Featured Articles

# Wider Adoption of Regenerative Medicine Driven by Open Innovation

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*OVERVIEW: The large-scale and safe production of cells for medical use is the greatest challenge to the wider adoption of regenerative medicine. Although the culturing of cells for medical use is largely performed manually at present, the key to more widespread use of regenerative medicine lies in the use of techniques for automated cell culture for the up-scaling and rationalization of cell production and the reliable supply of high-quality cells. Hitachi is combining technology from medical engineering to develop closed systems for automated cell culture and cell transportation techniques. The automated cell culture equipment developed by Hitachi can produce cells with quality equivalent to that of manual culture. Hitachi is also working on the development of cell transportation vessels that prevent contamination and maintain constant temperature and pressure. Based on this research and development, Hitachi is seeking to facilitate the wider adoption of regenerative medicine by establishing a cell value chain that can deliver high-quality cells to patients around the world.*

## INTRODUCTION

HIGH hopes are being placed on regenerative medicine providing the next generation of therapies that can treat patients who do not respond well to conventional pharmaceuticals, with benefits that include improving the patient's quality of life (QoL) and reducing social insurance costs. Along with the development of processing techniques for induced pluripotent stem (iPS) cells and other types of cells, the urgent challenges facing the establishment and spread of regenerative medicine also include the rationalization of costs without compromising efficacy and safety. Hitachi is seeking to establish a new cell value chain for regenerative medicine by consolidating technology and know-how developed in related activities as well as through research and development work that takes advantage of open innovation to commercialize basic research undertaken by universities. In this way, it is helping create a healthy society with a better QoL in which every patient can receive treatment.

## TRENDS IN REGENERATIVE MEDICINE

The market for regenerative medicine is forecast to expand rapidly after 2020 to reach 17 trillion yen by 2030[(1)]. Japan's Institute of Physical and Chemical Research (RIKEN) became the first in the world to commence clinical research into the use of iPS cells for retinal disease in September 2014. It is anticipated that treatments for numerous diseases will become available in the future through the use of iPS cells. There is also a trend toward such treatments involving allogenic rather than autologous transplantation, with the expectation that this will become a widespread practice. The enactment of a new law on regenerative medicine in November 2014 (the Act on the Safety of Regenerative Medicine) included the introduction of a system for the early approval of cell-based products and permission for the outsourcing of cell processing. It is anticipated that facilities for the safe and efficient production of cells will be established by specialist companies in the future. Whereas the market has been dominated by venture businesses in the past, major Japanese corporations among others have been active in acquiring or establishing alliances with regenerative medicine companies, indicating that regenerative medicine is well on the way to becoming a recognized industry.

## ACTIVITIES BY HITACHI

The biggest challenge to be overcome if the wider adoption of regenerative medicine is to enable all patients to receive treatment with confidence is

the establishment of technology for the large-scale production of high-quality cells suitable for medical purposes at low cost. The high cost of regenerative medicine is also an obstacle to its wider adoption, with the current cost of cell production for each treatment being upward of one million yen.

By developing techniques for automated cell culture, Hitachi is seeking to encourage the wider adoption of regenerative medicine by making it possible to produce cells at high volumes and levels of reliable quality not possible when production is performed manually[2), 3), 4)]. In particular, development is proceeding on closed automated cell culture systems that provide the high degree of sterility needed for medical use, and on systems that incorporate techniques that culture multiple vessels at the same time. Also under development are large sub-culture systems that use large-scale surface culture vessels for volume production and techniques for air freighting live cells for medical use in ways that maintain their sterility and efficacy. The following sections describe these technical developments.

## Automated Cell Culture Equipment for Cell Sheets

One feature of Hitachi's automated cell culture equipment is its use of fully enclosed culture vessels and circuits to prevent contamination by bacteria or other sources from the external environment. Based on this core technology for closed automated cell culture, Hitachi has developed automated cell culture equipment for cell sheets incorporating tissue engineering undertaken jointly with Tokyo Women's Medical University, which has clinical experience with regenerative medicine.

Fig. 1 (a) shows the Automated Cell Culture Equipment 3 (ACE3) system for culturing up to 10 cell sheets at a time[5), 6), 7)]. In addition to using γ radiation to sterilize the set of closed culture vessels and circuits prior to use, the system has a detachable design that allows the culture vessel and circuit modules to be replaced for each patient (single-use modules) to prevent cross-contamination between patients when performing autologous transplantation. While the environment inside the closed culture vessel and circuit is maintained at high humidity (95% or higher) during culture, the other internal parts of the system are kept dry. Along with maintaining the cleanliness of the environment where the system is located to minimize the amount of dust generated during operation, its comparatively small installed size (1.7 m wide × 0.795 m deep × 1.58 m high) makes it suitable for installation at existing cell processing facilities (CPFs).

