May 13, 2025

To Shareholders,

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Announcement of winning the TOP40 (semi-finalists) and receiving the prize money in the global longevity competition XPRIZE Healthspan

XPRIZE Healthspan is a global competition hosted by the XPrize Foundation[1)] that aims to revolutionize therapeutic approaches to human longevity and tackle the challenging task of actively extending healthy lifespan by 10 years or more. The XPrize Foundation will pay a total of US$100 million to the research team that can extend healthy lifespan by 2030. We applied to this global competition, and we are pleased to announce that we have won the TOP40 (semi-finalists) and received the prize money of US$250,000.

The XPRIZE Foundation is a non-profit private foundation in the United States, and Elon Musk and others are among its sponsors. The foundation has held several competitions with prize money aimed at developing technologies that benefit humanity and solving global challenges, such as the world's first private lunar exploration and a competition for carbon dioxide (CO2) capture and storage technology.

XPRIZE Healthspan （https://www.xprize.org/prizes/healthspan）is a new competition that aims to revolutionize therapeutic approaches to human longevity and actively extend healthy lifespan by 10 years or more. The XPrize Foundation will pay a total of US$100 million to the research team that can extend healthy lifespan by 2030.

More than 600 pre-entries and More than 200 written applications were submitted from around the world, and various modalities were proposed as therapeutic approaches to human longevity, including small molecule drugs, biopharmaceuticals (vaccines, immunomodulators, monoclonal antibodies, and recombinant protein therapeutics), gene therapy, cell therapy, medical devices (medical treatment devices, game-based devices, digital health devices), electrical medical devices, magnetic medical devices, supplements, functional foods, dietary therapy, exercise therapy, and their combinations. Based on the anti-aging effects[2)] of the plasminogen activator inhibitor (PAI)-1 inhibitor RS5614, which we have been working on for many years, we applied to this XPRIZE Healthspan at the end of

last year in collaboration with domestic and international universities and research institutes and medical institutions, including Tohoku University, Northwestern University, Hiroshima University, Tokai University, and Institute of Science Tokyo, with the concept of "a new small molecule senolytic drug[3)] that removes senescent cells and suppresses aging-related diseases without promoting cancer."

At the XPRIZE Healthspan award ceremony held in New York, USA on May 12-14, 2025, we were selected as one of the TOP40 (semi-finalists) and received a prize of US$250,000. Semi-finalists will conduct a semi-final clinical trial[4)] within one year by the end of March 2026 and submit a report on the results to the XPRIZE Healthspan Evaluation Committee. Based on the results of this semi-final clinical study, the TOP10 (finalists) will be selected in the second half of 2026 (awarded US$1 million) and will conduct a four-year final clinical study[5)] for the final competition. The most outstanding research team among the TOP10 teams that conduct the final clinical study will be awarded a prize based on the number of years of lifespan extended (up to a maximum of US$81 million).

XPRIZE Healthspans Schedule

May 12, 2025: Announcement of semi-finalists (40 teams, $250,000 prize money)
August 1, 2025 - March 2026: Semi-final clinical trials
End of March 2026: Submission of semi-final clinical trial report
July - September 2026: Announcement of finalists (10 teams, $1 million prize money)
October 2026 - December 2029: Final clinical trials
February 2030: Submission of final clinical trial report
December 2030: Grand prize winner announcement

We are working towards the goal of "creating new medical treatments that allow people to enjoy lifelong health, both physically and mentally," and developing treatments for aging-related diseases is an important research and business issue for our company. In developed countries, including Japan, the super-aging society is progressing, and the difference between average life expectancy and healthy life expectancy (the period during which a person can live independently in both body and mind, minus the period of nursing care such as being bedridden or suffering from dementia) of about 10 years is a major issue. If various diseases that occur with aging, such as cancer, cardiovascular disease, respiratory disease, and diabetes, can be treated, it can lead to an extension of healthy life expectancy. These four diseases account for 70-80 % of the world's deaths, and are positioned by the World Health Organization (WHO) as important diseases associated with aging and lifestyle habits. We are working to solve the medical and socially important issue of developing medicines to extend healthy life expectancy, including medicines to treat these four diseases, and we would like the potential of the medicine we are developing to be evaluated in this global longevity competition, XPRIZE Healthspan.

At present, RS5614 is being developed as a medical drug for humans (a drug used based on a doctor's diagnosis or prescription), so clinical trials are being conducted to determine its suitability for treating individual diseases such as cancer. On the other hand, longevity is difficult to verify through clinical trials, so it is not eligible for medical drugs. On the other hand, longevity and anti-aging are important themes in the self-medication field, which is growing rapidly against the backdrop of the super-aging population, OTC drugs[6], and even the veterinary medicine market. There is also an example of RS5441 being used as a treatment for alopecia, and if our research into the anti-aging or longevity of PAI-1 inhibitors progresses further, we would like to consider applications other than medical drugs.

As for the impact on our performance, we expect to record the prize money of US$250,000 as non-operating income for the fiscal year ending March 2026.

[1] XPrize Foundation
A foundation sponsored by Elon Musk and others that holds various global challenge competitions with the mission of stimulating the creation of new industries and revitalizing markets by bringing fundamental breakthroughs for humanity.

[2] Anti-aging effects of PAI-1 inhibitor RS5614
We have been researching aging for many years, and through joint research with Northwestern University in the United States, we have revealed the following series of scientific facts suggesting that our PAI-1 inhibitor RS5614 may improve aging symptoms and lead to longevity in cells and aging mice.

• Cells in living organisms cannot proliferate indefinitely due to a phenomenon called cellular senescence[7]. This phenomenon involves shortening of gene telomere[8] length and cellular aging factors such as p53, p21, and p16ink4a. It has been found that aged cells have extremely high expression of PAI-1. The PAI-1 inhibitor developed by our company improves senescence biomarkers[9] and inhibits cellular senescence in cardiomyocytes, fibroblasts, and vascular endothelial cells (Oncotarget, 2016).

