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SBI Pharmaceuticals Co., Ltd

Tokyo Metropolitan University

**Publication of a Research Paper on 5-ALA from Tokyo Metropolitan University  
in *Human Molecular Genetics*  
- 5-ALA+SFC might improve symptoms of Electron Transfer Complex I deficiency -**

SBI Pharmaceuticals Co., Ltd., (Head office: Minato-ku, Tokyo; Representative Director & President: Yoshitaka Kitao; “SBI Pharmaceuticals”), a subsidiary of SBI Holdings, Inc., engaged in research and development of medical devices and pharmaceuticals using 5-aminolevulinic acid (5-ALA) \*, and Tokyo Metropolitan University (Hachioji City, Tokyo; President: Takaya Ohashi) hereby announce the publication of a research article entitled “5-Aminolevulinic acid bypasses mitochondrial complex I deficiency and corrects physiological dysfunctions in *Drosophila*” in an international academic journal, *Human Molecular Genetics*. The paper presents the findings of the joint research group led by Associate Professor Kanae Ando of Tokyo Metropolitan University (corresponding author) and Dr. Naoko Nozawa (first author) of the Kawasaki Research Institute of SBI Pharmaceuticals.

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| Journal  | : | <i>Human Molecular Genetics</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Title    | : | 5-Aminolevulinic acid bypasses mitochondrial complex I deficiency and corrects physiological dysfunctions in <i>Drosophila</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| URL      | : | <a href="https://academic.oup.com/hmg/advance-article/doi/10.1093/hmg/ddad092/7207871">https://academic.oup.com/hmg/advance-article/doi/10.1093/hmg/ddad092/7207871</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Abstract | : | Complex I (CI) deficiency in mitochondrial oxidative phosphorylation (OXPHOS) is the most common cause of mitochondrial diseases. While CI provides the most electrons to OXPHOS, complex II (CII) is another entry point of electrons. Enhancement of this pathway may compensate for a loss of CI. 5-Aminolevulinic acid (5-ALA) is a crucial precursor of heme, which is essential for CII, complex III, complex IV (CIV), and cytochrome c activities. We examined the possibility of compensating for the CI deficiency. Here, we show that feeding a combination of 5-ALA hydrochloride and sodium ferrous citrate (5-ALA-HCl+SFC) increases ATP production and suppresses defective phenotypes in <i>Drosophila</i> with CI deficiency. Knockdown of <i>sicily</i> , a <i>Drosophila</i> homolog of the critical CI assembly protein <i>NDUFAF6</i> , caused CI deficiency, accumulation of lactate and pyruvate, and detrimental phenotypes such as abnormal neuromuscular junction development, locomotor dysfunctions, and premature death. 5-ALA-HCl+SFC feeding increased ATP levels without recovery of CI activity. The activities of CII and CIV were |

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|  | upregulated, and the accumulation of lactate and pyruvate was suppressed. 5-ALA-HCl+SFC feeding improved neuromuscular junction development and locomotor functions in <i>sicily</i> -knockdown flies. These results suggest that 5-ALA-HCl +SFC shifts metabolic programs to cope with CI deficiency. |
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(\*) 5-aminolevulinic acid: An amino acid produced in mitochondria. It is an important substance that serves as a functional molecule related to energy production in the form of heme and cytochromes, and its productivity is known to decrease with age. 5-aminolevulinic acid is contained in food such as shochu lees, red wine, and Asian ginseng. It is also known as a material forming chloroplasts in plants.

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