With you CellSeed Vol.15

CellSeed
Regenerate the Future

CellSeed Inc.

Securities Code: 7776

Greetings

Thank you for your continued support.
In 2022, although economic activity gradually began to recover to the level prior to COVID-19, many changes occurred such as the price increases for daily commodities and food items due to the sharp decline in the yen and soring raw material prices, as well as instability overseas.

Updates on the regenerative medicine support business

In October 2022, our Cell Cultureware business have launched two new products as part of the new lineup of the UpCell® series: the flask type, UpCell® Flask and the cell culture insert-type, UpCell® Insert. Recently, there has been an increasing need for mass cell recovery not only for cell-sheet production but also for cell therapy and cultivated meat, and the UpCell® Flasks are expected to meet this need. We are focusing on the development of products that enable the recovery of cells in higher amount of cells without damage.
In December, UpCell® ADVANCE was registered to the Master File for Devices (MAF) of the FDA (The United States Food and Drug Administration). UpCell® ADVANCE cleared various quality control items for development of regenerative medicine and cell therapy products, and its high quality is assured.
Hereafter, pharmaceutical companies will no longer be required to submit information to us when submitting applications to the FDA for regenerative medicine products using UpCell® ADVANCE, but will be able to receive review based on the information registered in MAF.
Therefore, the MAF registration is expected to contribute to the increasing use of UpCell® ADVANCE and the development of regenerative medicine products.

Updates on the regenerative medicine business

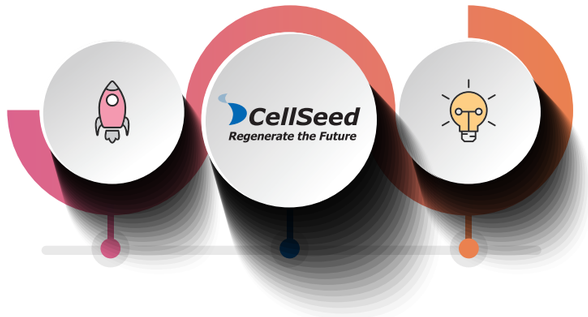
As the development of allogeneic chondrocyte sheets is being carried out with the aim of acquiring marketing approval under the Act on Pharmaceuticals and Medical Devices (the “PMD Act”), we continued to consult with the Pharmaceuticals and Medical Devices Agency (PMDA) with the aim of submitting the clinical trial application. Unfortunately, we were not able to submit the application by the end of December 2022, which was our initial target date. However, we are preparing for the start of the clinical trial in 2023.
The provision of cartilage tissues collected from patients with polydactyly which are approved for commercial use started in 2021 from the National Center for Child Health and Development, and in 2022, we constructed a system for constantly receiving the tissues suited to a wider industrial use. We established the master cell bank for clinical trials for which the safety and efficacy were confirmed.
In December 2022, we held a public symposium jointly with Tokai University on allogeneic chondrocyte sheets titled “Let’s learn and talk about the future of cartilage regenerative medicine – The frontline of clinical research for the treatment of knee osteoarthritis using cell sheets –.”
During the symposium, patients who received a transplant of allogeneic chondrocyte sheets in the clinical research conducted at Tokai University shared their valuable experience. We realized that allogeneic chondrocyte sheets are a beneficial treatment for patients, and we reconfirmed our determination to accelerate the development process to enable the use of allogeneic chondrocyte sheets by patients as soon as possible.

Future overview

To deliver treatments based on Japan-originated cell sheet engineering worldwide, we will make persistent efforts to commercialize products of cell sheet regenerative medicine. At the 22nd Congress of the Japanese Society for Regenerative Medicine held in March 2023, which was held face-to-face for the first time in four years, we made an oral presentation about the development of allogeneic chondrocytes sheets, as well as a poster presentation on cultureware that uses a temperature-responsive polymer. At the exhibition booth, we introduced our new UpCell® series products and our contract manufacturing services. We will continue to actively promote our research and development activities.
We sincerely ask the readers for your continued support.

Mission

We will take the initiative of contributing to global health care in the valuable and innovative field of regenerative medicine.



Vision

We will establish a cell sheet business platform and provide excellent regenerative medicine products around the world.