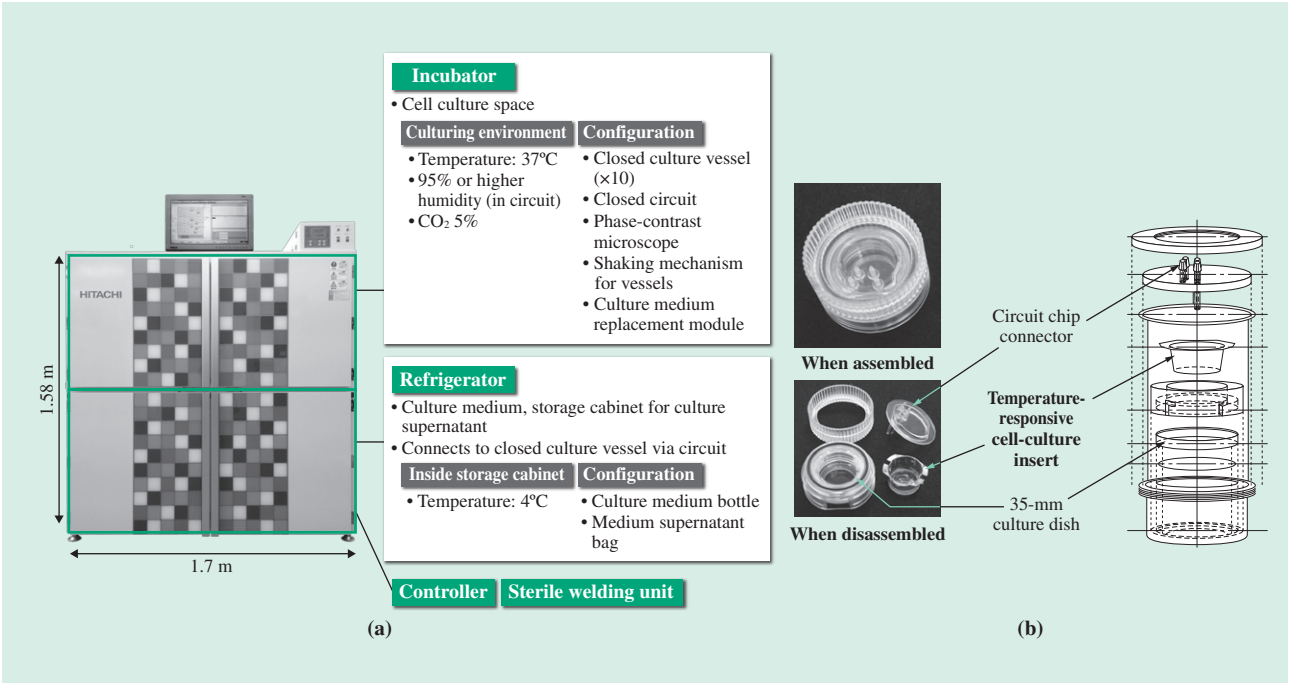


*Fig. 1—ACE3 Automated Cell Culture Equipment for Cell Sheets and Closed Culture Vessel.*
*(a) shows external view and configuration of Automated Cell Culture Equipment 3 (ACE3) system for culturing up to 10 cell sheets at a time. (b) shows configuration of closed culture vessel for double-layered culture with temperature-responsive cell-culture insert.*

The main features of the automated culture function of the ACE3 are cell seeding, maintenance of constant temperature and humidity, gas exchange, medium exchange, and observation using a phase-contrast microscope. The microscope can be used to automatically record images of designated points in each closed culture vessel at user-specified time intervals. The system also supports remote operation from outside the CPF, with a function that enables users to manually observe and photograph any location in the closed culture vessels whenever they want.

The closed culture vessels can be used for the double-layered culture of epithelial cells with a sealed structure enclosing a cell-culture insert [see Fig. 1(b)]. Furthermore, the permeable membrane that forms the culture surface of the cell-culture insert is grafted using a temperature-responsive polymer (by CellSeed Inc.). Varying the temperature from the culture temperature (37ºC) to room temperature (below the phase transition temperature of 32ºC) changes the culture surface treated with temperature-responsive polymer from hydrophobic to hydrophilic. This detaches the adhered cells, enabling the cell sheets to be harvested without the use of enzymes and without damaging the cells[8].

