With you
CellSeed
Vol. 9
2016.1.1~2016.12.31
Mid-term Business Plan (from 2017 through 2019)

- Obtain sales approval for the epithelial cell sheet for esophageal regeneration
- Accelerate development of the allogeneic regenerated cartilage sheet
- Promote business alliances with overseas companies
- Develop our own supporting product lineup
- Establish a supply chain system
- Start development of next regenerative medicine products

Our Mission and Vision

**Mission**

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

**Vision**

We establish a cell sheet business platform and provide excellent regenerative medicine products around the world
Cell Sheet Regenerative Medicine Technology Drives Evolution of Medical Treatment Forward

Cell Sheet Engineering

Cell sheet regenerative medicine technology targets diseases that are hard to treat by conventional medical care. It is a new technology that artificially manufactures different kinds of tissue from single cells, harvested from the patient or a donor, for therapeutic purposes. CellSeed is working toward rapid realization of cell sheet regenerative medicine products originated in Japan.

Cell sheet manufacturing

Cell sheet engineering*, a platform technology for preparing a sheet of cells using temperature-responsive cell cultureware, facilitates manufacturing with cells from various biological tissues and organs. We are pursuing research to manufacture tissue and organs of suitable thickness by stacking several layers of cell sheets.

Cell sheet applications

We seek to utilize cell sheets made through cell sheet engineering in various treatment applications.

For patients

The potential to treat diseases is enhanced through regeneration of functions that patients lose due to illness or injury.

*Cell sheet engineering is a platform technology in regenerative medicine whereby a temperature-responsive polymer, the properties of which change in response to temperature, is immobilized at a uniform nanometer-scale thickness on temperature-responsive cell cultureware, after which the cultured cells can be collected in sheet-like clusters—cell sheets.
Esophageal strictures may form To prevent esophageal strictures from forming

Lesion area of the esophagus resected with insulated-tip (IT) knife

Cell culture

Cell sheet

To prevent esophageal strictures from forming

Cell harvesting

UpCell® (See page 4)

CellSeed’s unique therapy to prevent formation of esophageal strictures

Squamous cell carcinoma:
A type of cancer that forms on the inner surface (mucosal epithelium) of the esophagus.

ESD:
An innovative, less invasive procedure developed in Japan and performed worldwide.
The surgeon uses a special knife to resect the lesion area of the mucous membrane in the esophagus.

If caught in the early stages, squamous cell carcinoma—the most prevalent form of esophageal cancer among Japanese—can be fully treated with a procedure called endoscopic submucosal dissection (ESD). However, a challenge with ESD is that removal of a cancerous lesion by this method causes an ulcer that often leads to poor post-surgery quality of life for patients over time, particularly when the ability to swallow is inhibited due to inflammation or the formation of strictures in the esophagus.

In response, clinical research was done on a treatment that suppresses early stage inflammation after surgery and prevents the stricture formation by transplanting cell sheets—epithelial cell sheets for esophageal regeneration—manufactured from oral mucosal epithelial cells in temperature-responsive cell cultureware to the resected area of the esophagus. Good results have been obtained with this approach. Clinical trials began in August 2016.

Regenerated Cartilage Sheets

Collect cells as a sheet, which preserves extracellular matrix

Layered cell sheets

Transplant

Layered arrangement of cartilage cell sheets (confirmed technique for preparing three-layer arrangement of cell sheets)

With the demographic balance rapidly tilting toward an aging population, osteoarthritis and other locomotor apparatus diseases that inhibit everyday activity and invite a deterioration in seniors’ quality of life have a link to Locomotive Syndrome* as well and are becoming a major concern from various perspectives, including social impact. The potential of sheets made from patients’ own cartilage cells to regenerate joint cartilage and thereby return function to knee cartilage through the regeneration of lost hyaline cartilage was confirmed in clinical research undertaken at the Tokai University School of Medicine. Clinical research on donor-derived cartilage cell sheets, as well, is in progress now.

*Locomotive Syndrome:
A high-risk condition where motor deterioration increases the chance of becoming bedridden or needing nursing care. The term was acknowledged by The Japanese Orthopaedic Association in 2007.
Regenerative Medicine Supporting Business

Providing Research Products to Support Regenerative Medicine

We have products to support basic research related to cell culture, including research into regenerative medicine. We provide innovative cultureware to fabricate cell sheets as well as other types of cultureware for embryoid body formation from ES and iPS cells.

*UpCell®/RepCell™/HydroCell™*

Temperature-responsive Cell Cultureware for Collecting Cell Sheets

Image of cell sheet collection

Collecting a cell sheet by temperature reduction

NIH/3T3 cells were cultured for one week (cells grown at confluence) and harvesting a cell sheet using CellShifter Membrane.

