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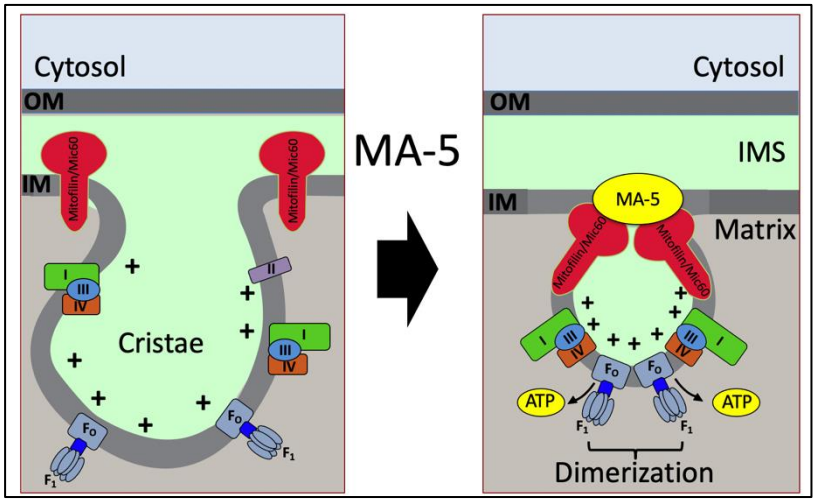
National University Corporation Tohoku University
Japan Agency for Medical Research and Development

A novel therapeutic drug, World's first, from Japan: First step to overcoming mitochondrial disease
MA-5, the Mitochondrial Disease Drug, Begins Clinical Trials in Healthy Adult Subjects.

Key points of the research
- MA-5 is an innovative mitochondrial disease therapeutic candidate compound developed by the principal investigator, whose efficacy has been confirmed in the cells of patients with mitochondrial disease and animal models of the disease.
- With the support of the AMED Moonshot Project, we will start a clinical trial in which MA-5 will be administered orally to 56 healthy adult subjects.
- The purpose of this clinical trial is to confirm the safety and pharmacokinetics of MA-5 in healthy adult subjects.

Research Outline
Mitochondrial disease [Note 1]. is a rare disorder that causes damage to mitochondria, the energy-producing factories in cells, resulting in decreased energy production (ATP [Note 2.]) in the neuromuscular, cardiovascular, metabolic, renal-urinary, hematological, visual, endocrine, and digestive systems. At present, however, there is no treatment other than taurine that has been proven to be effective in a rigorous clinical trial. The principal investigator, Professor Takaaki Abe, has developed Mitochonic acid-5 (MA-5), a novel compound for mitochondrial diseases with a completely new mechanism different from existing drugs. MA-5 inhibits cell death in cultured cells derived from patients with mitochondrial disease. Moreover, it improved cardiac and renal respiratory function and increased survival rates in mitochondrial disease mouse models.
By accelerating ATPase dimerization through binding with mitofilin/Mic60.



The principal investigator's group with the support of AMED Moonshot Research and Development Project [Note 3.] will conduct a Phase I clinical trial from January 2022 to confirm the safety of MA-5, which is expected to be the world's first mitochondrial disease treatment from Japan, in healthy adult subjects. This study will confirm whether MA-5 can be safely administered to humans (safety), how the human body absorbs MA-5, how it is transported in the blood, and metabolized (pharmacokinetics).

Upon completing this study, we plan to conduct a phase II clinical trial in which MA-5 will be administered to actual patients. This clinical trial of MA-5 is expected to lead to the inhibition of the progression and treatment of mitochondrial diseases, which are rare and intractable diseases for which there is currently no effective treatment, and in the future, MA-5 is expected to be helpful in the prevention and treatment of diseases such as deafness, sarcopenia, ALS, and Parkinson's disease, which are also caused by reduced mitochondrial function.

Research Contents

Mitochondria are cellular organelles that can be called energy-producing factories within cells, and they produce about 96% of the energy (ATP) necessary to maintain vital activities. It has been shown that when mitochondria function abnormally, ATP production declines, resulting in systemic organ damage, the so-called mitochondrial disease. Mitochondrial diseases have been treated by taking vitamin supplements. However, the organ damage caused by mitochondrial disease is progressive, and there is no effective treatment, and early development of a therapeutic approach has been desired.

