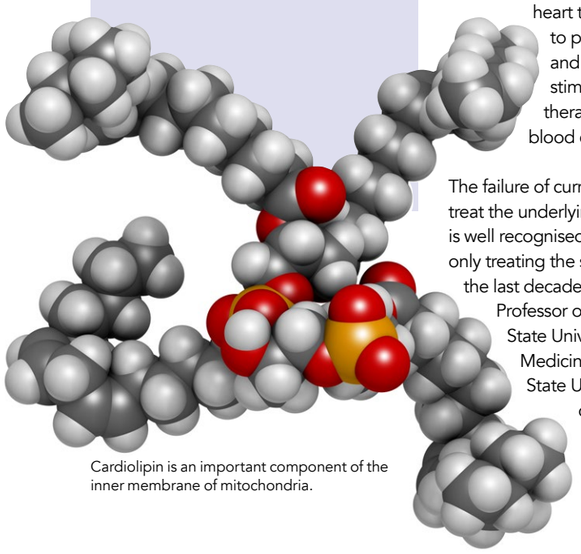
The heart of the matter

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.



Cardiolipin is an important component of the inner membrane of mitochondria.

First diagnosed in 1983 by Dr Peter 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.

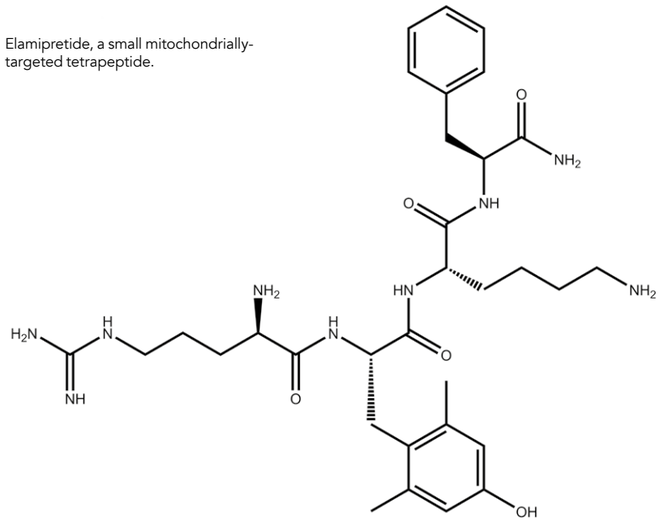
The failure of current medications to treat the underlying cause of the disease is well recognised, with most therapies only treating the symptoms. Over the last decade, Dr Hani N Sabbah, Professor of Medicine at Wayne State University and Professor of Medicine Research at Michigan State University, 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 fall 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.



Elamipretide, a small mitochondrially-targeted tetrapeptide.

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.

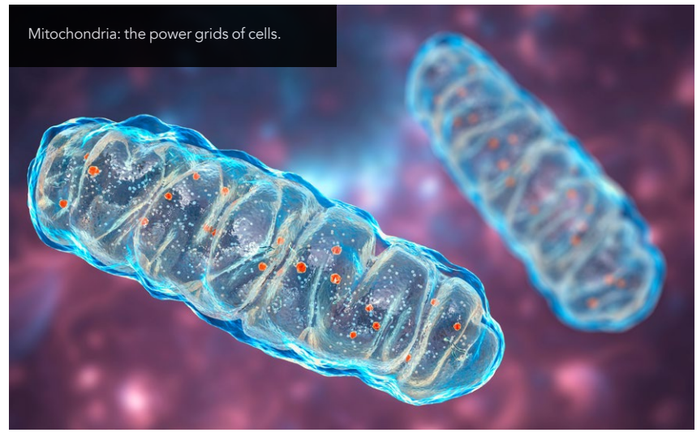
STABILISING EFFECTS OF ELAMIPRETIDE

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. The increase in ATP production helps match demand and has beneficial cellular effects, including normal gene and protein expression. Normal genes and proteins aid mitochondrial repair as well as enabling normal pathway signalling, returning the heart's muscle cells (cardiomyocytes) to a healthier state. Furthermore, elamipretide has also been shown to normalise calcium cycling in the sarcoplasmic reticulum (a structure in muscle cells) that lead to the poor left ventricular relaxation found in BTHS.

