

# With you CellSeed Vol.14



 **CellSeed**  
*Regenerate the Future*

CellSeed Inc.

Securities Code: 7776

## Greetings



We sincerely appreciate your continued support.

While the development of therapeutic drugs and the spread of vaccines for COVID-19 have brought a sign of economic recovery, the soar of crude oil prices and transportation costs that are pressuring economic activities have kept the future unpredictable. CellSeed is actively introducing remote work and keeping efforts in the regenerative medicine support business and the cell sheet regenerative medicine business.

### Updates on the Regenerative Medicine Support Business (Cultureware Business, Regenerative Medicine Contract Services)

In our cultureware business, we have started supplying cultureware products to new markets, which play a part in developing new methods for preventing and treating COVID-19 and other infectious diseases. To address the increasing demand for cultureware products, "Aomi Cell Cultureware Innovation Center," a facility for development and manufacturing, was newly built and is now up and running.

In our regenerative medicine contract services, we manufactured autologous chondrocyte sheets for the Advanced Medicine B program contracted by Tokai University at the Cell Processing Facility (CPC), in continuation from the previous year. (CPC obtained approval to manufacture specified cell processing products acquired pursuant to the Act on the Safety of Regenerative Medicine.)

### Updates on the Cell Sheet Regenerative Medicine Business

Since an application for clinical trials on epithelial cell sheets for esophageal regeneration was submitted in October 2020 under the Act on Pharmaceuticals and Medical Devices (the "PMD Act"), additional clinical has been started.

For the allogeneic chondrocyte sheets, we are currently promoting our research to obtain marketing approval under the PMD Act. In December 2020, we received a permission for commercial use of chondrocytes that were collected from patients with polydactyly at the National Center for Child Health and Development. Also, in July 2021, the allogeneic chondrocyte sheet project was awarded a grant project in a public invitation issued by the Japan Agency for Medical Research and Development (AMED). This intends to accelerate the commercialization of knee osteoarthritis products and speed up our R&D activities to initiate corporate-sponsored clinical trials as early as possible. Additionally, we plan to submit the clinical trial application at the end of 2022 and ultimately achieve marketing approval as regenerative medicine products under the PMD Act.

### Future Overview

To deliver treatments worldwide based on Japan-originated cell sheet engineering, we will make persistent efforts to commercialize products of cell sheet regenerative medicine. As one of our recent efforts, the 21st Congress of the Japanese Society for Regenerative Medicine was held online from March 17 to 19, 2022. CellSeed participated as a sponsor by displaying our cultureware products and contract services as well as giving co-organized academic seminars and short presentations. The seminar featured development of allogeneic chondrocyte sheets. We sincerely ask our shareholders for your continued support.

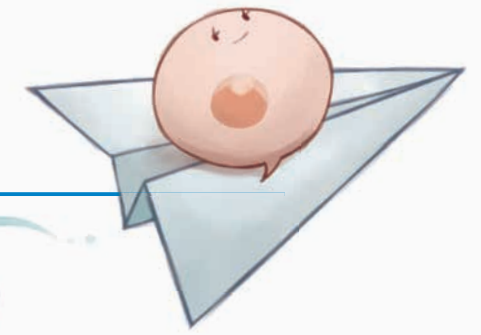
#### Mission

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.

## History



### 2021

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

### 2019

The 1st Cell Sheet Engineering Innovation Forum held

### 2017

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

### 2015

CellSeed Sweden AB, a subsidiary in Sweden, established

### 2010

Listing on JASDAQ NEO

### 2004

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



### 2020

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

### 2018

Start of regenerative medicine contract services

### 2016

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

### 2014

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

### 2007

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

### 2001

CellSeed founded



## Aomi Cell Cultureware Innovation Center newly established



In September 2021, we established a new R&D and manufacturing facility for new cell cultureware products, Aomi Cell Cultureware Innovation Center, in order to meet the increase in sales volume, mainly overseas. We will strive to secure long-term, stable profits and increase the corporate value while working on enhanced production system and secured quality in the development and manufacture of flask products, such as *UpCell*® and *HydroCell*®.