*RepCell™*

Temperature-responsive Cell Cultureware for Cell Collection

*HydroCell™*

The Ultimate Low Cell Binding Cultureware

*cellZscope*

The Automated Cell Monitoring System

Ensures thermal control of the cell cultureware during observation under a microscope and medium replacement.

CellSeed Inc. is the exclusive distributor of the cellZscope and ThermoPlate™ II for UpCell®/RepCell™ only in Japan.

ThermoPlate™ II
for *UpCell®/RepCell™*
Seeking to Provide the Best Technology to Patients Around the World

Special Interview Session

Accelerate practical application of regenerated cartilage sheets for knee osteoarthritis indication to be the fundamental therapy

Masato Sato
Setsuko Hashimoto

Provide high-quality treatment to many of the estimated 7 to 8 million people or more who suffer from osteoarthritis of the knee

Hashimoto—CellSeed formed a basic agreement with Tokai University to facilitate clinical trials aimed at turning clinical research on regenerated cartilage sheets into practical treatment and to develop a pipeline to underpin approval applications to manufacture and sell these sheets. Research on regenerated cartilage sheets conducted in Dr. Sato’s lab, based on eight case studies using cell sheets created from the patients’ own cells, was successful. I am keen to see him build on these results to open the treatment pipeline to patients as soon as possible.

Over the last few years, we have pursued joint research with his lab, providing original equipment, such as the inserts for UpCell® temperature-responsive cell cultureware needed to cultivate cartilage cells. In addition, at our Cell Processing Facility, we are in the process of taking over the cell sheet manufacturing activities currently done by his lab. With permission granted in March 2017 to pursue the processing and manufacturing of specified cells at our Cell Processing Facility, we finally put in place a structure for company-initiated clinical trials. We are also making preparations for a cell bank that will store harvested cells safely and securely.

Sato—With the cooperation of CellSeed, we are in the process of perfecting a treatment using high-quality regenerated cartilage sheets. Osteoarthritis of the knee causes the surface of cartilage to wear away and disintegrate, causing pain in the joint and making it difficult to bend and straighten the knee. In recent years, the incidence of osteoarthritis of the knee has increased, paralleling the graying of society, and the number of people with noticeable symptoms is estimated at 7 to 8 million.

Clinical research on autologous cells (a person’s own healthy cartilage cells harvested and cultured) has already been concluded, and with CellSeed, we will move into the company-initiated clinical trial phase. We are also preparing to apply for approval inside the framework for advanced medical treatment.

Hashimoto—When I am out and about giving presentations, I often hear comments like “I have knee pain” and “Members of my family have knee osteoarthritis.” Those people are eagerly awaiting a viable treatment.

Sato—I am sure they are. Autologous cell treatment is important, of course,
but to make treatment available to as many people as possible, we must also demonstrate successful therapy using allogeneic cells, which would facilitate manufacturing of a considerable amount of regenerated cartilage sheets from the cartilage of other people to help even more people. Right now, we have just started our first case study of clinical research for allogeneic cells. Going forward, we are planning to do clinical research with 10 patients. We will first assess safety, and if all goes well, we will again look to you, Dr. Hashimoto, for CellSeed’s help on allogeneic cell regeneration sheets.

Hashimoto—Of course, we will be pleased to work with you. Cell sheet transplant therapy with allogeneic cells has tremendous potential from a business perspective as well. Cartilage cells surgically removed from the ligated extra fingers of polydactyl babies can be cultured and produced in large quantities as sheets for transplantation. This would save the time and effort of harvesting autologous cells from patients prior to transplantation and increase the number of patients undergoing the procedure, so we will eagerly track the progress of clinical research based on these 10 case studies.

Autologous cells are like a tailor-made suit, and allogeneic cells are like prêt-à-porter. But if the quality of allogeneic cells is evaluated by lot, a large amount with uniform quality can be produced, thereby providing stable treatment for many patients. Conversely, autologous cells require each cell sheet to undergo a separate quality check, which really bumps up costs.

Sato—The cost issue is an extremely critical factor. Coming up with a treatment method is great, but it will fall short of success if access is limited to only some of the people who need it. What I am getting at is this—if one treatment costs in the range of ¥2 million and if all the patients eligible for treatment were to undergo the procedure, costs would exceed ¥14 trillion. That is just not realistically possible. However, if costs could be lowered, maybe to one-tenth, then treatment would more likely become mainstream.

Hashimoto—Yes. The needs in this field are great, and many companies are getting involved. However, your regenerated cartilage technology is hugely superior because you have targeted hyaline cartilage, a strong type of cartilage. The knee is a joint that bears the body’s full weight, and satisfactory treatment results will not be achieved if the cartilage is not strong enough.