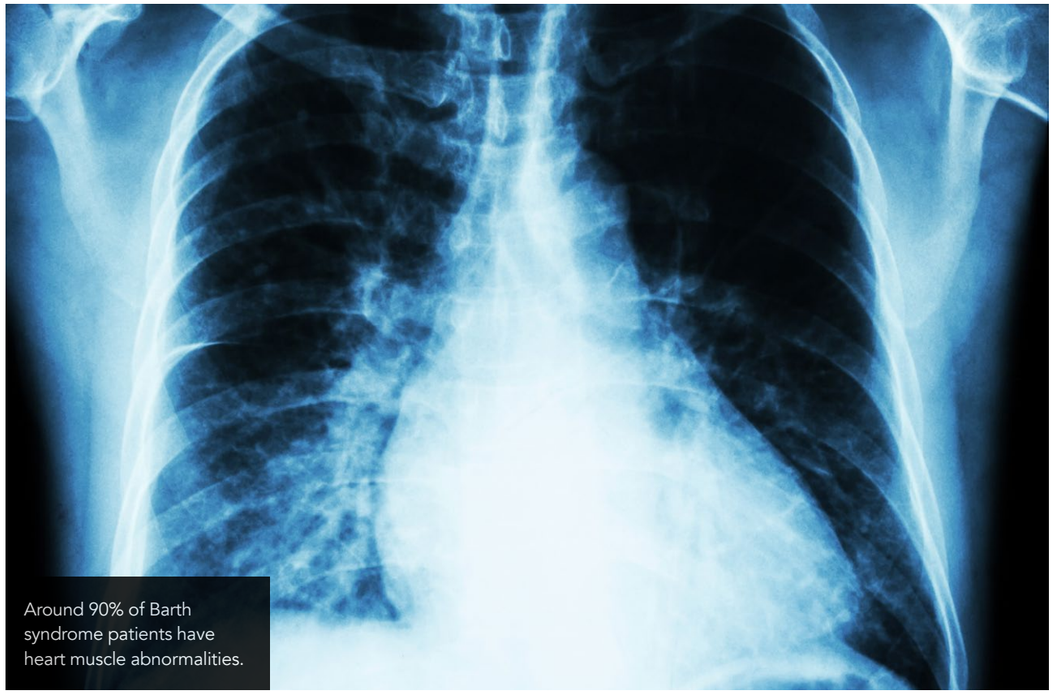
Sabbah and colleagues were the first to report the beneficial effects of long-term treatment with elamipretide in dogs with heart failure.

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. Furthermore, in a pig model of HFpEF, elamipretide improved left ventricular relaxation, 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.



Mitochondria: the power grids of cells.



Around 90% of Barth syndrome patients have heart muscle abnormalities.

THE TAZPOWER CLINICAL TRIAL

In a separate study, researchers at Johns Hopkins Hospital, Baltimore, USA, conducted a placebo-controlled clinical trial evaluating the safety, tolerability, and efficacy of elamipretide in children with BTHS. The first part of the trial evaluated the efficacy of elamipretide compared to the placebo. Although the drug was well tolerated, the researchers did not observe a statistical difference between patients who had received placebo versus those treated with elamipretide. In the second part of the trial, all participants were eligible to receive elamipretide. The study was recently completed and demonstrated improvements after 48 weeks of treatment in the distance patients could walk in six minutes, BTHS symptom scores, knee and muscle strength, and certain cardiac function factors. The authors suggest the delay in seeing improvements could be because cardiac and skeletal muscle take considerable time to structurally change following treatment. The animal study data and the significant findings from this clinical trial strengthen the case for using elamipretide in the treatment and management of BTHS patients. Pending adequate safety, the researchers are also contemplating assessing the effects of elamipretide in younger children with BTHS, as receiving the drug earlier could have more significant effects.

