inherited form of vision loss. There is one gene therapy compound and one compound for the treatment of muscle weakness in Phase III. There are compounds for the treatment of Leigh syndrome, TK2 deficiency and muscle weakness in Phase II. NeuroVive's KL1333 drug candidate, for long-term oral drug delivery for various types of mitochondrial disease, is in late-stage Phase I and is now being prepared for Phase II trials. NV354, NeuroVive's candidate compound for the treatment of conditions including Leigh syndrome, is being prepared for Phase I clinical trials.

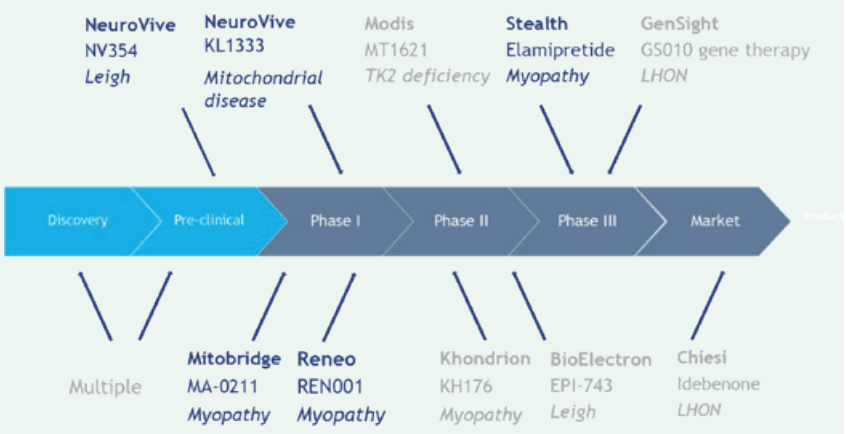
Various strategies

Research has shown that lack of energy is not the only problem in mitochondrial disease, which is why drug development within the field is being performed through different general strategies. Some compounds, including idebenone, target the free radicals caused by the disruption of the electron transport chain, while others are looking into the possibility of stabilizing the inner mitochondrial membrane to allow more efficient electron transport. NeuroVive's KL1333 targets the relationship between NADH and NAD+ in order to promote energy production, but also to stimulate mitochondrial biogenesis. Other drug candidates also work by triggering biogenesis through enzyme activation. Biogenesis through activation increases total energy production, which could prevent the symptoms that arise.

There are gene-specific strategies, such as delivery of substances needed for mitochondrial DNA replication, delivery of compounds, that bypass a mitochondrial defect caused by a specific mutation – as in the case of NeuroVive's NV354 – and local gene therapy.

Some of the drug compounds target specific manifestations of the disease, such as symptoms from the central nervous system, eyes or muscles. Others – like NeuroVive's KL1333 – target more peripheral and general manifestations of the disease.

Drug development landscape for mitochondrial disease



Rare disease trials

What are the challenges?

Clinical trials – or research studies performed in people – are strictly regulated. In clinical trials for drug development in rare diseases, there are several other important aspects to consider when planning and conducting a trial. This was the topic chosen by Kristina Sjöblom Nygren, from pharmaceutical company Santhera (the company that developed the compound idebenone for the treatment of LHON), in her presentation at Mitochondria Day.

One of Kristina's best tips for succeeding in bringing the many promising compounds that exist for the treatment of rare diseases to market, is partnerships.

"You have to build partnerships – and not just within your own company. You must also build partnerships with authorities, payers, clinical and academic experts, and – most of all – with patients and patient organizations to gain insight into the experiences of patients and their family members. Furthermore, patient organizations can usually help to recruit patients for the trial."

95% of all rare diseases lack an approved treatment and 65% of all rare diseases are considered severe. 30% of children with a rare disease will not live to see their fifth birthday. At the same time, it can take a very long time for patients to receive an accurate diagnosis, which can be extremely challenging. As new therapies emerge, it is becoming increasingly important to receive an accurate diagnosis as early as possible.