2001
CellSeed founded

2004
Sales of *RepCell*® and *HydroCell*® launched

2007
- Sales of *UpCell*® launched
- Clinical trial on epithelial cell sheets for corneal regeneration initiated in France

2010
Listing on JASDAQ NEO

2014
Setsuko Hashimoto appointed as Representative Board Director and President/CEO (to present)

2015
CellSeed Sweden AB, a subsidiary in Sweden, established

2016
- Head office relocation to the Telecom Center Building
- Cell Processing Center established
- Clinical trial on esophageal epithelial cell sheets for regeneration initiated

2017
- Approval to manufacture specified cell processing products acquired
- Cell sheets for the esophagus and autologous chondrocyte sheets licensed-out to MetaTech

2018
Start of regenerative medicine contract services

2019
The 1st Cell Sheet Engineering Innovation Forum held

2020
Up Cell Biomedical Co., a joint venture in Taiwan, established

2021
- 20th anniversary of the foundation of CellSeed
- Aomi Cell Cultureware Innovation Center newly established
- The 2nd Cell Sheet Engineering Innovation Forum held

2022
- New products in the *UpCell*® series launched
- Public symposium held

2001 2004 2007 2010 2014 2015 2016 2017 2018 2019 2020 2021 2022

Cell Cultureware

By using the temperature-responsive cell cultureware developed by Professor Teruo Okano of Tokyo Women's Medical University in 1989, it is possible to recover cells by lowering the temperature.
Following the launch of RepCell® in 2004, we continue to provide UpCell® in 2007 and cell-culture related products that we develop to researchers worldwide for more than 20 years.
The use of UpCell® enables the damage-free recovery and use of cells while maintaining all the original functions and components of the cells.
Today, UpCell® is actively used in the development of products for regenerative medicine and cell therapy and is attracting attention for its new possibilities in new applications.

Our cell culture-related products

1

UpCell®

UpCell® is a cell culture device that enables cell recovery only by temperature change without damaging cells.
Cells recovered using UpCell retain their original physiological activity and cell surface proteins without digestion.

2

RepCell®

RepCell® has the same performance and features as the UpCell®, and has a unique surface "grid-wall" structure that enables single-cell and small cell-sheet recovery.

3

HydroCell®

HydroCell® has a super hydrophilic polymer fixed on it based on our unique nano-surface processing technology.
HydroCell® is useful for spheroid formation of iPS cells and cancer cells.

4

cellZscope®

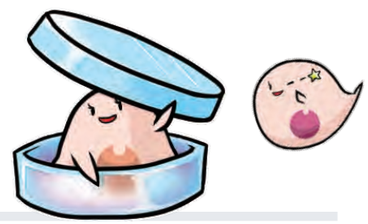
cellZscope evaluates the barrier function of tight junctions in an in vitro environment.
cellZscope enables highly reproducible measurements for toxicity and ADME evaluation of candidate compounds for pharmaceuticals and cosmetics.

5

ThermoPlate®|||

ThermoPlate® is a transparent heating element made of hard glass. By placing UpCell® or RepCell® on this product, microscopic observation and medium exchange are possible while maintaining constant temperature of the dishes and plates.

In our cell cultureware business, we have been developing various cell culture-related products. Here, we would like to introduce the UpCell® lineup.
UpCell® has been sold in dish and plate types since 2007 and has been used by many researchers in Japan and overseas mainly for cell sheet production..
Recently, the use of UpCell® for the purpose of mass culture of cells has been rapidly expanding mainly overseas, therefore we launched UpCell® Flask in October 2022.
In order to meet this new demand, we are focusing on the development of products that enable the damage-free harvest of even high amounts of cells.



Introduction of the UpCell® series products

UpCell® dish and plate type products

We supply dish and plate type UpCell® products in various sizes, which are used by many researchers around the world for basic research into regenerative medicine using cell sheets.
We also supply high-detachment and low-detachment types.

UpCell® Insert type products

UpCell® Insert can recover cell-sheets productedin a co-culture system that more highly mimics the in vivo environment that is possible with existing UpCell® products.

UpCell® Flask type products

UpCell® Flasks can collect high amounts of cells in an area up to three times larger than that of UpCell® 10cm dishes. This product is designed for mass culture of cells required for cell therapies using Macrophages, MSC, and other cells.

