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Original Article

A novel, flexible and automated manufacturing facility for cell-based health care products: Tissue Factory

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ABSTRACT

Introduction: Current production facilities for Cell-Based Health care Products (CBHPs), also referred as Advanced-Therapy Medicinal Products or Regenerative Medicine Products, are still dependent on manual work performed by skilled workers. A more robust, safer and efficient manufacturing system will be necessary to meet the expected expansion of this industrial field in the future. Thus, the 'flexible Modular Platform (fMP)' was newly designed to be a true "factory" utilizing the state-of-the-art technology to replace conventional "laboratory-like" manufacturing methods. Then, we built the Tissue Factory as the first actual entity of the fMP.

Methods: The Tissue Factory was designed based on the fMP in which several automated modules are combined to perform various culture processes. Each module has a biologically sealed chamber that can be decontaminated by hydrogen peroxide. The asepticity of the processing environment was tested according to a pharmaceutical sterility method. Then, three procedures, production of multi-layered skeletal myoblast sheets, expansion of human articular chondrocytes and passage culture of human induced pluripotent stem cells, were conducted by the system to confirm its ability to manufacture CHBPs.

Results: Falling or adhered microorganisms were not detected either just after decontamination or during the cell culture processes. In cell culture tests, multi-layered skeletal myoblast sheets were successfully manufactured using the method optimized for automatic processing. In addition, human articular chondrocytes and human induced-pluripotent stem cells could be propagated through three passages by the system at a yield comparable to manual operations.

Conclusions: The Tissue Factory, based on the fMP, successfully reproduced three tentative manufacturing processes of CBHPs without any microbial contamination. The platform will improve the manufacturability in terms of lower production cost, improved quality variance and reduced contamination risks. Moreover, its flexibility has the potential to adapt to the modern challenges in the business environment including employment issues, low operational rates, and relocation of facilities. The fMP is expected to become the standard design basis of future manufacturing facilities for CBHPs.

Abbreviations: CBHP, cell-based health care product; fMP, flexible Modular Platform.

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1. Introduction

Cell-based health care product (CBHP) is 'health care product that contains or consists of pro- or eukaryotic cells or cell derived biological entities as an essential ingredient' as defined in ISO 18362:2016 [1]. These products were also known as Advanced-Therapy Medicinal Products or Regenerative Medicine Products although there are some differences between their definitions. CBHPs are revolutionary new medicines that have recently been made possible and are going to form a new industrial field [2–3]. However, current production facilities for CBHPs are still dependent on manual techniques performed by skilled workers, with ongoing problems of quality variation, microbial contamination risk, and productivity limitations [4–6]. We believe that a more robust, safer and more efficient manufacturing system will be necessary as we expect this new industrial field to expand significantly in the future. Thus, we designed a whole new manufacturing system for CBHPs, aiming for a true "factory", to replace conventional "laboratory-like" manufacturing methods.

Fundamentally, the authors agreed that automation of key processes is essential in order to achieve mass production and ensure stable quality [7–9]. Generally, there are two types of automatic culture apparatus. One is a versatile type that carries out various processes with one device, and the second is a single function type that carries out only one sub process. The former is usually designed to mimic manual work by industrial robots, and it is not possible to exceed manual productivity. In contrast, the second is very efficient for a specific process although it requires manual work to bridge each process. Therefore, we decided to develop an 'open platform' that connects multiple single function apparatuses together and mediates the exchange of materials and information between each apparatus. The characteristics of CBHP manufacturing dictate that the time required for culturing cells is much longer than the time required for cell manipulation. This meant that the design of a CBHP production system should not be a production line method, but rather a cluster-type production method, where articles can be transferred between arbitrary modules via transfer robots. In a production line method, the entire manufacturing facility is engaged during the cell culture period, but in a cluster-type production method, the other apparatuses are separate and can be used during the cell culture period. This dramatically increases the operating efficiency of the manufacturing apparatuses. Moreover, to maximize the efficiency of this cluster production method, it is preferable that each production apparatus has the capability to be easily attached or detached based on the specific production needs.