• The PAI-1 inhibitor developed by our company was found to reduce DNA damage in fibroblasts of Hutchinson-Gilford syndrome[10] (designated intractable disease 333), a human premature aging disease, improve mitochondrial disorders, and correct cellular abnormalities in Hutchinson-Gilford syndrome (Cell Death and Disease, 2022).

• It is known that PAI-1 expression is high not only in cells but also in aged tissues and individuals (mice and humans). In a non-clinical study using klotho mice[11], a well-known aging model, it was found that the PAI-1 inhibitor improved the main symptoms of aging in klotho mice (Proc Natl Acad Sci USA. 2014). We tested the blood of the Amish[12] living in the United States, confirmed that many of them were deficient in the PAI-1 gene, and reported that these PAI-1 gene deficient individuals lived about 10 years longer than those with the same gene (Science Advances, 2017). This human epidemiological study is consistent with the results of experiments on cells and mice. This fact was introduced in an article in the New York Times on November 21, 2017 (November 11, 2021). Furthermore, it was recently shown that mice with the same PAI-1 gene mutation as Amish humans have a lifespan that is about 20% longer than normal mice.

• PAI-1 expression is extremely high in organs with age-related diseases such as cancer, blood vessels (arteriosclerosis), lungs (emphysema, chronic obstructive pulmonary disease), metabolism (diabetes, obesity), kidneys (chronic kidney disease), bones and muscles (osteoporosis, sarcopenia), and the brain (cerebrovascular disease, Alzheimer's disease, dementia), and joint research with many universities in Japan and abroad has revealed that administering our PAI-1 inhibitors can improve the pathology (see figure below).

Preclinical studies using PAI-1 inhibitors developed by our company

疾患	文献
chronic myelogeneous 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
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

疾患	文献
cardiovascular (atherosclerosis)	☐ Circulation. 2013 ☐ Oncotarget. 2016 ☐ Science Advances. 2017
metabolic disease (diabetes mellitus、obesity)	☐ Br J Pharmacol 2016 ☐ Oncotarget 2017 ☐ Hepatol Commun 2018 ☐ Front Pharmacol 2020 ☐ Mol Med Rep 2020 ☐ Science Reports 2021 ☐ Obesity 2021
osteoporosis sarcopenia	☐ FEBS Open Bio 2018 ☐ BBRC 2021
brain (Alzheimer's disease)	☐ PLoS One 2015 ☐ J Alzheimers Dis 2018 ☐ Psycopharmacology (Berl) 2023
kidney (CKD)	☐ Arterioscler Thromb Vasc Biol. 2013 ☐ PLos One 2016

[3)]Senolytic drug

Senolytic drug is a drug that suppresses aging-related diseases without promoting carcinogenesis. The word is a combination of senescence and lytics.

[4)]Semi-final clinical trial of the XPRIZE Healthspan

A clinical study that evaluates the effects of short-term therapeutic intervention over 1-2 months on a small number of patients (up to 20 people) aged 50 or older. In addition to the effectiveness of the intervention, safety and subject protection measures, approval by the Certified Review Board (CRB), feasibility of patient registration, and ability to collect, manage, and submit data are evaluated comprehensively.

[5)]Final clinical trial of the XPRIZE Healthspan

A crossover clinical study that evaluates the effects of therapeutic intervention over a period of 4 years on approximately 100 people (up to 200 people) aged 50 or older. Compared to the control group, the intervention group must demonstrate at least 10 years of functional improvement in all three evaluation functions (muscles, cognition, and immunity).

[6)]OTC drugs

These are not "medical drugs" that are prescribed by a doctor, but "prescription drugs" and "general use drugs" that can be purchased without a prescription at pharmacies and drugstores. Prescription drugs are OTC drugs that have first appeared on the market and need to be sold carefully, so pharmacists are required to explain the drug (it is difficult to sell it on the Internet, etc.). OTC drugs other than prescription drugs are called general use drugs (depending on the classification, a pharmacist's explanation is required).

[7)]Cellular senescence

The cells of living organisms cannot proliferate indefinitely due to a phenomenon called cellular senescence. This phenomenon involves the shortening of the telomere length of genes and cellular senescence factors such as p539). It has been found that senescent cells have extremely high expression of 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.

[8)]Telomere

Telomeres are structures at the ends of chromosomes and are known to shorten with each cell division. Telomere length is closely related to cell lifespan and aging, and maintaining telomere length plays an important role in health and the prevention of age-related diseases.

[9)]Senescence biomarkers

As biomarkers for senescent cells, cell cycle regulators (p16ink4a, p21, p53, p16, IGFPB3), senescence-associated β-galactosidase (SA-β-gal) staining, senescence-associated secretory phenotype (SASP) such as interleukins such as IL-6, and DNA damage response are analyzed.

Overseas researches have reported that the PAI-1 inhibitor developed by our company improves these aging biomarkers (Oncotarget 2016, Cell Death and Disease 2022).

[10)]Hutchinson-Gilford syndrome

This disease was named after Jonathan Hutchinson in 1886 and Hasting Gilford in 1897. It is one of the most severe hereditary progerias, and severe vascular disorders of the brain and heart due to arteriosclerosis often occur in the teens, with an average lifespan of 14.6 years.

[11)]klotho mice

Genetically modified mice with reduced or missing expression of the anti-aging gene klotho show aging phenomena similar to human progeria.

[12)]Amish

A group living in the Midwestern United States, who maintain the lifestyle they had at the time of their immigration and live a self-sufficient life through farming and livestock farming.