UpCell® ADVANCE [*1]

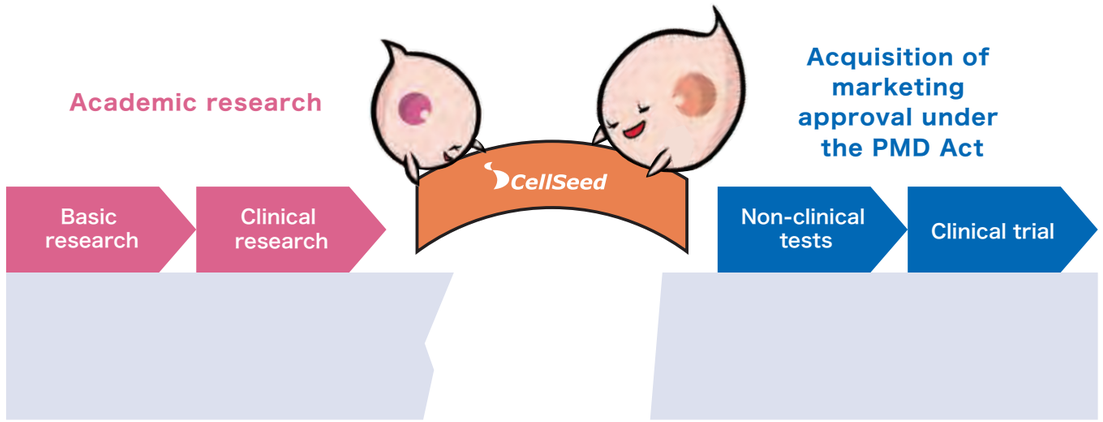
UpCell® ADVANCE has passed many quality control requirements as a product for developing regenerative medicine and cell therapy products. And it is currently used for several regenerative medicine products in Japan.
In December 2022, UpCell® ADVANCE was registered with the Master File for Devices (MAF)[*2, *3] of the US FDA.

*1 : UpCell® ADVANCE is provided with safety test data for each production lot and is different from cataloged UpCell® products, which are intended for research use only.
*2 : MAF is a system in which the supplier registers with FDA the corporate data, manufacturing know-how, other company secrets, and other data in advance as MAF. This enables pharmaceutical and medical device manufacturers to file applications for marketing approval with FDA just by citing the MAF number.
*3 : The completion of the MAF registration does not mean the completion of quality and safety confirmation or assessment by the FDA.

Regenerative Medicine Contract Services

CellSeed's Cell Processing Center acquired an approval to manufacture specified cell processing products in March 2017, followed by the approval to manufacture regenerative medicine products in October 2018. We are currently providing various contract services. We will continue to provide safe, high-quality products and services with our experienced staff members.

Solve the issues and gaps faced by our clients



There are two laws concerning regenerative medicine in Japan: the Act on the Safety of Regenerative Medicine (the "Safety Act"), which regulates regenerative medicine conducted under the responsibility of physicians, and the Act on Pharmaceuticals and Medical Devices (the "PMD Act"), which regulates manufacturing and sales by companies of the products, to approve as a "regenerative medicine product." The clinical research conducted by a university or research institute is regulated by the Safety Act. On the other hand, physician-initiated clinical trials and sponsor-initiated clinical trials are regulated by the PMD Act. As a result, our clients often face issues and gaps. CellSeed will solve these issues and gaps through our experience in developing regenerative medicine products and providing contract services.

Track record of our contract services

*Only the services that can be disclosed

- Contract manufacturing of autologous chondrocyte sheets for the Advanced Medical Care B program conducted by Tokai University
- Contract manufacturing of autologous epithelial cell sheets for a clinical research on regenerative medicine in pediatric patients undergoing congenital esophageal atresia surgery
- Contract manufacturing of allogenic periodontal ligament cell sheets prepared from periodontal ligament-derived mesenchymal stromal cells for an physician-initiated clinical trial
- Assist in preparing documents related to the regenerative medicine provision plan
- Cell sheet culturing and harvesting training

Details of the contract services

1 Development of manufacturing methods and contract manufacturing for cell sheet products

- Development of cell sheet manufacturing methods (optimization)
- Contract manufacturing of cell sheet products
- Quality testing of cell sheets, etc.

2 Facility management and application support

- Support for preparing and submitting applications
- Support for document preparation/consulting
- Support for operation and maintenance of facilities equipment/management system, etc.

