

Air Conditioning Solution for Regenerative Medicine

Regenerative medicine using processed cells is recognized for its potential to treat diseases that have previously been difficult to treat, with research underway globally on getting it to the stage of clinical use. There has also been considerable work done on its commercialization in Japan with a new law on regenerative medicine (Act on Safety of Regenerative Medicine) enforced in November 2014 along with changes to the Pharmaceutical and Medical Device Act. The size of the market for treatments based on regenerative medicine is predicted to reach one trillion yen by 2030 and there is also a strong public interest case for the enhancements it could bring to patients' quality of life⁽¹⁾. Against this background, Hitachi Global Life Solutions, Inc. is utilizing technology for precisely controlling air quality in terms of temperature, humidity, cleanliness, and pressure to supply the regenerative medicine industry with air conditioning solutions for cell processing facilities. In the process of supplying these solutions, the company draws on its total engineering capabilities for coordinating air conditioning solutions and equipment at cell processing facilities in collaboration with the wide range of other companies involved in facility operation, thereby delivering economic value to customers in forms that include reduced business losses and the provision of the right environment by supplying the air conditioning solutions that they actually want.

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1. Introduction

Past pharmaceuticals have included the use of low-molecular-weight compounds and cell secretions as medicines. Recent years, however, have seen extensive research into regenerative medicine that involves processing the very cells that make up living organisms in ways that address particular illnesses and using those cells to treat the illness, and there is strong demand for its clinical use.

Currently, regenerative medicine and related products authorized for use in Japan mainly involve the

use of stem cells and other cells that are then cultured into the desired cell type or tissue for use in treatment. Induced pluripotent stem (iPS) and embryonic stem (ES) cells can resolve the problem of how to source the stem cells required by regenerative medicine and high hopes are being placed on clinical research in this area. The use of chimeric antigen receptor T cells (CAR T cells) has attracted attention, having been approved for cancer treatment in Japan. This involves extracting the patient's own T cells and then genetically modifying them for use in treatment.

The cells used in regenerative medicine are mainly produced at what are known as cell processing facilities. These facilities are made up of sterile clean rooms

Table 1 — Maximum Permitted Particle Counts in Sterile Clean Room

The table lists the different grades of air cleanliness for areas used in sterile pharmaceutical production.

Grade	No production in progress		Production in progress	
	Maximum permitted suspended particle count/m ³ 0.5 µm	Maximum permitted suspended particle count/m ³ 5 µm	Maximum permitted suspended particle count/m ³ 0.5 µm	Maximum permitted suspended particle count/m ³ 5 µm
A	3,520 or less	20 or less	3,520 or less	20 or less
B	3,520 or less	29 or less	352,000 or less	2,900 or less
C	352,000 or less	2,900 or less	3,520,000 or less	29,000 or less
D	3,520,000 or less	29,000 or less	No restriction	No restriction

Source: World Health Organization (WHO) Technical Report Series, No. 961, Annex 6, 2011

with separate zones for the different processes used, and maintain high levels of sterility in accordance with the stipulated criteria for each zone. A feature of these facilities is that the air cleanliness, temperature, humidity, and pressure differences between rooms are classified into separate grades (see **Table 1**).

The Air Conditioning Systems Engineering Business Unit of Hitachi Global Life Solutions, Inc. (Hitachi GLS) has put a lot of effort into special-purpose air conditioning applications that utilize control technology for precisely controlling air quality, including clean rooms for medical research and manufacturing, biohazard rooms for testing pathogens, and industrial clean rooms for semiconductor manufacturing. Meanwhile, there has been an upsurge in involvement by private-sector companies resulting from the introduction in November 2014 of the Act on Safety of Regenerative Medicine that permitted the construction of privately-run cell processing facilities. It is against this background that Hitachi GLS is seeking to create a sustainable society by means of air conditioning solutions for the regenerative medicine industry that utilize control technology from special-purpose air conditioning applications.

2. Solution Overview and Features of Clean Rooms

To strengthen its air conditioning solutions business for cell processing facilities, Hitachi GLS identified the following additional four points as important for managing production facilities.

