Featured Articles

Realizing the Future that Regenerative Medicine Will Open

Shizu Takeda, Ph.D.

OVERVIEW: Regenerative medicine is an innovative approach to medicine that will make it possible to overcome diseases that are difficult to treat with conventional medicine. It also represents a new industry in which high growth is anticipated. Regenerative medicine is still in its infancy with many challenges still remaining, such as conducting research and development of therapeutically effective cells, assuring safety, reducing cell production costs, establishing cell logistics, and establishing hospitals for regenerative medicine. It is hoped that regenerative medicine will enter widespread use, overcoming these challenges and establishing the capabilities to deliver high-quality cells to hospitals in sufficient quantities and at a reasonable cost. In addition to engaging in research and development aimed at commercializing and popularizing the latest basic and applied research through a process of open innovation, Hitachi will bring together the technology and know-how it has acquired through related business activities to establish new cell value chains. In this way it will contribute to the creation of a society in which everyone can live a long and healthy life with access to the benefits of regenerative medicine.

INTRODUCTION

REGENERATIVE medicine, the technique of transplanting cells, the smallest units of life, into the human body to treat disease is now entering practical use. Regenerative medicine is subject to high public expectations as an innovative approach to medicine that will make it possible to cure diseases that are difficult to treat with conventional medicine, treating them instead by transplanting certain healthy biological tissues into the body.

The production of cells for regenerative medicine involves many steps from harvesting the source cells from an individual to finally transplanting the cells into the patient, including cell preparation, culturing, processing, testing, and transportation. Essential to the commercialization and popularization of regenerative medicine will be the establishment of new cell value chains that differ significantly from the ways in which conventional low-molecular-weight drugs and biopharmaceuticals are produced and supplied. There are high hopes that wider use of regenerative medicine will restore large numbers of patients to health by supplying hospitals with sufficient quantities of cells that are therapeutically effective and safe, in a timely manner.

This article describes what Hitachi is doing to facilitate wider adoption of regenerative medicine.

HOPES AND CHALLENGES FOR REGENERATIVE MEDICINE

Regenerative medicine opens up the possibility of providing previously unavailable new treatments such as using processed cells for overcoming previously untreatable diseases and for reconstructing tissues. By providing cures for patients, it can also help reduce medical costs and health insurance premiums by eliminating the need for long-term hospitalization or drug regimes.

It is being forecast[1] that the market for regenerative medicine will grow rapidly from 2020 onwards as increasing clinical use is made of induced pluripotent stem (iPS) or embryonic stem cells, reaching a predicted market size of 17 trillion yen globally by 2030, including the associated industries.

Currently still in its infancy, one of the most important issues currently facing regenerative medicine is the research and development of therapeutically effective cells. Precise and efficient culturing techniques for getting cells to differentiate into the desired cell type based on basic findings are actively

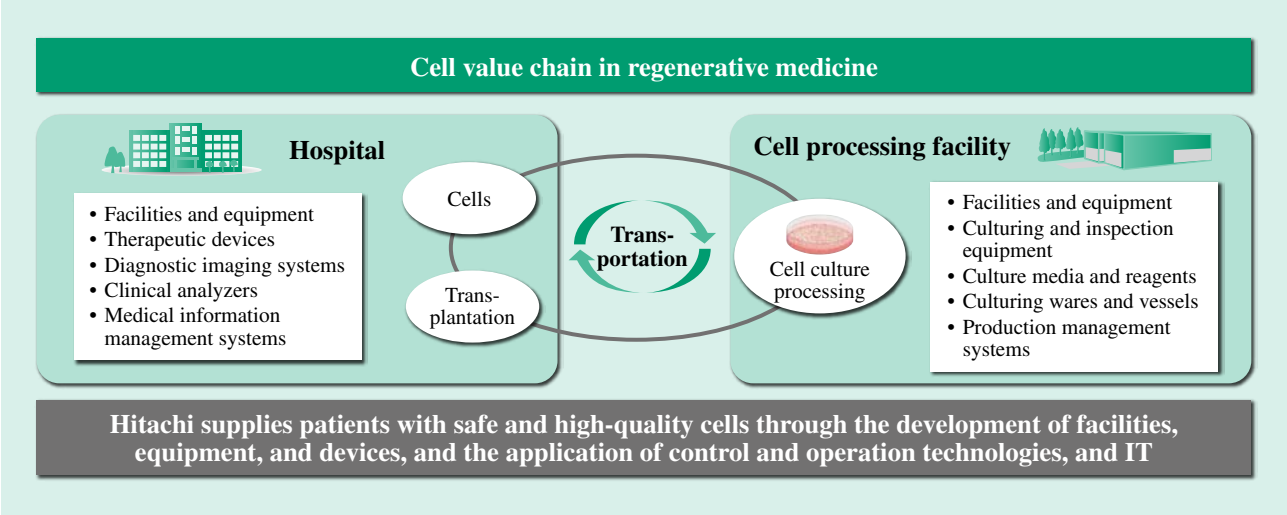


Fig. 1—Cell Value Chain in Regenerative Medicine.
Hitachi uses the technology and know-how acquired through its research and development and business activities to provide comprehensive support for regenerative medicine.