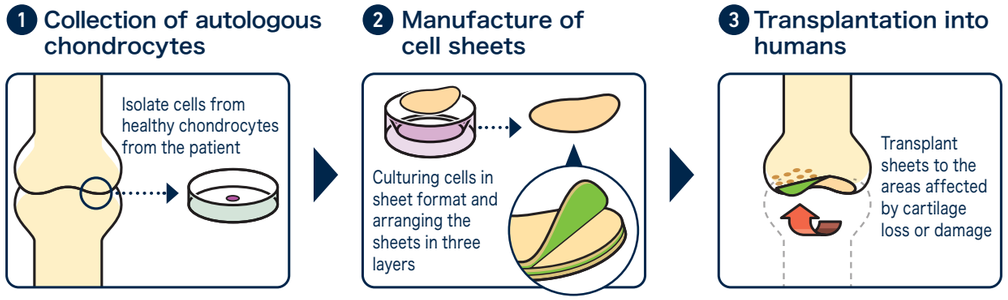
3 Cell culturing technicians

- Training of cell sheet culturing
- Training of cell sheet harvesting, etc.

Examples of contract services

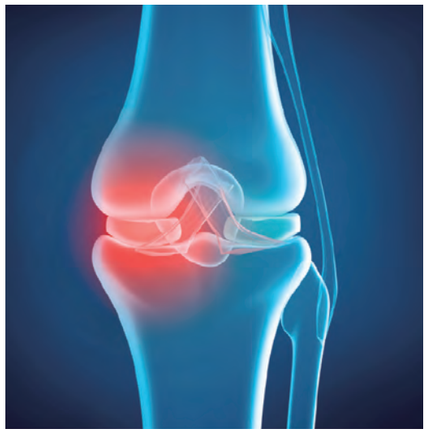
Autologous chondrocyte sheets

Professor Masato Sato of Tokai University developed chondrocyte sheets with the aim of providing definitive care for knee osteoarthritis. Tokai University is currently conducting therapy using autologous chondrocyte sheets as the Advanced Medical Care B program, and we are conducting the contract manufacturing of the autologous chondrocyte sheets.



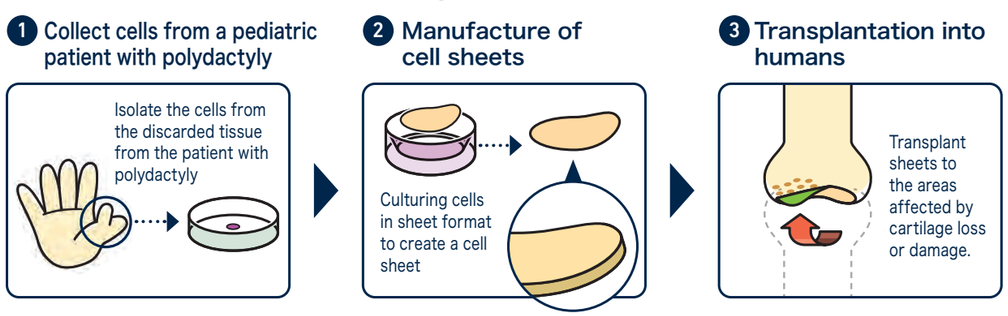
See here for more information about the Advanced Medical Care B program conducted by Tokai University

Allogeneic Chondrocyte Sheets



Knee osteoarthritis is a slowly progressive, intractable degeneration of articular cartilage for which no fundamental medical therapy has been established. It is estimated that approximately 30 million people potentially have knee osteoarthritis in Japan, out of which approximately 10 million people are symptomatic. The prevalence rate is higher in elderly people, and women suffer from this condition 1.5 to 2 times more likely than men. As the number of patients is expected to increase due to the aging of society, knee osteoarthritis is definitely a pressing matter to be resolved in terms of the national healthy life expectancy, nursing care, and medical costs. We are working to realize practical applications of the chondrocyte sheet therapy developed by Professor Masato Sato at Tokai University. We collect chondrocytes from the tissue removed in surgery from patients with polydactyly to create cell stocks. We are aiming to provide definitive care for knee osteoarthritis by transplanting the allogeneic chondrocyte sheets created from the cell stocks to the knees with decreased cartilage.