## The 2nd Cell Sheet Engineering Innovation Forum held

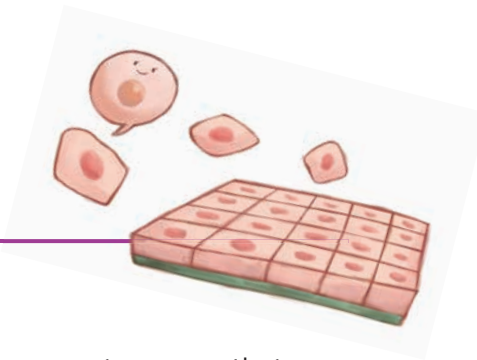


Despite the cancellation of the 2nd Cell Sheet Engineering Innovation Forum due to the spread of COVID-19 in 2020, it was held online on November 1, 2021, and welcomed a large number of participants across Japan. A total of 30 applicants presented posters. We provided a cyber environment where the participants can communicate as if they do in a real poster session. The videos on forum presentations are available on YouTube. We hope you find them useful.

Please scan this QR code to watch our YouTube videos.



# CellSeed's Regenerative Medicine



Regenerative medicine is a new field of medicine that aims to treat and regenerate organs that are lost, damaged, or with compromised functions. In Japan, legislation for regenerative medicine was developed in 2014, such as: the Act on the Safety of Regenerative Medicine to provide safe regenerative medicine swiftly and smoothly; and the Act on Pharmaceuticals and Medical Devices to supply more products as fast as possible.



CellSeed has been engaged in conducting clinical trials based on the results of university research as development seeds and strive to commercialize them as regenerative medicine products. CellSeed's cell sheet engineering is our base technology where a thin sheet of the cells can be recovered just by lowering the temperature. The cell sheet can be transplanted to the affected area of the body for cells and organ to regenerate. Cell sheets using this technology are expected to enable treatment of diseases which could not be treated with conventional medicine. At CellSeed, we are developing epithelial cell sheets for esophageal regeneration and chondrocyte sheets as our pipelines, and aim for early commercialization. Additionally, we concluded a business partnership agreement with the Taiwanese company MetaTech in 2018 and started a joint venture in Taiwan in 2020. We will continuously aim to contribute to medicine in Japan and globally.

## Progress on CellSeed's pipelines

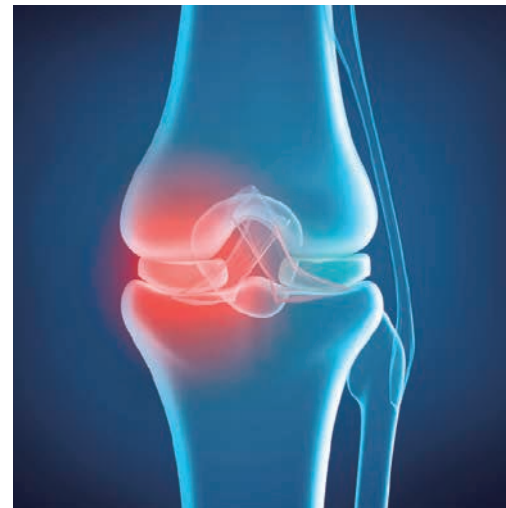
The Act on the Safety of Regenerative Medicine (the “Safety Act”)		The Regenerative Medicine Promotion Act			The Act on Pharmaceuticals and Medical Devices (the “PMD Act”)		
Clinical research	Medical costs not covered by health insurance	Manufacture and sales					
Pipelines	Basic research	Clinical research	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*						
Autologous chondrocyte sheet	In accordance with the Safety Act*, clinical trials were conducted after approval was granted for the Advanced Medicine B program. Contract manufacture of cell sheets was also conducted.						
Allogeneic chondrocyte sheets	Conducted basic and clinical research at Tokai University						
	A clinical trial is currently underway pursuant to the PMD Act.						

\*The PMD Act: The Act on Pharmaceuticals and Medical Devices. 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 Safety Act: The Act on the Safety of Regenerative Medicine. 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.