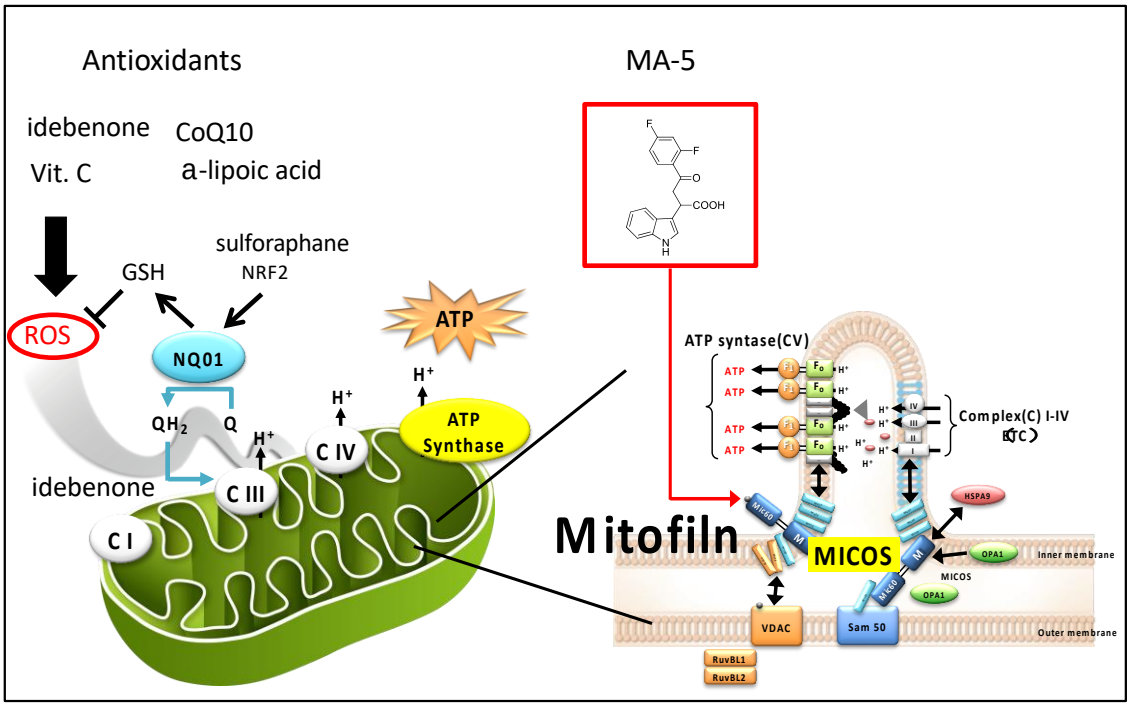
A group led by Professor Takaaki Abe at Tohoku University Graduate School of Medicine and Graduate School of Biomedical Engineering has discovered that the blood of kidney disease patients contains indole compounds that increase ATP production. They screened a library of compound derivatives and discovered a new compound, MA-5, which binds to mitofilin [Note 4.], an essential protein that maintains the internal structure of mitochondria (Cristae [Note 5.]) and forms a complex with ATP synthase to increase the efficiency of ATP production. The compound seems to have a new mechanism of ATP synthesis.

Their previous studies found that MA-5 has a protective effect against oxidative stress-induced cell death in 24 (96.6%) of 25 dermal fibroblasts derived from mitochondrial disease patients with various genetic backgrounds and that it is effective regardless of which part of the electron transfer system is impaired. It has also been shown to improve heart and kidney respiration and increase the survival rate of a mouse model of mitochondrial disease (Mito-mouse), which has an abnormal mitochondrial gene.

As shown above, the efficacy of MA-5 has been demonstrated in cultured skin cells of mitochondrial disease patients and animal models, but its effects in humans are not yet known. It

is also unclear how MA-5 is absorbed and metabolized in the human body and affects various organs when administered orally. Therefore, we have decided to start a phase I clinical trial of MA-5 with Professor Takaaki Abe as the principal investigator. In this study, 56 healthy males ranging in ages from 20 to 45 years old will be given different doses of MA-5 during the study period to investigate how much MA-5 is absorbed by the human body and how it appears in the bloodstream, and to confirm the safety of MA-5 administration through physiological and blood tests. In addition, we are planning to conduct a study to confirm the safety of MA-5 administration through physiological and blood tests.

If the safety and pharmacokinetics of MA-5 in humans are confirmed through this research, the next step will be to conduct Phase II clinical trials to administer MA-5 to patients as a treatment for mitochondrial diseases. Suppose the safety and pharmacokinetics of MA-5 are confirmed in humans through this research. In that case, it is expected that MA-5 will be used as a therapeutic agent for mitochondrial diseases and other diseases such as deafness, sarcopenia, ALS, and Parkinson's disease, which are caused by mitochondrial dysfunction. In addition, this research



will significantly contribute to the Moonshot-type research and development project, which aims to "detect aging and frailty at an early stage and achieve a healthy society with longevity through intervention and treatment without burdens.

Please note that Tohoku University and Tohoku University Hospital are not recruiting study participants (adult healthy subjects) for this clinical trial.

Support: This research will be supported by the AMED Moonshot Research and Development

Project and the Center for the Promotion of Clinical Research at Tohoku University Hospital (CRIETO).
The mechanism of action for MA-5. MA-5 facilitates the ATP production of mitochondria by binding to the mitofilin localized in the inner membrane of mitochondria.

Explanation of terms
Note 1. Mitochondrial disease: A disease caused by abnormal function of mitochondria, which produce about 95% of ATP, the energy necessary for life. Since mitochondria are present in all nucleated cells, disorders such as neuropathy, cardiomyopathy, renal failure, and diabetes mellitus can occur in any organ of the body, including the brain, heart, kidneys, and pancreas.
Note 2. ATP (adenosine triphosphate): A chemical substance that is used as energy in the body. It is synthesized by an enzyme in the mitochondria.
Note 3: AMED Moonshot-type research and development project: A project to promote challenging research and development based on bold ideas that are not extensions of conventional technologies to create disruptive innovations originating in Japan. AMED is working on research and development to achieve Moonshot Goal 7: "By 2040, prevent and overcome major diseases and realize sustainable medical and nursing care so that people can enjoy life without health concerns until the age of 100."
Note 4: Mitofilin: A protein found in the cristae structure of the mitochondrial inner membrane. It plays an essential role in maintaining the cristae structure.
Note 5: Cristae: A folding structure in the inner mitochondrial membrane. It forms characteristic folds to increase the surface area of the inner mitochondrial membrane for chemical reactions to occur.

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