being researched, primarily in academia. A second important issue, assuring safety, is of equal importance to efficacy. As the amount of clinical data available on regenerative medicine remains comparatively small, the time and expense for research on safety is as much as or even more than that for research on safety. A third challenge for the commercialization and popularization of regenerative medicine is how to bring down cell production costs, an issue that needs to be addressed by industry in particular. The current high cost of cell production is one of the major obstacles to the wider adoption of regenerative medicine.

To establish a suitable environment for industrialization, the Act on the Safety of Regenerative Medicine, etc. and the Revised Pharmaceutical Affairs Law came into force in Japan in 2014. The provisions included a system for accelerated approval of cell products and the ability to outsource activities to cell culturing providers. The companies involved in regenerative medicine need to develop products and services that enable the supply of safe and effective cells at a reasonable cost through collaboration between industry, government, and academia.

HITACHI'S VISION

Hitachi is currently engaged in numerous activities intended to facilitate the future medical practices made possible by regenerative medicine. As noted in the introduction, there are various different steps in the cell value chain, each of which requires a large number of products and services.

Hitachi can build cell value chains and provide comprehensive support for regenerative medicine by combining the facilities, equipment, device development capabilities, control and operation technologies, process management technologies, and information technology that it has built up primarily through its businesses in the medical product, semiconductor manufacturing, diagnostic, and healthcare fields[2), 3)] (see Fig. 1).

Hitachi bases its business operations around an extensive portfolio of technologies related to cell production, with existing businesses including the design and construction of cell processing facilities, safety cabinets and other equipment, bacteriological analyzers, and process management systems. Its clinical testing techniques for biochemistry and immunology can be extended, not only to blood testing before and after transplantation, but also to the monitoring of cell culture supernatants. Hitachi is also expanding its diagnostic imaging equipment business, which includes medical equipment for magnetic resonance imaging (MRI) and ultrasound before and after transplantation. In a new initiative, Hitachi Chemical Co., Ltd. plans to launch a contract cell manufacturing business for regenerative medicine in 2018.

In terms of research and development, Hitachi, Ltd.'s Center for Exploratory Research is developing[4)–7)] a closed-system automated cell culturing technique with excellent sterility. Automated cell culturing technology is critical to the growth of the regenerative medicine industry, being a key technology for resolving issues with existing manual techniques,

