



Stealth  
BIOTHERAPEUTICS

Leading  
Mitochondrial  
Medicine

## Company Background

Stealth BioTherapeutics is an innovative biopharmaceutical company developing therapies to treat mitochondrial dysfunction associated with genetic mitochondrial diseases and common diseases of aging, such as heart failure. Our team works with patients and advocacy organizations to better understand their journey and raise awareness of the unmet need our programs seek to address. We collaborate with top-tier academic and medical institutions, scientific thought leaders, and clinical

key opinion leaders in developing the first generation of targeted therapies focusing on mitochondrial dysfunction as it presents in rare genetic diseases and common diseases of aging, including cardiovascular disease. With these collaborative efforts, we continue to advance our platform of late-stage clinical programs and novel pipeline candidates.

Our lead compound, elamipretide, is currently in Phase 2 development for the treatment of patients with heart failure, where mitochondrial dysfunction is one of the main underlying causes. The current landscape in the management of these

patients is to treat the associated symptoms of heart failure; there are no FDA-approved therapies that fully address the pathology of disease. Our investigational drug, elamipretide, is formulated for systemic administration in this patient population, with the potential to modify disease through mitoprotection — the ability to preserve and restore normal energy production in mitochondria while decreasing oxidative stress.

We at Stealth BioTherapeutics are dedicated to supporting our lead investigational candidate by employing highly scientific methods to expand our clinical research program.

### Epidemiology of Heart Failure

In their 2016 statistical update, the American Heart Association reported that there were approximately 6.5 million US adults ( $\geq 18$  years of age) with heart failure, and the prevalence is projected to increase to more than 8.0 million adults by 2030. (Benjamin 2017) The total cost of heart failure in the US in 2012 was \$30.7 billion. (Benjamin 2017) By 2030, the total cost of heart failure in the US is projected to increase by 127%, to \$69.7 billion. (Benjamin 2017) Mortality and rehospitalization within 60–90 days after discharge from hospital can be as high as 15% and 35%, respectively. (Brown 2017) Approximately 40% of individuals with heart failure die within 5 years of diagnosis. Based on community trends, 960,000 new cases of heart failure occur each year, with an incidence approaching 21/1000 individuals older than 65 years of age.

### The Role of Mitochondrial Dysfunction in Heart Failure

It is well recognized that, in patients with heart failure, myocardial tissue does not have the energy resource to meet demand. (Bayeva 2013; Carelli 2013) Dysfunctional mitochondria are a key element in a variety of serious and debilitating diseases that are manifestations of mitochondrial dysfunction in heart failure, including myopathy, and kidney failure.

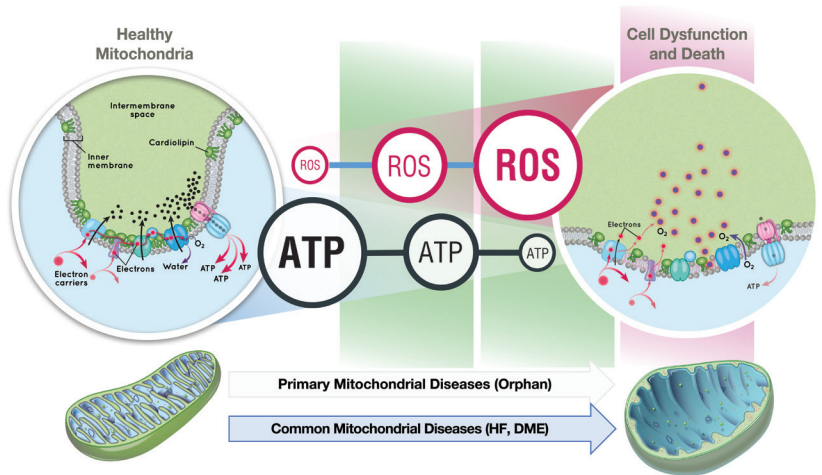
Evidence has shown that heart failure, a state of energy deficiency in the myocardium, is associated with decreased mitochondrial biogenesis and function in heart muscle and skeletal muscle, and impairment of bioenergetics is considered a primary factor in heart failure progression. (Rosca 2013) In the failing heart, dysfunctional mitochondria are thought to be a principal source of oxidative reactive oxygen species (ROS), which may lead to harmful effects and disrupt mitochondrial bioenergetics (Figure 1). (continued inside back cover)

Myocardial ATP must be synthesized and utilized to a degree that will continuously support optimal performance during periods of systolic and diastolic periods and sustain excitation-contraction coupling. (Rosca 2013) During maximal exercise, cardiac muscle uses 90% of its oxidative capacity, with 90% of this requirement being met by mitochondrial oxidative phosphorylation. In addition to cardiac muscle impairment, patients with heart failure also have skeletal muscle impairment, both of which are associated with a reduction in exercise capacity. However, the decrease in maximal exercise capacity is greater than predicted by indexes of left ventricular dysfunction because skeletal muscle myopathy becomes an independent phenomenon during heart failure.