Treatment method



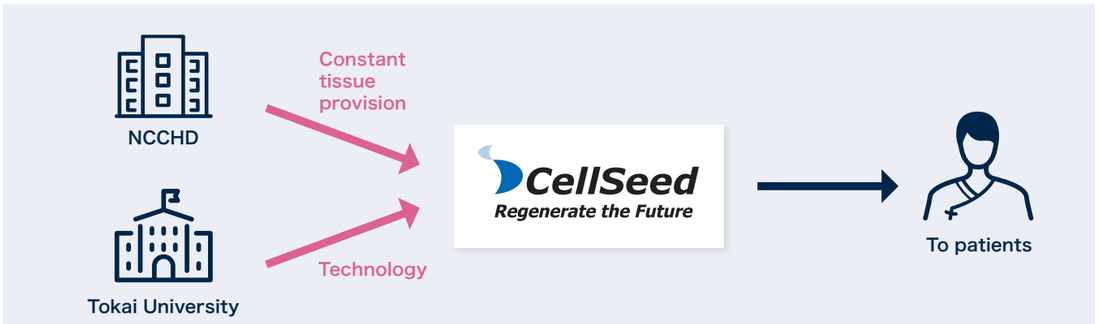
Updates on allogeneic chondrocyte sheets

2017 - 2019	Transplant surgery on 10 patients were performed as a part of a clinical research at Tokai University.
2018 - 2021	CellSeed was awarded research fund of AMED project :“Establishment of manufacturing procedures for the Product development of allogenic chondrocyte cell sheets (CLS2901C),”
2021 -	Provision of commercial-use tissue from the National Center for Child Health and Development (NCCHD) started.
2021 - 2023	CellSeed was awarded research fund of AMED project : “Research and development for starting the clinical trial by industry, including the establishment of a cell bank for the commercialization of an allogeneic chondrocyte sheet (CLS2901C).”
2023	Start of clinical trial (plan)

In the clinical research (10 cases from 2017-2020) conducted by Tokai University on the allogeneic chondrocyte sheets, no safety related problems were found, and improvement in the clinical results were observed in all patients, including their symptoms. With these results, the effectiveness of the allogeneic chondrocyte sheets was confirmed, and the results were publicized in the “npj Regenerative Medicine,” a sister journal of Nature.

- Journal：npj Regenerative Medicine (online)
- Title：Polydactyly-derived allogeneic chondrocyte cell-sheet transplantation with high tibial osteotomy as regenerative therapy for knee osteoarthritis
- DOI：https://doi.org/10.1038/s41536-022-00272-1

Based on these results, we are carrying out development with the aim of acquiring a marketing approval as a regenerative medicine product.



Held a public symposium titled “Let’s learn and talk about the future of cartilage regenerative medicine – The frontline of clinical research for the treatment of knee osteoarthritis using cell sheets –.”

In December 2022, we held a public symposium jointly with Tokai University on allogeneic chondrocyte sheets. Because the respective AMED projects at CellSeed and Tokai University entered the final year, we reported on the results and interviewed the patients who received allogeneic chondrocyte sheet transplants in the clinical research conducted by Tokai University. In the interviews, we were able to hear experiences that can only be shared by patients who have actually received an allogeneic chondrocyte sheet transplant.
We realized that allogeneic chondrocyte sheets are a beneficial treatment for patients, and we reconfirmed our determination to accelerate the development process to enable the use of allogeneic chondrocyte sheets by patients as soon as possible.
A video summary of the symposium is available on YouTube. Please take the time to watch it.

See the digest version here.

CellSeed's Regenerative Medicine

CellSeed is working to commercialize regenerative medicine products based on regenerative medicine seeds developed by universities utilizing "cell sheet engineering," including the chondrocyte sheets developed by Tokai University.
In 2022, Professor Masato Sato was appointed as a scientific advisor. Since then, he has been providing us with advices on our development of regenerative medicine from the standpoint of a physician and researcher.