"One of the most important factors when planning a clinical trial is how the disease presents. Will patients become progressively worse if the disease is left untreated, is the disease intermittent or does it present in some other way? In short, what is the disease progression? Another important factor that you must understand is the healthcare system's guidelines for treatment. These can vary widely between hospitals, and obviously affect how the trial should be designed. Therefore, it is important to choose hospitals for the trial that offer the most similar type of treatment as possible."

Other important aspects when planning a trial are, of course, the number of patients involved and where they are based. This is where patient organizations can become invaluable partners. Many patients may also have severe disabilities. You have to consider practical aspects like whether the patients can get to the hospital, or whether the treatment should be carried out in their homes. Furthermore, both patients and hospital staff must receive the (easy-to-understand) information they need.

"A very important question is what happens after the trial. It can take a long time after trial completion before the drug becomes generally available. Who is going to supply the drug to the patients during that period? It's very important to ask yourself these questions. You must also be familiar with the national regulations that apply in this area."

The participants

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JONAS VILJANEN
Rare Disease Manager, Chiesi Pharma AB

ALFONS HEETJANS
Director of the Board of International Mito Patients

KARIN NAESS
Pediatric neurologist, Karolinska University Hospital.

MARTIN ENGVALL
Neurologist, Karolinska University Hospital.

LENA JACOBSON
Ophthalmologist, Karolinska University Hospital.

FREDRIK LINDEMARK GUZMÁN
Chairman of LHON Eye Society.

MAGNUS HANSSON
CMO, NeuroVive.

KRISTINA SJÖBLOM NYGREN
CMO, Santhera.

Light Up for Mito

Global Mitochondrial Disease Awareness Week (September 15-21, 2019) opened with Light Up for Mito. Around the world, more than 100 monuments and landmarks were illuminated in green to raise awareness of mitochondrial disease (mito).
In Sweden, the LHON Eye Society organized the first Mito Run. The course wound through Hagaparken in Stockholm.

The number of illuminated monuments in each country was: Australia 53, UK 41, Canada 23, Finland 23, Spain 16, Italy 16, Austria 5, US 2, Mexico 2, Northern Ireland 1, Gibraltar 1.

Spreading the word

FDA's workshop - Developing Therapies for Primary Mitochondrial Diseases: Bridging the Gaps: Washington DC, USA, on 6 September 2019

NeuroVive's team consisted of Chief Medical Officer & VP Preclinical and Clinical Development, Magnus Hansson, and Director Clinical & Regulatory Affairs, Matilda Hugerth. The symposium presented a unique opportunity for NeuroVive to discuss drug development for genetic mitochondrial diseases with leading experts within the field.

Nordic Life Science Days: Malmö (SE) and Copenhagen (DK), on 10 – 12 September 2019

NeuroVive's VP Business Development, Mark Farmery attended this partnering conference that gathers leading persons within the Nordic biotech- and pharmaceutical industry.

Journal of Internal Medicine Symposium: Mitochondria in Human Disease: Stockholm, Sweden, 16 – 18 September 2019

Magnus Hansson, NeuroVive's Chief Medical Officer & VP Preclinical and Clinical Development, together with Alvar Grönberg, Director of Preclinical Development, took part of world leading experts' latest mitochondrial medicine research.

The 19th Annual Biotech in Europe Forum: Basel, Switzerland, on 25 – 26 September 2019

NeuroVive's VP Business Development, Mark Farmery attended the partnering conference – one of the most important international life science and biotech investor- and partnering meetings.

About NeuroVive

NeuroVive Pharmaceutical AB is a leader in mitochondrial medicine, with one project in clinical phase I (KL1333) for chronic treatment of genetic mitochondrial diseases and one project, in preparation for clinical trials (NV354), for treatment of genetic mitochondrial diseases with Complex I deficiency. NeuroSTAT for traumatic brain injury is another clinical phase project. The R&D portfolio also consists of projects for mitochondrial myopathy, NASH and cancer.

NeuroVive's ambition is to take drugs for rare diseases through clinical development and all the way to market, with or without partners. For projects for common indications the goal is out-licensing in preclinical phase. A subset of compounds under NeuroVive's NVP015 program has been licensed to Fortify Therapeutics, a BridgeBio company, for the development of a local treatment of Leber's Hereditary Optic Neuropathy (LHON).

Marketplace
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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