Patients with heart failure can have preserved or reduced ejection fraction (systolic or diastolic heart failure, respectively), which respond differently to various classes of therapies. (Yancy 2013) The American Heart Association's 2016 statistical update reported that among hospitalized patients with heart failure events, the percentages of patients with either preserved or reduced ejection fraction were each approximately 50% (47% and 53%, respectively). (Benjamin 2017) When cases of hospitalized heart failure were stratified by demographics, the highest rate of cases with reduced ejection fraction occurred among black men (70%) and the highest rate of cases with preserved ejection fraction occurred among white woman (59%). (Benjamin 2017) Despite implementation of evidence-based optimal therapy for patients with heart failure, rates of rehospitalization within 90 days of discharge (35%) and death within 5 years of diagnosis (40%) remain high. (Yancy 2013; Brown 2017; Benjamin 2017)

Treatments for patients with heart failure that target intrinsic cardiac function may improve survival. Mitochondrial dysfunction is an important target in the development of therapy to directly improve cardiac function in patients with heart failure with either preserved (HFpEF), or reduced ejection fraction (HFrEF). (Brown 2017) Impaired or decreased mitochondrial capacity and function in heart failure to generate and transfer energy within heart cells results in energy deficits, most notably the processes of contraction and relaxation. The high mitochondrial content of cardiomyocytes is not only needed to meet the enormous energy requirement for contraction, but for the active process of relaxation. About 90% of cellular ATP is utilized to support the contraction-relaxation cycle within the myocardium which is evidenced in patients with HFpEF. (Brown 2017)

Figure 1. The role of mitochondria in disease.



## Evidence That Elamipretide Restores Mitochondrial Bioenergetics

Elamipretide's unique mechanism of action made it a candidate for further evaluation in preclinical models of heart failure. A study that used a dog model of advanced heart failure showed that long-term therapy with elamipretide improved left ventricular systolic function, normalized plasma biomarkers, and reversed mitochondrial abnormalities in the left ventricular myocardium. (Sabbah 2016) In this study, young healthy dogs failed to show the changes in mitochondrial morphology, mitochondrial proteome, respiration, ATP synthesis or ROS production that were shown in older dogs with heart failure after receiving elamipretide.

Promising efficacy in preclinical trials led to the clinical development of elamipretide in heart failure (**Figure 3**). Phase 1 results showed that elamipretide had the potential to augment cardiac function in patients with heart failure and reduced ejection fraction. (Daubert 2016) Results of this trial also established the safety of elamipretide with no serious adverse events being reported. Phase 2 trials evaluating elamipretide efficacy and safety either in patients with heart failure and reduced ejection fraction (NCT02788747) or patients hospitalized with congestive heart failure (NCT02914665) are currently ongoing. In addition, a phase 3 trial that will assess efficacy and safety of elamipretide in patients hospitalized with acute heart failure is in the planning stages of development.

Figure 2. Proposed role of Elamipretide in Dysfunctional Mitochondria.

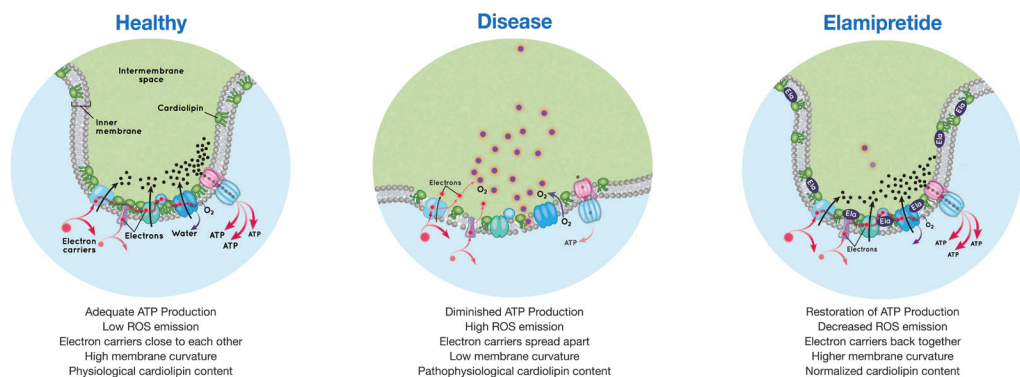
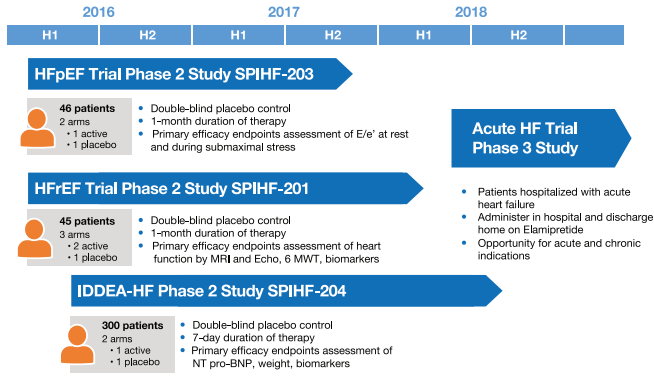