- (1) Use of flat panels to ensure cleanliness and ease of cleaning
- (2) Use of centralized hydrogen peroxide biodecontamination system to maintain sterility

- (3) Use of the exiida service for remote monitoring and predictive diagnosis as a monitoring system for preventing unexpected faults in air conditioning equipment
- (4) Coordination of equipment used in production

Based on a belief that a more vibrant market for regenerative medicine in Japan would come about if solutions that address these points could be provided, plans were made to build a cell processing facility at Nihonbashi in the Chuo district of Tokyo. As Hitachi GLS handled the production and sale of all of the construction materials and equipment used to build the facility, it set out to overcome the challenges of achieving these four points through collaborative creation with other companies.

2.1

Collaborative Creation with Other Companies

In cooperation with Hitachi, Ltd.'s Building Systems Business Unit, Hitachi GLS engaged in collaborative creation on the construction of the cell processing facility with the Life Science bases of Mitsui Fudosan Co., Ltd. in Nihonbashi, Tokyo.

Nihonbashi is home to a number of organizations that work in the life sciences, including pharmaceutical companies and the offices of the Japanese Society for Regenerative Medicine, and Hitachi GLS plans to locate its cell processing facility showroom in the neighborhood. Normal practice at cell processing facilities is to restrict access to only those people needed for the cell processing work and this obviously presents difficulties when wanting to show around customers looking to build such a facility of their own. The Regenerative Medicine Innovation Center, which integrates the latest technologies, was established as a way to overcome this problem, taking advantage of the Nihonbashi location.

The equipment at the center is arranged differently than most other facilities. This is so that collaborative creation partners can bring along the latest equipment equipped with functions that integrate with those of other vendors.

The collaborative creation partners share a common desire to boost activity in the market for regenerative medicine, and the aim is for engineering work that looks ahead to the future automation of equipment and systems to be undertaken in parallel with “One HITACHI” initiatives.

2. 2
Features of Regenerative Medicine Innovation Center

The following subsections (1) through (5) describe features of the cell processing facility at Hitachi GLS’s Regenerative Medicine Innovation Center.

(1) Layout of cell processing facility
The clean rooms that make up the clean environment at the cell processing facility are a cell preparation room (approx. 33 m²), a quality control area (12 m²), and an equipment storeroom (23 m²), as well as storerooms and dispatch rooms (see **Figure 1**).

Each of these rooms is equipped with equipment that uses Hitachi GLS’s special-purpose air conditioning technology for the precise control of temperature, humidity, cleanliness, and pressure. The grade B rooms used for cell processing and the secondary dressing room use a centralized system for automatic entire-room decontamination by the direct injection of hydrogen peroxide gas for sterilization.

(2) Flat panels
The two main construction materials used in sterile clean rooms at a cell processing facility are boards with steel reinforcing and insulation-filled panels. On

Figure 1 — Plan for Hitachi GLS’s Regenerative Medicine Innovation Center
The plan shows the systems, equipment, and construction materials used by the cell processing facility.