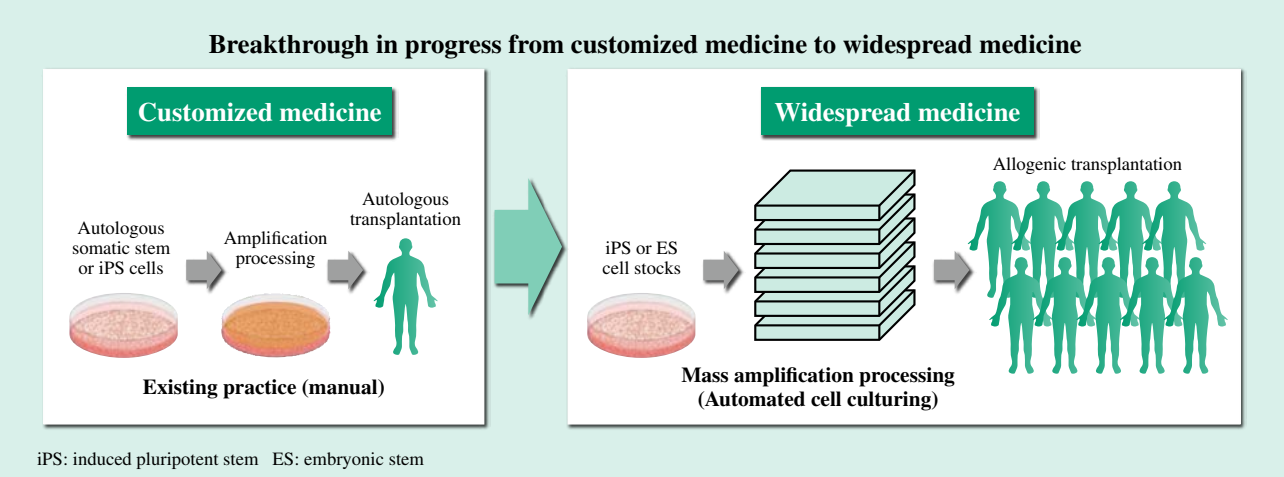


Fig. 2—Breakthrough in Progress from Customized Medicine to Widespread Medicine.
The use of high-volume automated culturing to produce cells at a reasonable cost can transform regenerative medicine from customized medicine to widespread medicine.

which include productivity, achievement of reliable quality, labor costs, and the operation and maintenance costs of cell processing facilities. While customized medicine using somatic stem cells and autologous transplantation is currently in the mainstream, the production of cells in high volumes will be essential in the future for regenerative medicine using allogenic transplantation, which involves use of iPS cells, an area in which Japan is a world leader (see Fig. 2). Because regenerative medicine using autologous transplantation involves single-lot cell production, the cell production unit cost for each treatment is expensive. In particular, there are significant costs associated with culturing the source iPS cells and pre-delivery quality inspection after production when these are used in regenerative medicine, and this is a high barrier to its becoming a widespread medicine.

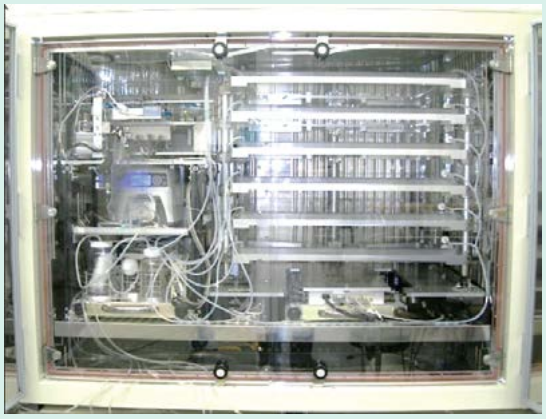
Kyoto University is currently building up a stock of iPS cells for use in allogenic transplantation for regenerative medicine. Allogenic transplantation involves the high-volume production of cells, with one lot capable of being used in the treatment of many patients, so it has the potential to significantly reduce the cost of production through economies of scale. This should prove particularly beneficial in the application of iPS cells where the costs associated with production and quality inspection are high. High-volume production also has great benefits for quality management. Although it uses cells from a donor, which requires patients to take immunosuppressants, allogenic transplantation is recognized for its potential to supply patients with therapeutic cells produced from iPS cells at a reasonable cost. To facilitate the wider adoption of regenerative medicine, it is hoped that allogenic transplantation using iPS cells will soon enter practical use.

RESEARCH AND DEVELOPMENT BASED ON OPEN INNOVATION

To achieve wider adoption of regenerative medicine, Hitachi is developing techniques for the mass production of cells by engaging in open innovation with academic institutions that have leading-edge cell culturing techniques and working with national projects. A particular feature of these techniques is the use of automated culturing in a closed space to maintain a sterile environment in accordance with the Good Gene-, Cellular-, and Tissue-based Products Manufacturing Practice (GCTP). The closed-system culturing space that prevents contamination by microorganisms from the outside environment, etc. is a minimal amount of space, limited to just the interior of the culture vessel, the connected fluid supply tubes, and bottles. Detachable modules are used for the culture vessel, tubes, and bottles that make up the contiguous culture space and fluid supply circuit, and their interiors are sterilized using gamma radiation prior to automatic culturing. Modules have an extremely safe design[(5)–(7)] because they are single-use to prevent cross-contamination between patients and between lots. Furthermore, a unique fluid supply mechanism enables culturing to be performed in parallel using multiple vessels.

Hitachi's automated cell culture equipment can be used for a wide range of adherent cells, including

(a) Automated cell culture equipment for cell sheets



(b) Automated cell culture equipment for high-volume culturing

FIRST Program: Funding Program for World-leading Innovative R&D on Science and Technology
* The automated cell culture equipment for cell sheets was developed under the Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program of the Ministry of Education, Culture, Sports, Science and Technology. The automated cell culture equipment for high-volume culturing was developed under the FIRST Program of the Cabinet Office.