Figure 3. Elamipretide's heart failure program.



Heart failure is a complex condition that is associated with skeletal muscle and renal dysfunction, both of which may be improved with elamipretide treatment. Study results showed that elamipretide reversed mitochondrial dysfunction and oxygen demand, and improved sustained exercise performance in the muscle of healthy elderly subjects with evidence of mitochondrial dysfunction.(Conley 2016) When compared with placebo, elamipretide increased ATP<sub>max</sub> at 2 hours after treatment ( $P=0.055$ ; **Figure 4**). Results of a phase 2a pilot study showed that patients with atherosclerotic renal artery stenosis who received elamipretide (versus placebo) before and during stent revascularization had an attenuation of the renal hypoxia that developed 24 hours after contrast imaging and the procedure (**Figure 5**). (Saad 2017) Patients who received elamipretide also had increased renal blood flow, cortical perfusion, and estimated glomerular filtration rate when measured after 3 months ( $P<0.05$ , all endpoints versus placebo). Results of these studies indicate that elamipretide, through its unique mechanism of action, may improve skeletal muscle and renal dysfunction in patients with heart failure.

Figure 4. Elamipretide improved mitochondrial function, thereby increasing ATP production.

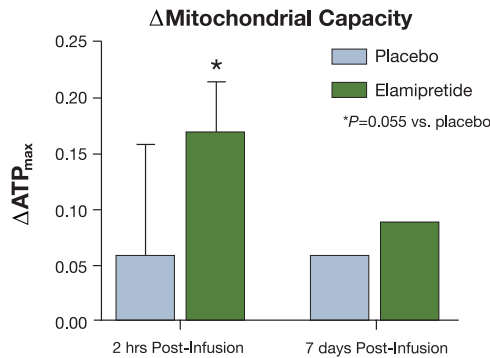
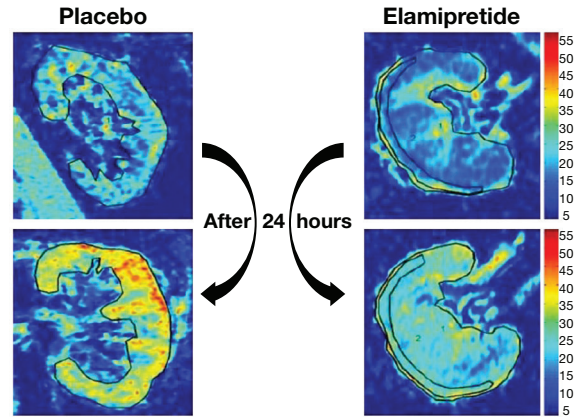


Figure 5. Elamipretide attenuated renal hypoxia 24 hours after contrast imaging and percutaneous transluminal renal angioplasty. (Saad 2017)



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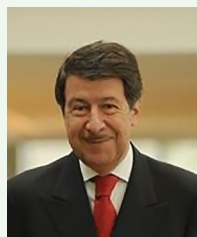
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**In Memoriam: Mihai Gheorghiad, MD**

We at Stealth BioTherapeutics were saddened to hear of the recent passing of our respected friend and collaborator, Dr. Mihai Gheorghiad. Dr. Gheorghiad will be remembered for his tremendous contributions to the medical community investigating the treatment of patients with cardiovascular disease and heart failure. We at Stealth specifically appreciate his most recent effort shepherding the Nature Reviews Cardiology consensus paper on heart failure that was published earlier this year. His insights as a thought leader and contributor to our work at Stealth were also tremendously appreciated. Dr. Gheorghiad's passion for his work, and compassion for others, will be missed by all who knew him. Our thoughts and prayers go out to his family and friends, and the worldwide community of his colleagues.