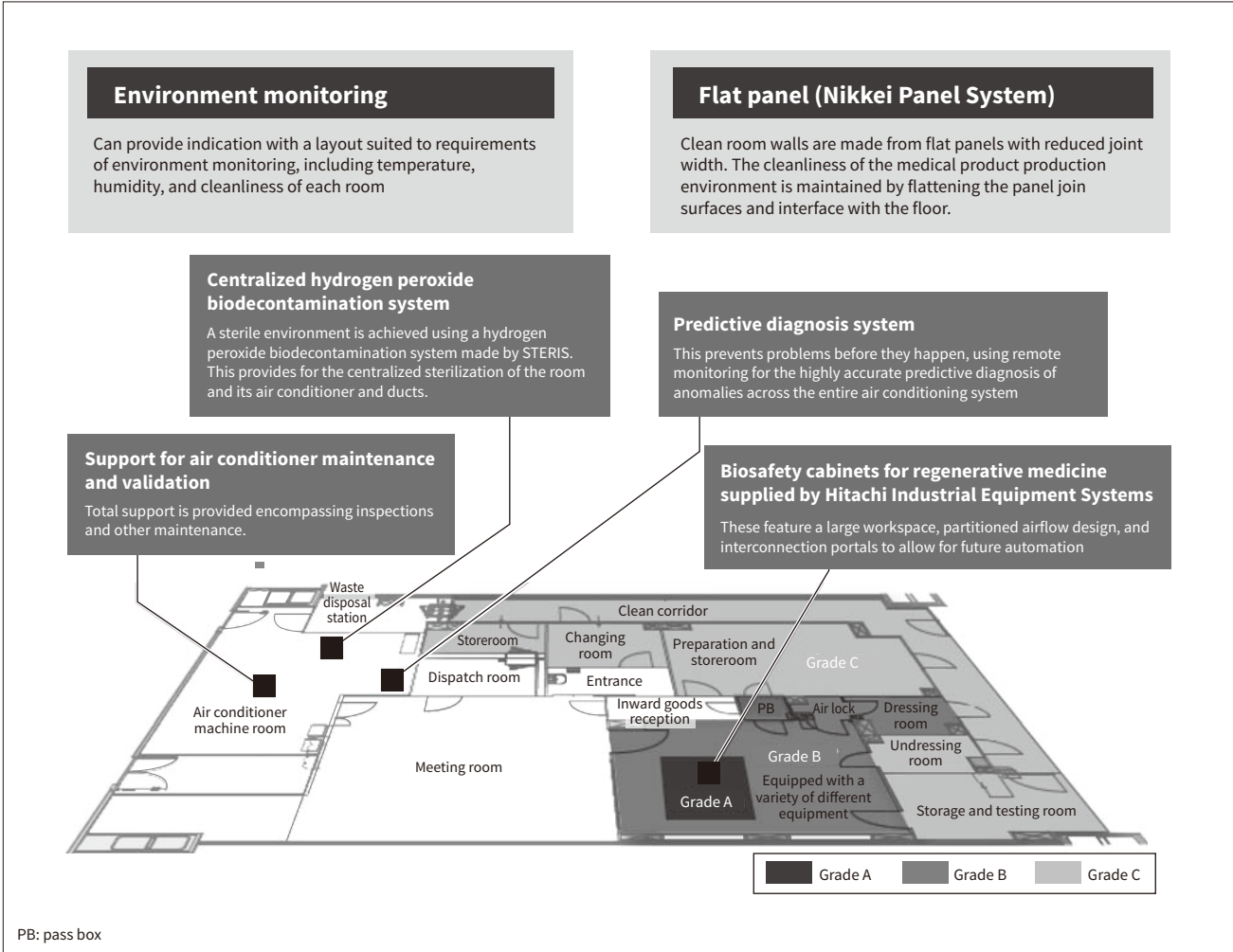


Figure 2 — Grade B Room

The photograph shows the newly constructed grade B room equipped with biohazard equipment.



this matter, Hitachi GLS undertook a joint study with Nikkei Panel System Co., Ltd. that resulted in insulation panels being adopted for reasons of both shorter construction times and better airtightness. With reference to what is being done in the USA and Europe in particular, panels with flat joints were chosen to comply with Building Standards Act and to allow for the prevalence of earthquakes in Japan (see **Figure 2**). In addition to the panels, a door supplier also participated in this planning and flat profiles are now used wherever possible.

(3) Centralized decontamination system

Sterilization of the interior of the cell processing facility is done by a hydrogen peroxide biodecontamination system that uses the dry process of STERIS

PLC that is widely used internationally, especially in the USA. A feature of the dry process for hydrogen peroxide decontamination is that it is less likely to be harmful to the panels or other equipment and materials.

Hydrogen peroxide decontamination is commonly performed as part of the changeover process when the cells being cultivated are replaced, and the system is configured such that the decontamination process for the cell preparation and other rooms can be started by switching the air conditioning from normal operation mode to sterilization mode. Hitachi GLS uses a centralized system that vaporizes the hydrogen peroxide in the intake duct of the air conditioner when performing the decontamination process such that the hydrogen peroxide remains in gaseous form as it sterilizes the cell preparation room from the primary side of the high-efficiency particulate air (HEPA) filter that forms part of the clean room (see **Figure 3**). (4) Use of the exiida service for remote monitoring and predictive diagnosis as a monitoring system for preventing unexpected faults in air conditioning equipment

Control of air quality is crucial for a cell processing facility, requiring the precise control of temperature, humidity, pressure, and cleanliness. Air conditioning systems play a central role in this and it is vital that outages do not occur during cell production.