Fig. 3—Hitachi's Automated Cell Culture Equipment.
Hitachi equipment can meet both current and future needs on multiple scales from small to large by using closed-system automated cell culturing technologies that have excellent sterility.

epithelial and iPS cells. They can be broadly divided into small-scale systems with comparatively small culture vessels that are easier for processing cell products such as cell sheets, etc., and systems intended for culturing on a high-volume scale where the aim is cell amplification. These systems can meet both current and future needs on multiple scales, from small scale to large scale (see Fig. 3). Hitachi has engaged in joint research with Tokyo Women's Medical University to undertake trials of automated cell sheet culturing of rabbit corneal epithelium and human oral mucosal epithelium cell sheets for use in regeneration of the cornea and regeneration after surgery for the removal of esophagus cancer, demonstrating that automated culturing of cell sheets can achieve similar quality to manual culturing techniques[(4)–(10)].

Hitachi has participated along with Sumitomo Dainippon Pharma Co., Ltd. and Kyoto University in the Project Focused on Developing Key Evaluation Technology: Evaluation for Industrialization in the Field of Regenerative Medicine run by the Japan Agency for Medical Research and Development (AMED), developing key technologies for validating process improvements associated with the adoption of high-volume automated cell culture equipment for the mass production of iPS cells.

In an analysis of comprehensive gene expression in undifferentiated iPS cells using DNA microarrays, which serve as one of the primary assessment criteria, a strong correlation with respect to gene expression between closed system cultures with a large area (500 cm^2) and the conventional manual open system cultures with 6-well (10 cm^2) plates [see Fig. 4 (a)]. Furthermore, flow cytometry using the SSEA-4 and TRA-1 antibodies that act as undifferentiated markers found a high marker positive rate for closed system cultures with a large area, similar to that for manual culturing, indicating that the iPS cells had been maintained in an undifferentiated state [see Fig. 4 (b)].

CONCLUSIONS

It is thought that many patients may be looking forward to the commercialization and popularization of regenerative medicine as a way to overcome diseases that are difficult to treat using conventional medicine. Hitachi would like to create a future society in which everyone can benefit from regenerative medicine by combining not only its facilities, production equipment, and various instrument businesses, but also its cell transportation technologies, operational technologies, and information management technologies to build cell value chains that can deliver sufficient quantities of high-quality cells.

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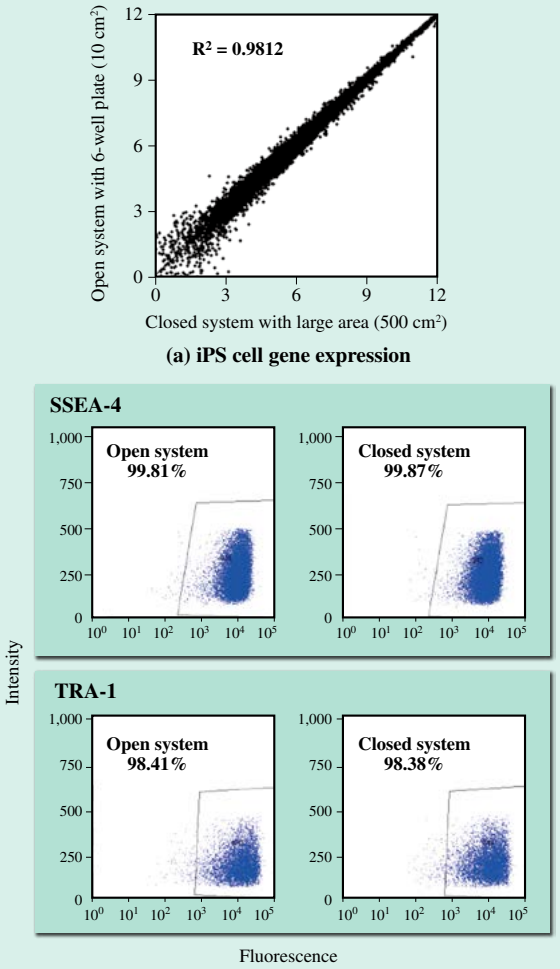

DNA: deoxyribonucleic acid
AMED: Japan Agency for Medical Research and Development
* Developed under the Project Focused on Developing Key Evaluation Technology: Evaluation for Industrialization in the Field of Regenerative Medicine run by AMED.

Fig. 4—Validating Process Improvements Associated with Adoption of High-volume Automated Cell Culture Equipment. (a) is a scatter plot of iPS cell gene expression levels obtained using DNA microarrays. (b) shows the analysis results (marker positive rates) for iPS cell undifferentiation obtained by flow cytometry.

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