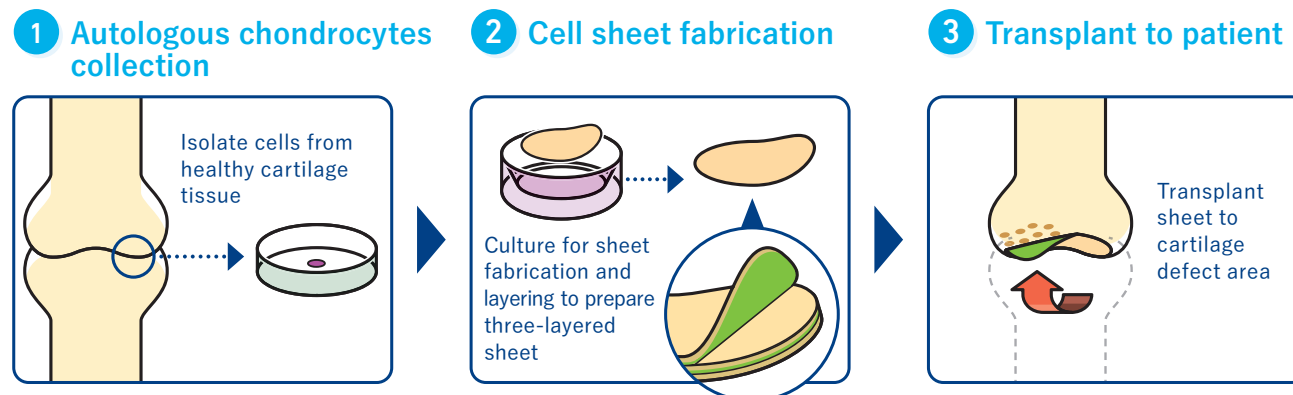


# Autologous Chondrocyte Sheets



Knee osteoarthritis is a slowly progressive, intractable degeneration of articular cartilage for which no definitive care 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. To address these issues, CellSeed Inc. has conducted joint research on regeneration of knee cartilage (hyaline cartilage) with Professor Masato Sato (Department of Orthopaedic Surgery, Surgical Science, Tokai University School of Medicine) at Tokai University and has currently manufactured autologous chondrocyte sheets for the Advanced Medicine B program as contracted by Tokai University.

## Treatment method



## Updates on autologous chondrocyte sheets

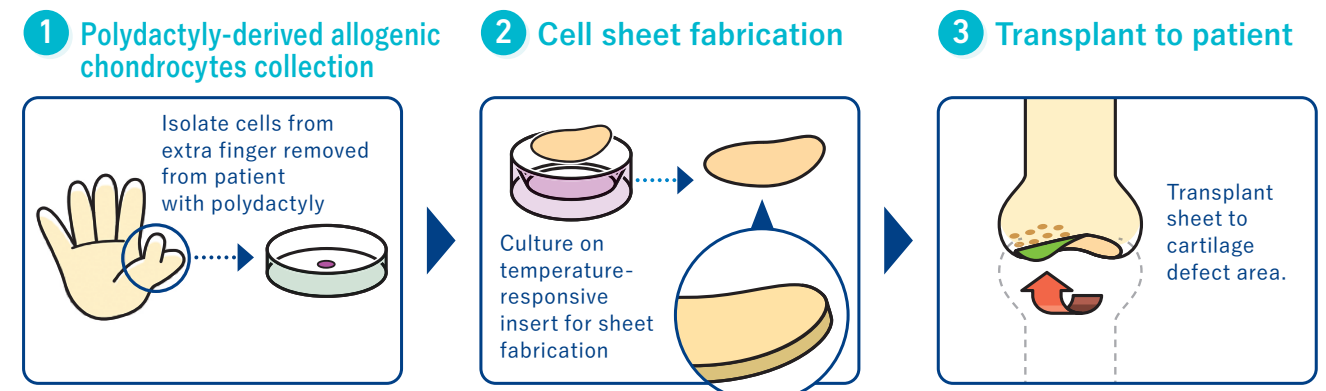
2011-2014	Autologous chondrocyte sheets were transplanted to eight patients in a clinical research at Tokai University School of Medicine.
2017	Licensing out Autologous cell sheet to MetaTech in Taiwan
January 2019	Tokai University filed an application at the Advanced Medical Conference held by Japan's Ministry of Health, Labour and Welfare, and the approval was granted as the Advanced Medicine B program.
June 2020	Started medical treatment in Tokai University as Advanced Medicine B program. Contract manufacture of autologous chondrocyte sheets started at CellSeed.
Present	Contract manufacture for the Advanced Medicine B program continues.

# Allogeneic Chondrocyte Sheets



Allogeneic chondrocyte sheets are developed as a cell therapy product: chondrocytes are isolated from extra finger removed from patient with polydactyly, cultured for sheet fabrication, and transplanted to cartilage defect area. This product is expected to reduce patient stress and treatment cost because patients can receive cell therapy without their own cartilage tissue collection.

