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SBI Holdings, Inc.

SBI Pharmaceuticals Co., Ltd.

Osaka City University

**Presentation of Research Paper on 5-ALA by Osaka City University  
to PLOS ONE, a U.S. Scientific Journal  
— Findings of ALA-PDT in killing MRSA, one of the major bacterial species causing  
in-hospital infections —**

SBI Pharmaceuticals Co., Ltd. (Head office: Minato-ku, Tokyo; Representative Director and CEO: Yoshitaka Kitao; “SBI Pharmaceuticals”), a subsidiary of SBI Holdings, Inc. (Head office: Minato-ku, Tokyo; Representative Director and CEO: Yoshitaka Kitao) engaging in research and development of pharmaceuticals, health foods and cosmetics using 5-aminolevulinic acid (“5-ALA”) (\*1) and Osaka City University (Campus: Osaka-shi, Osaka; President: Dr. Yoshiki Nishizawa) are carrying out joint research. They are pleased to inform you that a group led by Assistant Professor Toshiyuki Ozawa, Department of Dermatology, Graduate School of Medicine, Osaka City University, published a research paper “Photodynamic therapy using systemic administration of 5-aminolevulinic acid and 410nm wavelength light emitting diode for methicillin-resistant Staphylococcus aureus-infected ulcers in mice” in PLOS ONE, a U.S. scientific journal, as follows.

Journal carrying the paper:	<u>PLOS ONE</u>
Title:	Photodynamic therapy using systemic administration of 5-aminolevulinic acid and 410nm wavelength light emitting diode for methicillin-resistant Staphylococcus aureus-infected ulcers in mice
URL:	<a href="http://dx.plos.org/10.1371/journal.pone.0105173">http://dx.plos.org/10.1371/journal.pone.0105173</a>
Summary:	<p>The emergence of antibiotic resistant strains of bacteria has become a global issue. One of the treatments used to fight against these resistant strains is photodynamic therapy (*2). 5-ALA is a natural precursor (*3) of protoporphyrin IX, which is a photosensitizer. There have been a small number of reports that 5-ALA shows a photodynamic effect in experiments using methicillin-resistant Staphylococcus aureus (MRSA) (*4). However, for the first time in the world, photodynamic therapy using systemic administration of 5-ALA for infected animals showed a therapeutic effect on resistant strains.</p> <p>The study evaluated the therapeutic effect of 5-ALA and a 410nm wavelength light emitting diode (LED) on MRSA. As a result, the study</p>

	<p>discovered that photodynamic therapy using 5-ALA and an LED has an extremely high therapeutic effect on MRSA in experiments using both animals and cells. In addition, photodynamic therapy using 5-ALA improved wounds on the surface of ulcers and dramatically reduced the number of bacteria. Meanwhile, treatment using the antibiotic vancomycin (*5) did not improve wounds.</p> <p>The study indicates that photodynamic therapy using 5-ALA will lead to a new treatment on MRSA-infected wounds.</p>
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Based on the results of the study, the researchers confirmed that photodynamic therapy using 5-ALA and a 410nm wavelength light emitting diode (LED) is a new antibiotic-free treatment for MRSA infections that are becoming increasingly prevalent in hospitals. In addition, the study indicated that 5-ALA was metabolized to and stored as protoporphyrin IX within MRSA, where active oxygen was generated by a 410nm wavelength LED which killed MRSA through cell damage. While the existence of a wide variety of MRSA types has been confirmed, photodynamic therapy using 5-ALA and a 410nm wavelength LED is believed to be effective for all of these MRSA strains. Therefore, the findings have expanded the possibility of ALA-PDT research in the future.

\*1: 5-aminolevulinic acid (5-ALA):

An amino acid created in mitochondria. It is an important substance that serves as protein material related to energy production in the form of heme and cytochromes, and its productivity is known to decrease with age. 5-ALA is contained in food such as shochu distillation remnants and red wine. It is also known as a material forming chloroplasts in plants.

\*2: Photodynamic therapy is a method to kill lesions of cancer, infections, and other diseases with active oxygen that is generated by ingesting 5-ALA and irradiating it with a certain range of wavelength.

\*3: Precursor is a substance from which another substance is formed by a chemical reaction.

\*4: Methicillin-resistant Staphylococcus aureus (MRSA) is staphylococcus aureus showing multidrug resistance to a large number of medical agents such as penicillin including methicillin, beta-lactam antibiotic, aminoglycoside antibiotics, and macrolide antibiotics. It occurs as an opportunistic infection in post-surgery patients, immune compromised persons, and patients with long-term antibiotics, causing intestinal inflammation, blood poisoning, pneumonia, and other diseases with symptoms such as sudden high fever, low blood pressure, abdominal bloating, diarrhea, disturbed consciousness, leucopenia, thrombocytopenia, kidney dysfunction, and liver dysfunction.

\*5: Vancomycin was once famous as an antibiotic capable of killing methicillin-resistant Staphylococcus aureus (MRSA). However, MRSA showing resistance to vancomycin has emerged in recent years. Therefore, no effective treatment has been established.

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