January 22, 2025

To Shareholders,

Company Name: Renascience Inc.
Representative: Keisuke Furuta, President & CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Opening of the laboratory of the Potocsnak Longevity Institute of Northwestern University at the Tohoku University Renascience Open Innovation Lab (TREx)

We are pleased to announce that we have concluded a joint research agreement on aging with Prof. Douglas E. Vaughan, Director of the Potocsnak Longevity Institute at Northwestern University (Chicago, USA), and have agreed to open its branch at the Tohoku University Renascience Open Innovation Lab (TREx), our open innovation hub within Tohoku University.

Developed countries, including Japan, are facing an ultra-aging population, and aging is an urgent issue not only medically but also socially. We aim to clarify cellular senescence[1)] at the molecular level, develop new medicines to treat diseases associated with tissue and individual aging[2)], and ultimately contribute to medical innovation to improve human aging. For many years, we have been conducting pre-clinical studies in animals and epidemiological surveys of long-lived families[3)] in collaboration with Professor Douglas E. Vaughan, Northwestern University.

The Potocsnak Longevity Institute at Northwestern University
(https://www.feinberg.northwestern.edu/sites/longevity/centers/human-longevity-lab.html)
is working to accurately measure human biological age and conduct clinical trials to evaluate pharmaceuticals that may slow the aging process. We have reached an agreement with Douglas E. Vaughan, Director of the Potocsnak Longevity Institute at Northwestern University, to establish a Japanese laboratory at the Tohoku University RenaScience Open Innovation Lab (TREx), an open innovation hub within the Tohoku University.

The TREx-Longevity Lab will conduct multidimensional phenotyping to measure the biological age of Japanese people, aging analysis of human organs (cardiovascular, respiratory, neurocognitive, metabolic, musculoskeletal), and cutting-edge molecular profiling of aging biomarkers (epigenome, proteome, transcriptome), and will enroll a cross-sectional cohort of individuals from many ethnic and socioeconomic backgrounds across multiple countries, including the United States and Japan. In addition, we plan to conduct clinical trials to evaluate our pharmaceutical product that may control

aging (RS5614).

In January 2022, we opened TREx at the Tohoku University Graduate School of Medicine (Medicinal Hub, 2-1 Seiryo-cho, Aoba-ku, Sendai, Miyagi Prefecture, Faculty of Medicine Building No. 5) in the belief that a place is needed to utilize cutting-edge scientific and technological achievements in many disease areas, a place for face-to-face interaction with doctors and researchers, and a place for open innovation with government and medical industry companies. In addition, in April 2023, we signed a comprehensive collaboration agreement with Hiroshima University and opened the Hiroshima University Renascience Open Innovation Lab (HiREx) as one of the domestic bases for investigator-initiated clinical trials. The Japanese Laboratory of the Potocsnak Longevity Institute at Northwestern University (TREx-Longevity Lab) will be established as a research base for creating medical innovations to improve aging, an important medical issue that we have set forth, and for developing anti-aging medicine.

At this time, there is no particular impact on our performance due to this matter.

[1)] Cell Senescence

Cells in living organisms cannot proliferate indefinitely due to a phenomenon called cellular senescence. This phenomenon involves shortening of gene telomere length and cellular senescence factors such as p53. It has been found that senescent cells have extremely high expression of plasminogen activator inhibitor (PAI)-1 in addition to p53. It has been revealed that the phenomenon of cellular senescence can be inhibited by suppressing p53 and PAI-1.

[1)] Tissue and individual aging

It has been reported that PAI-1 expression is high not only in cells but also in aged tissues and individuals (mice and humans). In a joint study conducted by our company, Tohoku University, and Northwestern University in the United States, the main symptoms of aging could be improved in klotho mice, a well-known aging model, by inhibiting the expression and activity of PAI-1 at the gene or protein level (Proc Natl Acad Sci USA. 2014).

[3)] Epidemiological study of longevity families

We have been conducting joint research with Northwestern University School of Medicine and have elucidated the influence of PAI-1 on aging (Science Advances. 2017). We tested the blood of Amish people and confirmed that some people were missing the PAI-1 gene. We noted that these people who lacked the PAI-1 gene had a longer lifespan (1- years) than other Amish people who had the same gene. This epidemiological study in humans is consistent with the results of experiments in cells and mice.

This news was featured in an article in the New York Times on November 21, 2017.

[4] Medicine that may control aging

As we age, various related diseases develop, such as cancer, blood vessels (arteriosclerosis), lungs (emphysema, chronic obstructive pulmonary disease), metabolism (diabetes, obesity), kidneys (chronic kidney disease), bones and joints (osteoporosis, osteoarthritis), and brain (cerebrovascular disease, Alzheimer's disease, dementia). Interestingly, PAI-1 expressions are extremely high in the tissues of these diseases, and joint researches with many universities both in Japan and overseas have revealed that the administration of our PAI-1 inhibitors improve their pathologies. Furthermore, in the aging model klotho mice, the administration of a PAI-1 inhibitor improves various symptoms of aging (Proc Natl Acad Sci USA. 2014).

Pre-clinical studies on age-related disorders (published with our PAI-1 inhibitors)

Diseases	literature
Cancer (chronic myeloid leukemia)	☐ Blood 2012 ☐ Stem Cells. 2014 ☐ Blood. 2017 ☐ Biochem Biophys Res Commun. 2019 ☐ Haematologica 2021 ☐ BBRC 2021 ☐ Tohoku J Exp Med. 2022 ☐ Cancer Med. 2023
Cancer (malignant melanoma)	☐ PLoS One. 2015 ☐ Cancer Biol Ther. 2015
Lung (emphysema, COPD)	☐ Arterioscler Thromb Vasc Biol 2008 ☐ Am J Respir Cell Mol Biol 2012 ☐ Proc Natl Acad Sci USA. 2014 ☐ PLos One 2015 ☐ Am J Physiol Lung Cell Mol Physiol 2016 ☐ Am J Respir Cell Mol Bio 2020 ☐ Environ Pollut 2021

Diseases	literature
Cardiovascular	☐ Circulation. 2013 ☐ Oncotarget. 2016 ☐ Science Advances. 2017
Metabolism (diabetes, obecity)	☐ Br J Pharmacol 2016 ☐ Oncotarget 2017 ☐ Hepatol Commun 2018 ☐ Front Pharmacol 2020 ☐ Mol Med Rep 2020 ☐ Science Reports 2021 ☐ Obesity 2021
Bone and joint (osteoporosis, osteoarthritis)	☐ FEBS Open Bio 2018 ☐ BBRC 2021
Brain (Alzheimer's disease and multiple sclerosis)	☐ PLoS One 2015 ☐ J Alzheimers Dis 2018
Kidney (CKD)	☐ Arterioscler Thromb Vasc Biol. 2013 ☐ PLos One 2016