

FOR IMMEDIATE RELEASE

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Nagasaki University (Japan)

neopharma Japan Co., Ltd.

5-ALA Shows Results in Improving Glucose Tolerance in Patients with Mitochondrial Diabetes

～Potential Candidate for Future Development as Therapeutic Agent～

National University Corporation, Nagasaki University^{*1} (hereinafter referred to as ‘Nagasaki University’), in association with neopharma Japan Co., Ltd.^{*2} (hereinafter referred to as ‘NPJ’), today announced that they have confirmed the efficacy of 5-aminolevulinic acid ^{*3} (hereinafter referred to as ‘5-ALA’) and sodium ferrous citrate (‘SFC’) in improving glucose tolerance in patients with mitochondrial diabetes^{*4} (aka. ‘Maternally Inherited Diabetes and Deafness’, hereinafter referred to as ‘MIDD’), a disease characterized by impaired insulin secretion due to impaired mitochondrial ATP production. Based on these results, we would like to report that a new and effective adjunctive treatment for MIDD has possibly been discovered.

This research was published in the international journal ‘Diabetes Therapy’ on November 22nd, 2022 (JST).

[URL]

<https://link.springer.com/article/10.1007/s13300-022-01335-8>

[Research Topics]

- Maternally Inherited Diabetes and Deafness (MIDD) is estimated to be present in approximately 1% of diabetic patients in Japan.
- We investigated the efficacy of 5-ALA/SFC as an adjunctive treatment to insulin injections for patients with MIDD.
- After 24 weeks of 5-ALA/SFC administration, we carried out a glucose tolerance test on the patients and obtained the following results.
 - A significant decrease in blood glucose levels was observed.
 - A tendency for insulin secretion levels to increase was observed.

- The mean level of glycated hemoglobin (HbA1c), while not changing significantly, was confirmed to have decreased from $8.3 \pm 1.2\%$ at baseline to $7.9 \pm 0.3\%$ after 24 weeks.
- We thus believe that following further research, 5-ALA/SFC may be a novel and effective adjunctive treatment for MIDD.

[Outline]

Maternally Inherited Diabetes and Deafness (MIDD) is a form of diabetes caused by mutations in mitochondrial genes, characterized by hearing loss and ultimately requiring treatment via frequent insulin injections. Meanwhile, 5-aLA is a naturally occurring amino acid that has already been used in various healthcare products for more than 10 years. By focusing on 5-ALA's functional properties, Nagasaki University has been diligently working on the development of therapeutic agents*5 for use against COVID-19 and malaria. Furthermore, as 5-ALA improves mitochondrial function when administered in combination with sodium ferrous citrate (SFC), we decided to conduct a preliminary study and investigate its efficacy as an adjunctive therapy to insulin injections in patients with MIDD.

The results of this study showed a significant decrease in the late phase of glucose excursion (AUC60-120 min); a tendency towards increased insulin secretion (AUC0-120 min); and a trend towards decreased HbA1c levels detected in glucose tolerance tests after 24 weeks of 5-ALA/SFC administration. Thus, we believe that further studies can clarify and demonstrate the potential efficacy of 5-ALA/SFC administration as a new and effective adjunctive therapy for MIDD.

[Paper Title & Authors]

Title:

Pilot Trial on the Effect of 5-Aminolevulinic Acid on Glucose Tolerance in Patients with Maternally Inherited Diabetes and Deafness

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[Glossary]

***1 Nagasaki University**

Nagasaki University is a national university established in 1949. The campus was relocated and integrated in the 1950s and 1960s, and the medical faculties and research institutes (such as the School of Medicine, the School of Dentistry, the Nagasaki University Hospital, and the Institute of Tropical Disease) are now found on the Sakamoto Campus. Nagasaki University has an outstanding track record in the fields of tropical medicine, infectious diseases, and radiological science due to its geographical and historical background, and with its abundant accumulation of research and an unrivaled team of infectious disease researchers, it has become a well-known educational and research base for those studying virulent diseases in Japan and abroad.

<http://www.nagasaki-u.ac.jp/>

***2 neopharma Japan Co., Ltd.**

neopharma Japan Co., Ltd is a pharmaceutical company specializing in the research, development, and commercialization of 5-aminolevulinic acid (5-ALA), a natural amino acid. Our Company aims to capitalize on the utility of 5-ALA, which has been confirmed through many years' worth of research on plants, animals, and humans, in a variety of applications in numerous fields. We are also the only company in the world with facilities capable of 5-ALA mass-production, and we produce the raw materials for 5-ALA foodstuffs under the same

quality control as we do for our pharmaceutical products. neopharma Japan is committed to contributing to global healthcare through 5-ALA.

<https://www.neopharmajp.co.jp/>

*3 5-Aminolevulinic Acid (5-ALA)

Human, animals, and plants all maintain their vital functions by producing energy within the organelles called mitochondria inside their cells. 5-aminolevulinic acid (5-ALA) plays an especially significant role in ensuring the functionality of these mitochondria. It is a very safe amino acid that has been used in health foods, cosmetics, pet supplements, animal feed and fertilizers for over a decade. In addition, 5-ALA is known to improve mitochondrial function, and a phase 3 physician-led clinical trial for mitochondrial disease is underway, led by Saitama Medical University.

<http://5ala-journal.com/>

*4 Mitochondrial Diabetes

Mitochondria play an essential role in energy production and other intracellular processes. They are known to have their own DNA (mitochondrial DNA), with diabetic conditions caused by mutations in mitochondrial DNA often referred to as mitochondrial diabetes. Despite being overlooked often, mitochondrial diabetes is believed to be present in approximately 1% of diabetes patients in Japan, making it the single more common form of monogenic diabetes. Furthermore, mitochondrial DNA is prone to acquiring mutations (somatic changes), which can accumulate with age and impair mitochondrial functionality. There are several types of mitochondrial diabetes, including Type 1 diabetes, SPIDDM, and Type 2 diabetes. Symptoms are characterized by a high rate of sensorineural hearing loss (approx. 90%). Symptoms of cardiomyopathy, cardiac stimulation conduction defects and encephalomyopathy have also been observed to occur at higher rates than other types of diabetes.

*5 Published by Nagasaki University on April 13th, 2022

This press release was titled '*Confirmation of Inhibitory Effects of 5-Aminolevulinic Acid (5-ALA) Against Novel Coronavirus (COVID-19) Omicron Strain Infections*'. Previous studies at Nagasaki University had demonstrated that, above a certain concentration in cultured cells, 5-ALA can completely inhibit infections by SARS-CoV-2 (the causative virus of COVID-19) as well



as its four mutant strains, including the delta strain. Similarly, in this study, 5-ALA was shown to inhibit infection by the Omicron strain in cell-based tests.

<https://www.nagasaki-u.ac.jp/ja/science/science266.html>

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