Figure 3 — Layout of Ducting for Centralized Hydrogen Peroxide Biodecontamination

The system for generating the hydrogen peroxide used for decontamination connects to the air conditioning ducts to sterilize the associated area.

Centralized hydrogen peroxide biodecontamination system (STERIS)



Efficient sterilization is achieved using centralized decontamination

VHP: vaporized hydrogen peroxide

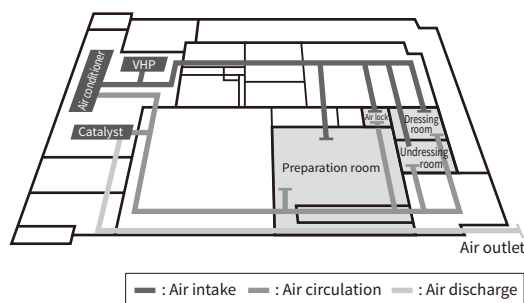


Diagram of decontamination cycle

At Nihonbashi, Hitachi GLS installed a system it developed that uses the Internet of Things (IoT) for advance detection of problems in air conditioners. This is called the exiida service for remote monitoring and predictive diagnosis. In the event an anomaly is detected, the maintenance response can be coordinated with operations to minimize any impact on production.

(5) Coordination of equipment used in production

Biosafety cabinets designed specifically for regenerative medicine and supplied by Hitachi Industrial Equipment Systems Co., Ltd. provide the grade A areas that are crucial to cell manipulation at the cell processing facility. The Hitachi cabinets are equipped with the following six features that are frequently needed in regenerative medicine applications (see **Figure 4**).

- (a) 800-mm-deep workspace, 200 mm larger than standard models
- (b) Built-in monitor for displaying work instructions or viewing cells
- (c) Portals can be installed on either side to facilitate future integration with other equipment
- (d) Function for rapid completion of hydrogen peroxide decontamination process that can be performed independently for each cabinet
- (e) Built-in intercom for communication with people outside the clean room
- (f) Allow retrofitting of a microscope, dust box, and other accessories as needed

Figure 4 — Cell Preparation Cabinet Installed in Grade B Area

The cabinet is designed to meet the cell processing requirements of regenerative medicine.



Hitachi GLS is also working to coordinate equipment for future automation requirements, such as the installation of incubators equipped with an automatic culture replacement unit.

2.3

Future Challenges

Keeping equipment functional through ongoing maintenance and regular validation are important tasks at a cell processing facility. Hitachi GLS has its own vendor service network that provides the infrastructure for customers to use their air conditioning systems with confidence.

Given that depopulation and other issues associated with aging demographics and a low birthrate will make the recruitment and skills transfer of maintenance staff more difficult for customers in the future, technology that uses the IoT to deal pre-emptively with problems in air conditioners will be essential. It is also anticipated that manufacturing will shift away from manual operation and toward greater automation in order to ensure more reliable quality.

In the future, Hitachi GLS intends to proceed with the development of concepts for the next generation of cell processing facilities that will feature modularization and greater efficiencies, working with customers and collaborative creation partners to enhance the automation needed for these regenerative medicine facilities and the use of workflow planning to increase productivity per unit of floorspace. The Regenerative Medicine Innovation Center will play a central role in this work. With regard to product development for the equipment used in clinics, as many cell processing facilities will be located in leased buildings, the company will also develop proposals that include automation at the Regenerative Medicine Innovation Center, which is itself located in a leased building in Nihonbashi.

3. Conclusions

This article has focused on the Regenerative Medicine Innovation Center to describe the work being done by Hitachi GLS on an air conditioning solution for the regenerative medicine market, one of the company's

special-purpose air conditioning solutions. The technology of regenerative medicine is advancing rapidly and Hitachi GLS intends to keep pace with this progress, continuing to publish information so that it can continue supplying solutions that contribute to society as well as business growth.

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Reference

- 1) The Ministry of Economy, Trade and Industry, "METI Releases the Report by the Study Group on Commercialization and Industrialization of Regenerative Medicine," (Feb. 2013), <https://www.mhlw.go.jp/stf/shingi/2r9852000002v591-att/2r9852000002v5dn.pdf> in Japanese.

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