Progress on CellSeed's pipelines

The act on the safety of regenerative medicine (the "Safety Act")
- Clinical research
- Advanced medical care
- Medical treatment at one's own expense

The regenerative medicine promotion act

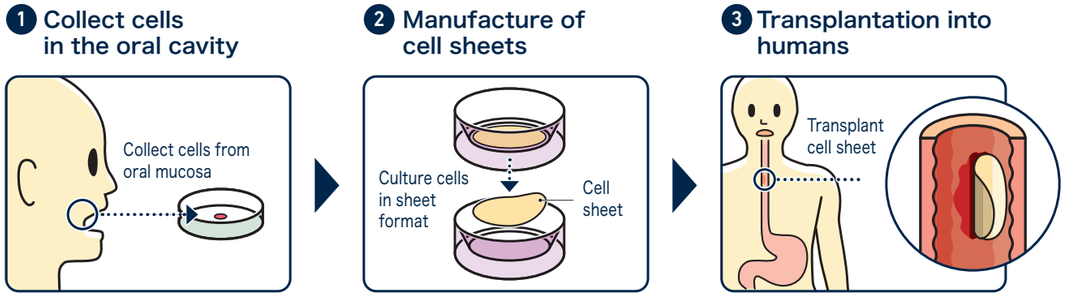
The act on pharmaceuticals and medical devices (the "PMD Act")
- Manufacture and sales

Pipelines	Basic research	Clinical research	Clinical trial			Application and approval	Sales
			Phase I	Phase II	Phase III		
Epithelial cell sheet for esophageal regeneration	A clinical trial is currently conducted under the PMD Act*						
Allogeneic chondrocyte sheets	Conducted basic and clinical research at Tokai University						
	A clinical trial is currently in preparation pursuant to the PMD Act.						

*The Safety Act: The Act on the Safety of Regenerative Medicine. An act to restrict regenerative medicine that is performed under the responsibility of a physician, and applicable to clinical studies conducted at universities and advanced medical care, etc.
*The PMD Act: The Act on Pharmaceuticals and Medical Devices. An act under which, if corporates and other organizations intend to obtain approval for a product, the manufacturing, sales, and approval of the product should comply with this act.

Epithelial cell sheets for esophageal regeneration

In Japan, over 90% of patients with esophageal cancer are given a diagnosis of squamous cell carcinoma, and their five-year relative survival rate is under 50% in both men and women—41% in men and 46% in women. While more endoscopic submucosal dissection (ESD) is performed as a treatment method, this sometimes causes the adverse effect of postoperative esophageal stenosis. Epithelial cell sheets for esophageal regeneration are cell sheets used as a treatment method that was developed at Tokyo Women's Medical University for preventing esophageal stenosis.



CellSeed Management Team / Financial Condition

Management team of CellSeed

Representative Board Director and President/CEO
Setsuko Hashimoto

Outside Director/Audit and Supervisory Committee Member
Toshio Yamaguchi

Outside Director/Audit and Supervisory Committee Member
Kenji Oeda

Outside Director/Audit and Supervisory Committee Member
Yukiko Endo

Financial statements

■ Financial results for December 2022

Sales ····· 126 million yen
Operating income ····· -743 million yen
Ordinary income ····· -754 million yen
Earnings per share ····· -36.31 yen

■ Financial forecast for December 2023

Sales ····· 200 million yen
Operating income ····· -840 million yen
Ordinary income ····· -840 million yen

(Note: Fractions smaller than 1 million are rounded off)

■ Point

In the regenerative medicine support business, we launched UpCell® Flask that can be sold in new markets in the cell cultureware business in order to respond mainly to the overseas demand for the mass culture of cells. In the regenerative medicine contract services, we continuously provide contract manufacture services of autologous chondrocyte sheets in the Advanced Medical Care B program for Tokai University from last year, and recorded sales of three cases a year.
In the cell sheet regenerative medicine business, we are carrying out the development of allogeneic chondrocyte sheets with support from AMED, and plan to start a clinical trial in 2023. Also, we are working to conclude business tie-ups and joint development agreements with multiple companies.