Sato—That is right. Most cartilage treatments available to date have used fibrous cartilage, which achieves a certain degree of improvement and eliminates pain. But it is not strong enough for extended weight-bearing and will eventually break down.

The regenerated cartilage sheets we develop are notable for having a special protein to facilitate autologous repair through transplantation, bringing about the repair and regeneration of hyaline cartilage.

Hashimoto—You mentioned autologous repair, which is extremely important in cell therapy. It is...
unnatural for cells to be separated or scattered. In the body, cells are connected, forming tissue, so if the cell sheet structure is close to that found in the body, then the cells will function extremely well. This is the real advantage of cell sheet engineering.

Sato—We are very focused on hyaline cartilage regeneration because it is important for patients to be provided treatment with the best cartilage to ensure long-lasting results and keep the knee in good shape.

We are aiming for regenerated cartilage that works for 10 years, but if conditions worsen after 10 years, cell sheets cultured from allogeneic cells will facilitate immediate procurement of the material needed to return the joint to a healthy state. We intend to make our method the gold standard for treating knee osteoarthritis.

Hashimoto—I am in awe of your culture technology. You have approached culture methods with such ingenuity.

Sato—Thank you. We adopted a co-culture method that cultures synovial cells and cartilage cells. In the joint, cartilage cells are found together with synovial cells. To recreate this condition in cultureware, we first laid down synovial cells in a culture plate, then cartilage cells were seeded into culture inserts above the synovial cells. This process allowed for quick culture and enhanced cell sheet performance. The structure will contribute to the regeneration of high-quality cartilage tissue.

Cell sheet engineering technology has the potential for use with organs as well

Sato—We saw that lots of the cytokines needed for autologous repair are produced when harvested cells are properly cultured so that cells work with each other. It is really quite amazing. Some products have been developed overseas to produce a special protein through methods that include gene induction. However, we found that an extremely important protein could be created just by carefully turning cells into sheets. I believe that this concept is not limited to cartilage and could be applied to any cell.

Hashimoto—Indeed. Our cell sheet engineering technology has many advantages as basic technology in regenerative medicine, and has attracted attention not only in Japan but from overseas as well. CellSeed relocated its headquarters a year ago and just recently completed construction of the Cell Processing Facility. This is something we were really keen to set up. Currently, clinical studies are under way on epithelial cell sheets for esophageal regeneration. Once this is done, we will move into the sales approval application phase, then begin clinical trials on regenerated cartilage sheets. Already we have had an offer on this therapy from a company in Taiwan. I would really like to promote activities that deliver new therapies developed jointly with Japanese universities for use in places outside Japan, for patients all over the world.

Sato—in today's discussion, the spotlight was on our ultimate goal—to use allogeneic cells to treat a lot of patients—but the number of patients who would prefer treatment using their own cells is not at all insignificant. So it is my hope that CellSeed will establish a higher standard in cell manufacturing technology to facilitate the regeneration of high-quality cell sheets from autologous cells provided by various persons.

Hashimoto—Of course, we will. CellSeed will continue to polish its technology to respond with the highest possible quality, on both the tailor-made and ready-made pipelines.

2 Cartilage is divided into three types: fibrous, elastic and hyaline (glass). Strong and rich in lubricating qualities, hyaline cartilage covers the articulating ends of bones to facilitate smooth movement of joints.

3 Any of various proteins, secreted by cells, that act as intercellular mediators in cell-signaling, such as activating immune and inflammation responses and regulating the proliferation and division of cell populations.
The Cell Processing Facility, completed in August of 2016, is a facility that operates in compliance with the Act on the Safety of Regenerative Medicine, which went into force in November 2014. This facility manufactures CellSeed-developed cell sheet products and also accepts orders for cell sheets from other companies on an outsourcing basis.
Looking Toward Overseas Expansion

CellSeed’s Management Team

As we, the management team at CellSeed Inc., unite and work toward conducting business activities as one, we extend our sincere appreciation for your continued support and guidance.

Overseas Business Developments

To expand treatment methods using cell sheet engineering, a platform technology for regenerative medicine developed in Japan, to Europe, CellSeed established a subsidiary, CellSeed Sweden AB. We will also continue to pursue various possibilities, including development activities on our own and alliances with overseas companies such as MetaTech (AP) Inc. in Taiwan, to rapidly promote widespread use of cell sheet engineering in the United States, Europe and Asia.
Steady Progress Toward Commercialization

CellSeed’s Financial Status

Consolidated P/L
Fiscal 2016
(January 1–December 31, 2016)

Net sales .............................. ¥100 million
Selling, general and administrative expenses .......................... ¥1,494 million
Operating loss ......................... ¥1,413 million
Net loss attributable to owners of parent ............................... ¥1,414 million

Point 1
Booked net sales of ¥50 million as mobilization fees with derivative consideration aimed at licensing commercialization of cell sheet regenerative medicine products in Taiwan

In December 2016, CellSeed began discussions with MetaTech (AP) Inc., an OTC-listed company in Taiwan, on licensing commercialization of cell sheet regenerative medicine products in Taiwan. As the first step in this process, we signed an agreement that will provide us with ¥50 million as mobilization fees with derivative consideration.

