The heart of the matter

Elamipretide in the treatment of Barth syndrome

Barth syndrome (BTHS) is an ultra-rare but debilitating genetic disease affecting cell mitochondria. High infant mortality due to cardiac complications and a weakened immune system significantly decrease life expectancy. Current medications treat symptoms but not the cause, leaving an unmet clinical need to develop effective treatments that target the underlying pathology. Dr Hani N Sabbah, Professor of Medicine at Wayne State University and Professor of Medicine Research at Michigan State University, USA, led early research on the use of elamipretide in animals. In a recent paper he reviews the evidence supporting the potential use of elamipretide as a therapeutic agent in BTHS, highlighting both the opportunities and challenges faced.

First diagnosed in 1983 by Dr Peter B. Barth, Barth syndrome (BTHS) is a genetic disease affecting the X sex chromosome, meaning the disease is commonly passed down from mother to son. Although rare, with an estimated prevalence of one in every 300,000–400,000 live births, the condition is thought to be under diagnosed.

BTHS CARDIOMYOPATHY AND THE NEED FOR EFFECTIVE TREATMENT

Approximately 90% of BTHS patients have cardiomyopathy (heart muscle abnormalities) with other clinical manifestations of skeletal myopathy (weakened skeletal muscles), neutropenia (low neutrophils in the blood), and growth delays. Cardiomyopathies in BTHS can lead to heart failure and death. The varied clinical presentation makes diagnosis difficult, and different phenotypes have been found even within the same family. Biochemical testing and gene sequencing enable a definitive diagnosis, with the latter able to detect disease in antenatal samples and the identification of female carriers. Current therapies for BTHS include routine supportive treatment for cardiomyopathy and heart failure, heart transplant, antibiotics to prevent infections, and granulocyte colony-stimulating factor (G-CSF) therapy to stimulate white blood cell production.

The failure of current medications to treat the underlying cause of the disease is well recognised, with most therapies only treating the symptoms. Over the last decade, Dr Hani N Sabbah, Professor of Medicine at Wayne State University and Professor of Medicine Research at Michigan State University, USA, has contributed significantly to the study of this field, highlighting and researching a new drug candidate – elamipretide – that can target the mitochondrial pathology in patients with BTHS.

MITOCHONDRIAL POWER GRIDS

Mitochondria are the ‘power grids’ of cells, producing adenosine triphosphate (ATP), the energy all cells require for their functionality. The heart needs a huge amount of energy to contract and relax and, for its weight, is more metabolically active than any other organ in the body. This enormous energy consumption requires an abundance of mitochondria to power it and there are more mitochondria in cardiac tissue than any other bodily tissue. ATP cannot be stored; therefore, it must be produced quickly when needed in organs with high energy demands like the heart. Cardiac mitochondria are particularly efficient and respond rapidly, ensuring that energy supply can meet varying demand, for example during physical activity. Any form of mitochondrial dysfunction, therefore, can cause energy supply to fail behind demand.

In BTHS, there is a defect in the TAZ gene which codes for an enzyme needed for the function of cardiolipin, a phospholipid that is part of the mitochondrial inner membrane and is important to maintaining mitochondrial structure and function. Cardiolipin is central to mitochondrial function – mitochondrial complexes I and IV are influenced by cardiolipin activity and defects in these complexes can lead to the excessive production of reactive oxygen species (ROS) and subsequent alterations in ATP synthesis. In the heart, increased ROS and oxidative stress initiates inflammation that damages cells. Furthermore, mitochondrial-driven apoptosis (programmed cell death) is part of heart failure pathophysiology.

Cardiomyopathies vary between BTHS patients, and the underlying causative mechanisms and reasons remain unknown. The cardiomyopathies in BTHS usually lead to what is known as poor left ventricular relaxation. This relaxation is an active process that requires ATP, and failure to match energy demand leads to exercise intolerance, a common symptom in heart failure and BTHS. In chronic heart failure, some patients still have a preserved left ventricular ejection fraction (HFpEF), meaning the left ventricle can pump blood out but does not refill with enough blood, so insufficient volumes are pumped out to the body. Some of the cardiac manifestations seen in HFpEF are also noted in BTHS, suggesting any treatments developed for this pathology may also be of benefit in patients with BTHS.

STABILISING EFFECTS OF ELAMIPRETIDE

Elamipretide is a peptide (a short chain of amino acids) that can enter the mitochondria and join to cardiolipin. Cardiolipin helps organise the respiratory complexes needed for oxidative phosphorylation (the introduction of phosphates, important for protein and enzyme function) as well as increasing the surface area available for the process. In BTHS, where cardiolipin is dysfunctional, studies so far have shown that elamipretide stabilises the inner mitochondrial membrane and helps normalise these processes, thus increasing ATP production.

What animal models tell us

Animal studies have been an important source of data demonstrating the positive effects of elamipretide on cardiac structure and function. Sabbah and colleagues were the first to report the beneficial effects of long-term treatment with elamipretide in dogs with heart failure. Long-term treatment with elamipretide normalised cardiolipin, thereby restoring normal mitochondrial function, increasing ATP synthesis, and decreasing ROS to normal levels in several organs. In doing so, elamipretide reduced the cardiomyocyte hypertrophy and associated interstitial fibrosis (reducing heart muscle thickening and stiffness) that leads to left ventricular remodelling. Left ventricular function was therefore improved to similar degrees as other commonly used heart failure medication, such as beta blockers and ACE inhibitors. However, studies in a pig model of HFpEF, elamipretide improved left ventricular remodelling, providing further testimony that this drug may benefit BTHS patients, especially those with a HFpEF phenotype. Interestingly, studies on animal models also revealed mitochondrial ‘repair properties’ of elamipretide in non-cardiac tissues.

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Sabbah and colleagues were the first to report the beneficial effects of long-term treatment with elamipretide in dogs with heart failure.
Behind the Research
Dr Hani Sabbah

Research Objectives
Dr Hani Sabbah has spent a decade researching the potential of elamipretide as a therapy for the Barth syndrome.

Detail
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References


Personal Response
What first motivated you to investigate the potential of elamipretide for treating heart failure and Barth syndrome?

My entire career has been devoted to expanding our understanding of the underlying causes of heart failure and its progression, and helping develop new drugs and devices to treat this syndrome and the extended life expectancy of patients suffering from this disease. During two decades of research, we began to recognise that mitochondria of the failing heart is abnormal and contributes in a large part to the worsening of heart failure. While we did recognise that correcting this mitochondrial abnormality may be beneficial, we had no drugs at the time capable of doing so. Elamipretide was the first drug with the potential to treat mitochondria in heart failure and by extension in Barth syndrome.

Elamipretide has a unique ability to act at multiple levels to restore mitochondrial function, cellular health, and reverse the remodelling of heart tissue.