After the sterile removal of the closed culture vessels from the system, the cell sheets in the closed culture vessels in which they have been automatically cultured are transported at constant temperature to the operating theater or other point of use in the transportation vessels provided with the system. This maintains the quality of the cells or regenerated tissue at the completion of production.

An ACE3 has been installed at Tokyo Women's Medical University for use in restoring the esophagus after the removal of esophageal cancer by endoscopic surgery[9], and its performance in automated culture is being assessed. Automated culture tests performed on the ACE3 using commercially available human oral mucosal epithelial cells demonstrated its ability to perform sterile production of cell sheets that satisfy the same criteria as applied to cell sheets produced manually, namely cell morphology, stratification, sheet separation and harvesting, cell count, cell viability, and marker protein positive rate.

Hitachi has also developed a large automatic human myoblast sub-culture system using closed large-scale surface culture vessels (59 cm × 70 cm) specially designed for cardiomyocyte regeneration through participation in a Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) based at Tokyo Women's Medical University. This system can culture human myoblasts automatically with a yield in the range of $10^9$ cells. As demand for mass culture applications such as cardiomyocyte regeneration and undifferentiated iPS cells is expected to grow in the future, Hitachi aims to use this system as a platform for developing mass culture production technology.

## Cell Transportation Technology

The commercialization of regenerative medicine and its establishment as an industry in its own right requires technologies for transporting the cells and tissue from the facility where they are produced to the recipient medical institution. The transportation options include road, rail, and air, depending on the distance, and whichever method is used, ensuring the sterility and efficacy (cell viability, morphology, and so on) of the manufactured tissue transportation is just as vital as it is beforehand. Maintaining quality requires control of the factors that cause environmental changes during cell transportation, with parameters like temperature and pressure in particular needing to be kept constant just as in the manufacturing

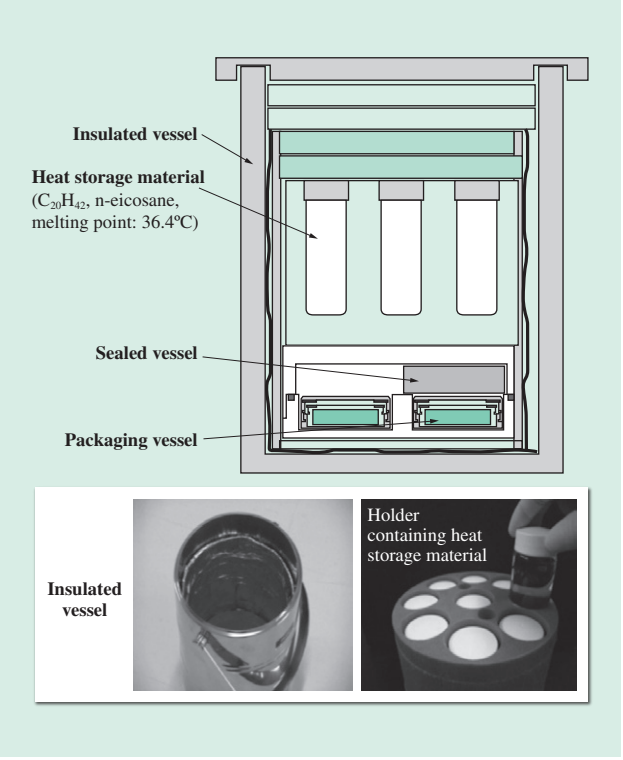


*Fig. 2—Cell Transportation Vessels.*
*By utilizing the latent heat of a heat storage material to avoid the need for a power supply, these vessels enable safe transportation by air.*

process. It is also important that transportation does not compromise the cleanliness achieved at the CPF.

Hitachi has developed cell transportation vessels suitable for use with cell sheets produced using regenerative medicine[10), (11)]. To enable air freighting, the vessels are designed to maintain temperature by using the latent heat from a heat storage material that does not require a power supply. To ensure that the cells are held in a suitable environment during transportation, the vessels are designed to control the pressure as well as the temperature, and to maintain the same level of cleanliness as the clean room used for culturing (see Fig. 2). The vessels are currently used mainly for clinical research that spans multiple facilities, primarily Osaka University – The University of Tokyo and Osaka University.