DURABILITY OF EFFECTIVENESS

Animal studies provide insight into the durability of elamipretide – how long it remains effective after stopping treatment. A canine study of chronic heart failure demonstrated improvements with elamipretide that lasted up to one week, and mice with left ventricular dysfunction showed improvements for up to two weeks. Considering this, Sabbah argues that the mitochondrial structural and functional improvements elicited by elamipretide are unlikely to be lost when the drug is withdrawn. Reviewing the evidence for the drug's potential in *Heart Failure Reviews*, Sabbah emphasises the unique ability of elamipretide to act at multiple levels (molecular, cellular, and global) to restore mitochondrial function and cellular health, and reverse the remodelling of heart tissue. With growing evidence supporting the use of elamipretide and recognition of the unmet clinical need for treatments in BTHS, the US Food and Drug Administration has granted what is known as 'fast track and orphan drug' designations for elamipretide, meaning it will expedite the movement of the drug into the public domain without the need for the usual volume of documentation, in recognition of the fact that therapies are so urgently needed for this very rare disease.

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

These significant developments bring hope that, one day soon, BTHS patients may have an effective therapy that treats the underlying causes of their disease.

Behind the Research

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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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Dr Hani N Sabbah is Director of Cardiovascular Research at Henry Ford Health, Professor of Medicine at Wayne State University in Detroit, Michigan, and Professor of Medicine Research at Michigan State University. He is a fellow of multiple societies including the American College of Cardiology, American College of Chest Physicians, American Heart Association, and the Heart Failure Society of America. Author of over 25 book chapters, 50 review articles, and over 450 original peer-reviewed articles, Dr Sabbah is also Co-Editor-in-Chief of the journal *Heart Failure Reviews*.

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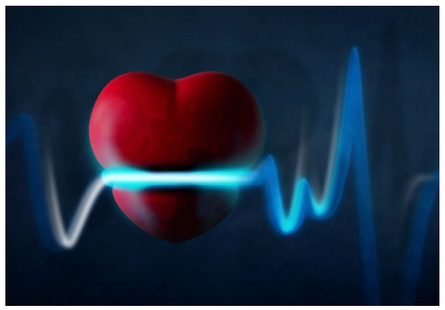

References

Sabbah, HN, (2022) Elamipretide for Barth syndrome cardiomyopathy: gradual rebuilding of a failed power grid. *Heart Failure Reviews*, 27, 1911–1923. doi.org/10.1007/s10741-021-10177-8

Sabbah, HN, (2020) Barth syndrome cardiomyopathy: targeting the mitochondria with elamipretide. *Heart Failure Reviews*, 26, 237–253. doi.org/10.1007/s10741-020-10031-3

Thompson, WR, Hornby B, Manuel, R, (2020) A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism. *Genetics in Medicine*, 23(3), 471–478. doi.org/10.1038/s41436-020-01006-8

Brown, DA, et al, (2017) Mitochondrial function as a therapeutic target in heart failure. *Nat Rev Cardiol*, 14(4), 238–250. doi.org/10.1038/nrcardio.2016.203

Sabbah, HN, et al, (2016) Chronic therapy with elamipretide (MTP-131), a novel mitochondria-targeting peptide, improves left ventricular and mitochondrial function in dogs with advanced heart failure. *Circ Heart Fail*, 9(2), e002206. doi.org/10.1161/CIRCHEARTFAILURE.115.002206

Clarke, SLN, et al, (2013) Barth syndrome. *Orphanet Journal of Rare Diseases*, 8(23), 1–17. doi.org/10.1186/1750-1172-8-23

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 extend 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."