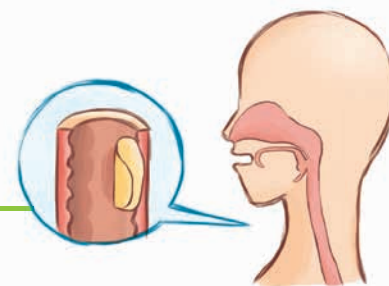
## Treatment method



## Updates on allogeneic chondrocyte sheets

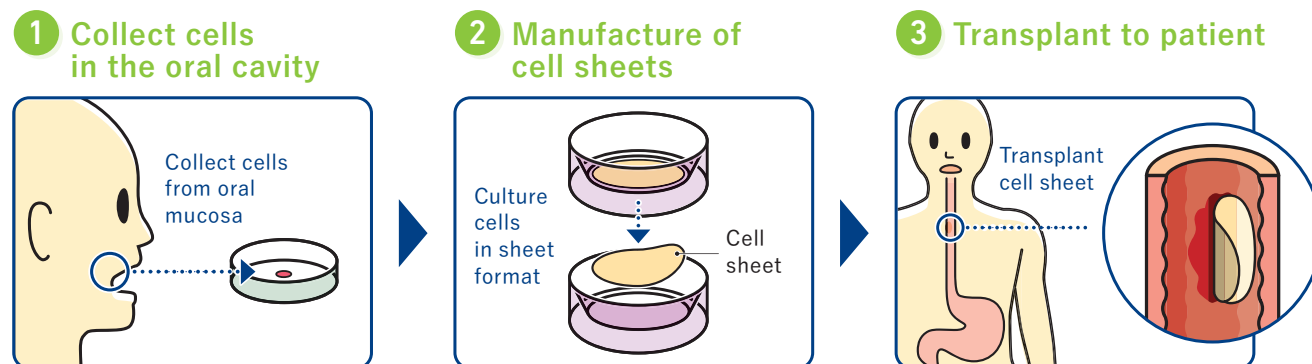
2017-2019	Allogeneic chondrocyte sheets were transplanted to ten patients in a clinical research at Tokai University School of Medicine.
2018-2021	Adopted as the ancillary project of AMED titled "Development of the evaluation methods for the efficacy of allogenic chondrocyte sheets"; project period: Oct. 2018 to Mar. 2021
2021-	Acquired cartilage for commercial purposes from the National Center for Child Health and Development
2021-2023	Adopted as the ancillary project of AMED titled "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)"; project period: Aug. 2021 to Mar. 2023
End of 2022	We plan to submit a clinical trial notification at the end of 2022.

# 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. To improve this condition, Tokyo Women's Medical University developed a treatment using epithelial cell sheets. This treatment is expected to prevent esophageal stenosis by promoting the healing of the wounds.

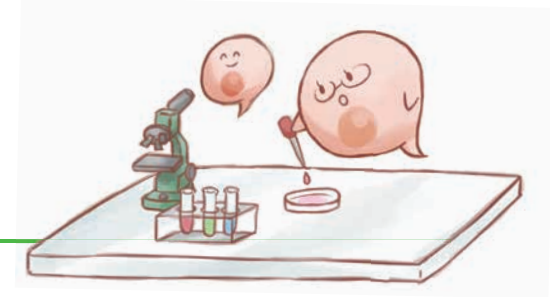
## Treatment method



## Current Status of Epithelial Sheets for Esophageal Regeneration

2016	Submitted clinical trial notification
2017	Designated "SAKIGAKE" system
2020	Submitted additional clinical trial notification
2021	Registered first patient in the additional clinical trial
2025	Applied manufacturing and marketing application (planned)

# Cell Cultureware



Using the temperature-responsive cell cultureware developed by Professor Teruo Okano at Tokyo Women's Medical University in 1989, cells can be detached simply by lowering the temperature and recovered as an intact one sheet, for the first time in the world. Currently and commonly used cell recovery technology based on proteolytic enzyme is used, cells are recovered damaged, which makes it difficult to retain the original function and components. However, introducing CellSeed's product has enabled the collection of cells intact, which means the recovered cells can be used as the material that maintaining all of the original function and components; consequently, attention has been brought to the possibility that industrial efficiency and effectiveness in new markets can significantly improve.

## Main products sold by CellSeed

1
**UpCell®**

This cultureware, with temperature-responsive polymers fixed on the surface, allows for the recovery of undamaged cell sheet without using enzyme that damage cells.

2
**RepCell®**

In addition to the same characteristics as those of **UpCell®**, this cultureware has surface grid wall that allows for the recovery of cells in a single cell or small colonies.

3
**HydroCell®**

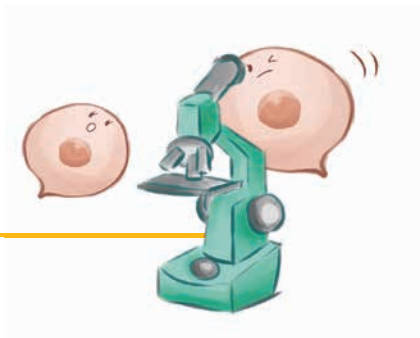
Using our proprietary surface design super-hydrophilic polymers are fixed to the surface of cultureware. It is most suitable for the preparation of embryoid bodies from ES cells and macrophage culture.