Consolidated Financial Status
Fiscal 2016
(As of December 31, 2016)

Total assets ........................... ¥1,343 million
Cash and deposits and investment securities .............. ¥1,056 million
Liabilities ................................ ¥179 million
Net assets ................................ ¥1,164 million

Point 2
Issued 16th series of stock acquisition rights, seeking to procure funds for future development and business activities

On March 6, 2017, CellSeed issued its 16th series of stock acquisition rights, directed toward the Evolution Biotech Fund, seeking to procure funds for regenerative medicine supporting business, for working capital and operating costs of a cell processing facility and for expenses incurred in setting up a development support structure in Taiwan. We raised about ¥1.1 billion through the issue.

Net Sales
(Millions of yen)

Cash and Deposits and Investment Securities
(Millions of yen)

Selling, General and Administrative Expenses
(Millions of yen)

R&D Expenses
(Millions of yen)
### Corporate Data

#### Company Outline  As of March 29, 2017

<table>
<thead>
<tr>
<th>Company name</th>
<th>CellSeed Inc.</th>
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| Principal businesses | Cell sheet regenerative medicine business  
Regenerative medicine supporting business |
| Head office | Telecom Center Building 15F  
5-10, Aomi 2-chome, Koto-ku, Tokyo  
135-0064 Japan |
| Date established | May 2001 |
| Management team | Setsuko Hashimoto, President & CEO  
Jun Onodera, Board Director & CFO  
Katsumi Katayama, Board Director  
Tomomitsu Hotta, Board Director (External)  
Kenji Oeda, Board Director (External)  
Masaki Sunaoshi, Audit & Supervisory Board Member  
Toshio Yamaguchi, Corporate Auditor (External)  
Mariko Hirose, Corporate Auditor (External) |
| Fiscal year-end | December 31 |
| Listed market | JASDAQ Growth (7776)  
Tokyo Stock Exchange |
| Subsidiary | CellSeed Sweden AB |

#### Corporate Milestones

- **May 2001**: CellSeed was established in Shinjuku-ku, Tokyo for the primary purpose of pursuing research and development related to cell sheet engineering.
- **September 2007**: Began domestic sales of UpCell® Temperature-responsive Cell Cultureware for Cell Sheets collection.
- **February 2008**: Launched sales of temperature-responsive cell cultureware in overseas markets.
- **March 2010**: Listed on JASDAQ NEO (now, JASDAQ Growth) section of Tokyo Stock Exchange.
- **May 2015**: Relocated to Aomi, Koto-ku, Tokyo (current location).
- **January 2016**: Initiated clinical trials on epithelial cell sheets for esophageal regeneration.
- **August 2016**: To present

#### Stock Information  As of December 31, 2016

<table>
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<th>Number of shares outstanding</th>
<th>9,214,419</th>
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</thead>
<tbody>
<tr>
<td>Number of shareholders</td>
<td>9,923</td>
</tr>
<tr>
<td>Minimum trading unit</td>
<td>100 shares</td>
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</tbody>
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### Shares of Shareholders

- **522,000** shares held by Foreign shareholders (5.67%)
- **549,000** shares held by Financial institutions (5.96%)
- **7,967,000** shares held by Other corporations (86.48%)
- **160,000** shares held by Financial instruments business operators (1.74%)
- **13,000** shares held by Individuals, other (0.15%)

Note: Treasury stock (127 shares) is included in “Individuals, other.”

#### Shareholder Notes

1. Following the dematerialization of stock certificates, shareholder requests for change of address, purchase and sale of shares less than one trading unit and other assorted administrative procedures are, in principle, handled by shareholder account administrators, primarily securities firms, where shareholders have opened such accounts. Inquiries regarding shareholder-related administrative procedures should therefore be directed to the securities firm where an account is held, because IR Japan, Inc., as the special account manager, is unable to address such inquiries.
2. Shareholders are asked to contact the Tokyo office of IR Japan, Inc., our special account manager, regarding assorted procedures related to stock recorded in special accounts.


However, in the event that electronic public notices cannot be provided due to unavoidable circumstances, public notices will appear in the Nihon Keizai Shimbun.