A clean environment is critical to CBHP production, so we considered the application of biological isolators [10,11]. Unlike biological safety cabinets, biological isolators provide a microbiologically sealed space, so the risk of infectious microorganisms being brought in from the outside is extremely low. In addition, biological isolators are often equipped with a decontamination device. Once an isolator chamber is decontaminated with evaporated disinfectants, the inner space of the chamber remains clean until the chamber is opened for maintenance or some other purpose. A drawback of biological isolators is the low manual operability owing to the need for thick gloves by operators to separate chambers. We thought that by combining automatic apparatuses and biological isolators it would compensate for any limitations that each had on its own and create a cost-effective manufacturing facility. To enable attachment and detachment of each manufacturing apparatus, they were designed to be covered with a separate isolator. Consequently, each manufacturing apparatus becomes a highly independent 'module', which can be attached and detached into a cluster. For this reason, we gave it the name 'flexible Modular Platform (fMP)' (Fig. 1). In this paper, we developed a fMP-based CBHP manufacturing facility that was named Tissue Factory, and performed the manufacturing of multi-layered myoblast sheets to demonstrate its cell- and tissue-manufacturability. In addition, we conducted the passaging culture of human articular chondrocytes and human induced pluripotent stem cells to confirm the feasibility of hydrogen peroxide decontamination and the flexibility of the system for multi-product manufacturing.

2. Methods

2.1. Tissue Factory

The concept for a fMP makes it possible to build a given manufacturing process by combining several modules. Here, the term 'module' refers to the smallest independent apparatus that can be connected to and detached from the manufacturing system. After defining the fMP concept, a demonstrative manufacturing system, named 'Tissue Factory', was built.

2.1.1. Modules

Tissue Factory was designed for manufacturing multilayered skeletal muscle myoblast sheets. A total of nine modules and a Material Preparation Isolator were assembled (Table 1 and Fig. 2). Although a system could potentially have multiple Transfer Modules, we made a hexagonal Transfer Module (M1) to serve as a hub of the manufacturing cluster. Modules can be connected to five of the six sides of the central hexagon. An industrial robot designed for silicon wafers with minimal dust emission was adopted to transfer articles between modules. Processing modules (M2–M5) commonly have connection ports to the Transfer Module (M1). Incubation Modules (M7–M9) perform long-term processes such as cell culture. The essential difference from a Processing module is the standalone operability that can run parallel to the cell culture processes. In this study, three types of Incubation Modules were assembled. In order to introduce materials into the system, a Material Preparation Isolator (M10) and a Material Loading Module (M6) were produced. The Material Loading Module (M6) has two interfaces. It can be connected both to the Transfer Module and to the Material Preparation Isolator (M10). The Material Preparation Isolator (M10) is a commercially available isolator for manual processing customized to be equipped with a port for connecting to the Material Loading Module (M6). To introduce materials into the system the materials are first prepared in the Material Preparation Isolator (M10), placed on a rack in the Material Loading Module (M6), and then, the entire Material Loading Module (M6) is moved to an empty port on the Transfer Module (M1).

Within this system only the Transfer Module (M1), Large Scale Culture Module (M9) and Material Preparation Isolator (M10) were fixed to the floor. The height of the Transfer Module (M1) was 2460 mm. The side of each hexagon of the Transfer Module (M1) was 535 mm long. Unlike the other incubation modules, the Large Scale Culture Module (M9) was designed to be stationary, and the module had no sealed chamber because it uses only sealed culture vessels with pre-assembled tubing (a closed system). The other modules (M2-M8) were movable, and the heights were limited to under 1650 mm to ensure stability during movement. These modules were equipped with casters, allowing one operator to move and connect or detach from the Transfer Module (M1). Base plates of the Processing modules (M2-M5) and Material Loading Module (M6) were set at 750 mm above the floor. Robots and processing units were attached to each base plate and covered with a chamber that isolates its operational space from the outer environment. Clean air was provided from the ceiling of the chamber through a High Efficiency Particulate Air (HEPA) filter, and the air was evacuated from the corners of the base plate. In open air operations, such as opening the lids of culture dishes, articles were