## WIDER ADOPTION OF REGENERATIVE MEDICINE DRIVEN BY OPEN INNOVATION

In the future, Hitachi aims to deepen open innovation, adopt the correct approach to the challenges of cell production for regenerative medicine, and achieve mass culture production at CPFs through the development and automation of cell processing technology. This involves establishing a smart cell value chain by integrating with related businesses, which include CPFs, bacteriological analyzers, process management systems, analyzers for biochemical and immunological testing, diagnostic imaging systems, and information technology (IT) management. In this way, it aims to create total solutions for regenerative medicine that can supply patients around the world with safe and effective cells (see Fig. 3). Through a combination of its technologies and business activities, Hitachi is working toward the wider adoption of regenerative medicine.

## CONCLUSIONS

This article has described the progress of development by Hitachi of automated cell culture equipment that facilitates the wider adoption of regenerative medicine by playing a core role in cell production, and transportation technology for supplying cells to patients around the world. Hitachi intends to supply total solutions and contribute to the wider adoption of regenerative medicine by establishing a smart cell

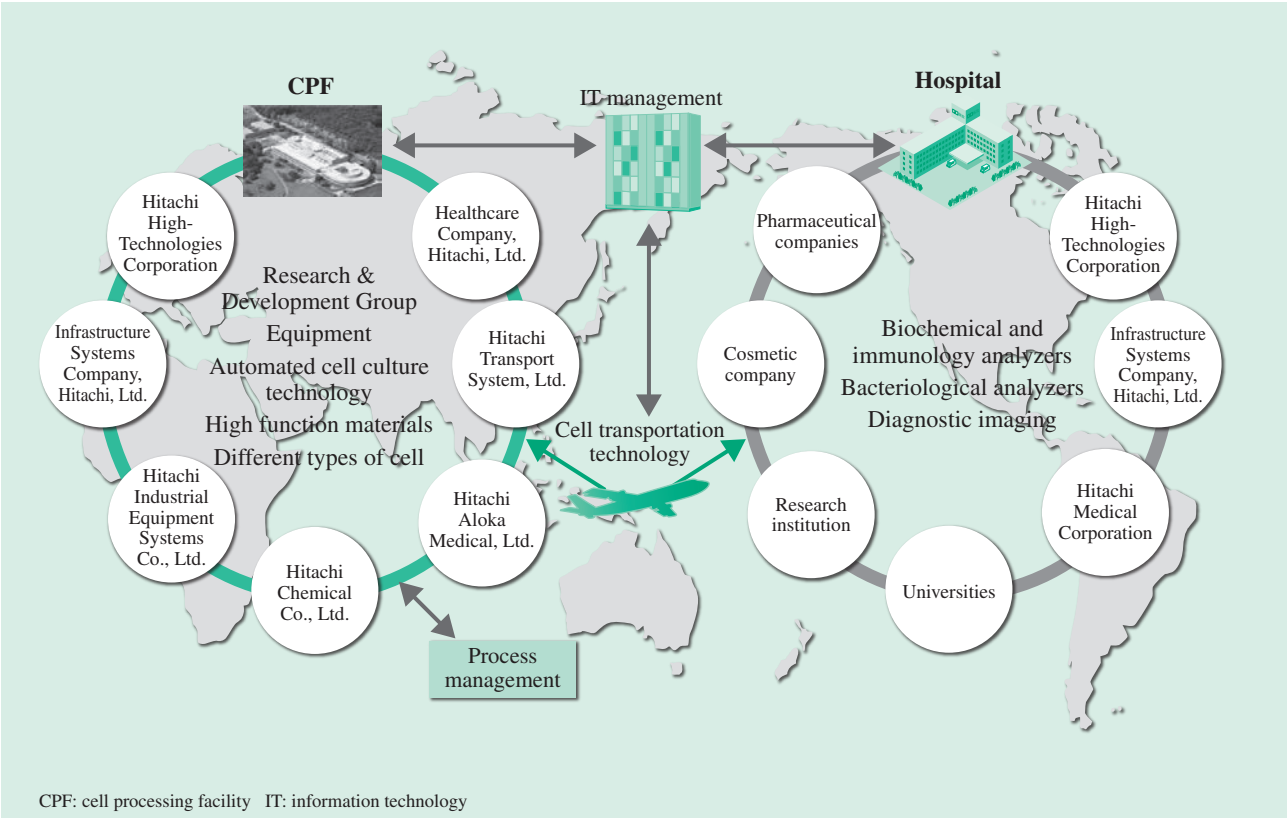


*Fig. 3—Future Form of Total Solutions for Regenerative Medicine Provided by Hitachi.*
*By combining technologies from affiliated companies, Hitachi is establishing a smart cell value chain to satisfy customer needs.*

value chain based on IT management systems through the integration of this research and development with its existing CPF and other healthcare businesses.

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