4
**cellZscope**

cellZscope is an automated measuring device for the transepithelial/endothelial electrical resistance value. This is a type of cultureware that is most suitable for the measurement of barrier functions, analysis of mechanism of absorption/discharge of compounds, and analysis of cytotoxicity.



## Contract Services



In March 2017, the approval to manufacture specified cell processing products was obtained, and in October 2018, the approval to manufacture regenerative medicine products was obtained. We have provided numerous contract services. Our highly experienced staff will continue to provide safe, high-quality products and services.

### Past contract services \*Only the services that can be disclosed

Autologous chondrocyte sheets	Cell sheets for the treatment of liver disease	Periodontal ligament cell sheets	Autologous oral mucosal epithelial cell sheets
Contract manufacturing of autologous cell sheets for the Advanced Medicine B program conducted by Tokai University	Conclusion of an agreement on technology transfer for the manufacture of cell sheets for the treatment of liver disease for clinical trial use	Contract manufacture of periodontal ligament cell sheets prepared from human (allogeneic) periodontal ligament-derived mesenchymal stem cells for an investigator-led clinical trial	Contract manufacture of autologous epithelial cell sheets for a clinical research on regenerative medicine for congenital esophageal atresia postoperative anastomotic stricture

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

- Development of cell sheet manufacturing methods
- 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 creation/consulting
- Support for operation and maintenance of facilities equipment/management system, etc.



#### 3 Cell culturing technicians

- Cell sheet culturing training
- Cell sheet harvesting training, etc.



## CellSeed Management Team / Financial Condition



### Management team of CellSeed



Representative Board Director and President/CEO  
Setsuko Hashimoto



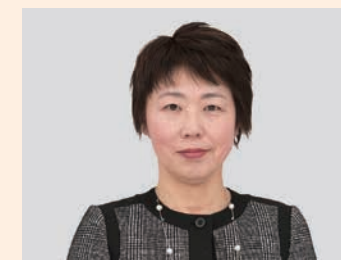
Board Director and CFO  
Jun Onodera



Outside Director  
Kenji Oeda



Outside Director/Audit and Supervisory Committee Member  
Toshio Yamaguchi



Outside Director/Audit and Supervisory Committee Member  
Noriko Taji



Outside Director/Audit and Supervisory Committee Member  
Mariko Hirose

### Financial condition

#### Performance report for December 2021

Sales	161
Operating income	-864
Ordinary income	-887
Yearly profit attributable to owners of parent company	-914
Earnings per share	-53.18 yen

#### Earnings forecast for December 2022

Sales	213
Operating income	-976
Ordinary income	-998
Yearly profit attributable to owners of parent company	-998

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

#### Highlights

In our cultureware product business, we have started supplying our products to new markets which play a part in developing new methods for preventing and treating COVID-19 and other infectious diseases. In addition, enhanced collaboration with existing sales partners and active promotional activities led to the highest sales of cultureware products in our company's history.

In our cell sheet business, we proposed an R&D project of allogeneic chondrocyte sheets and it was awarded the AMED's grant. Additionally, we conducted the manufacture for the Advanced Medicine B program as outsourced by Tokai University.

# Corporate Overview

As of March 25, 2022

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

# Stock Information

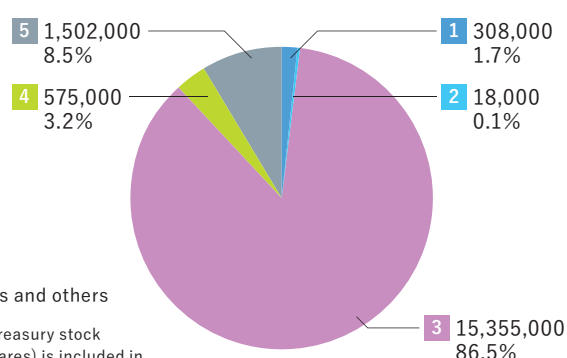
As of December 31, 2021

Total no. of issuable shares	35,537,600
Total no. of issued shares	17,759,419
No. of shareholders	13,278
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."



# 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	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)
Special account management institution	
Public notice posted online	URL: <a href="https://www.cellseed.com/ir/koukoku/">https://www.cellseed.com/ir/koukoku/</a> (However, if posting online is not possible due to unavoidable circumstances, public notice will be issued in the Nihon Keizai Shimbun.)

## Notes:

- 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.).
- With regard to procedures related to shares recorded in special accounts, please contact the special account management institution (IR Japan, Inc.).