Stock information

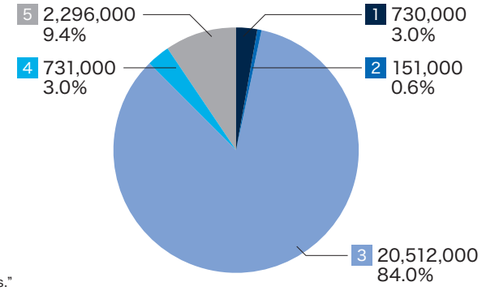
As of December 31, 2022

Total no. of issuable shares ···· 35,537,600
Total no. of issued shares ····· 24,422,619
No. of shareholders ····· 14,842
No. of shares constituting one unit ···· 100

Stock distribution by owner

1 Foreign corporations, etc.
2 Financial institutions
3 Individuals and others
4 Other corporations
5 Financial instrument brokers

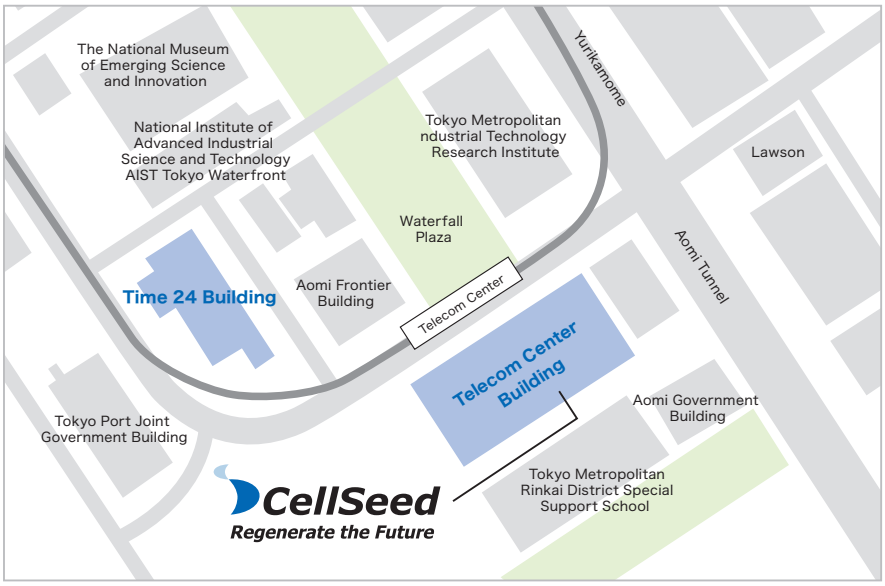
Note: Treasury stock (154 shares) is included in "Individuals and others."



Corporate Overview

As of March 28, 2023

Company name	CellSeed Inc.
Main businesses	Cell sheet regenerative medicine business Regenerative medicine support business
Head office	Telecom Center Building, East Tower 15F Aomi 2-5-10, Koto-ku, Tokyo, Japan
Date established	May 2001
Fiscal year end	December
Affiliated company	Up Cell Biomedical Co.
R&D	Cell Processing Center Telecom Center Building, East Tower 6F Aomi 2-5-10, Koto-ku, Tokyo, Japan Aomi Cell Culture Innovation Center Time 24 Building Aomi 2-4-32, Koto-ku, Tokyo, Japan



Telecom Center Building

Time 24 Building

CellSeed's YouTube Channel

We have created a YouTube channel to introduce the manufacturing method of cell sheets, CellSeed's cell cultureware, and the outline of our businesses. More videos will be uploaded from now on. We hope you find these videos useful.

Please scan this QR code to watch our YouTube videos.

Notes for Shareholders

Fiscal year end	December 31
General Shareholders' Meeting	March
Dividend declaration date	December 31 (Interim dividends declared June 30)
Shareholder registry administrator Special account management institution	IR Japan, Inc. 100-6026 Securities Administration Division, IR Japan, Inc. Kasumigaseki Bldg. 26F Kasumigaseki 3-2-5, Chiyoda-ku, Tokyo Tel: 0120-975-960 (toll-free)

Public notice posted online URL:https://www.cellseed.com/ir/koukoku/

(However, if posting online is not possible due to unavoidable circumstances, public notice will be issued in the Nihon Keizai Shimbun.)

Notes:

1. Along with the electronic conversion of stock certificates, we comply in principle with petitions for changes of address, purchase requests, and other types of procedures pertaining to the shareholder made through account management institutions (stock brokerage firms, etc.), where shareholders have established accounts. Please contact the stock brokerage or other institution where the account has been established. Please note that these changes cannot be handled by the shareholder registry administrator (IR Japan, Inc.).
2. With regard to procedures related to shares recorded in special accounts, please contact the special account management institution (IR Japan, Inc.).