NOVEL PROCESSING SYSTEM FOR CELL PRODUCTION: A CHALLENGE FOR DEVELOPMENT OF FLEXIBLE MODULAR PLATFORM

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ABSTRACT

In the last decade, cell and tissue therapies have encompassed a broad, rapidly growing field of medicine that involves the manipulation and administration of cells for the treatment of disease. Especially, the advances in cultured cell and tissue transplantation have offered promising strategies for reconstructing and repairing defective tissues in vivo, enabling damaged tissue to be replaced with cultured tissues that meet the needs of the individual patients.

The manufacture of cultured cells and tissues is still burdened by instability owing to the qualitative fluctuation of cell sources as raw materials and the risk of biological contamination. Efforts to commercialize cell-based therapies are driving the need for capable, scalable, manufacturing technologies including a bioreactor system (1). It should be certificated that these therapies meet regulatory requirements and are economically valuable at the industrial scale production. Innovative techniques of cell and tissue processing have been developed for therapeutic applications. In addition, the development of a processing system is considered to lead to safety, security and cost-saving for cell and tissue cultures. However, the criterion of facility design to date has not been clear (2).

In manufacturing, strict management against contamination and human error are compelled due to direct use of un-sterilizable products and the laboriousness of culture operations, respectively. Therefore, the system developments for ensuring a stable process and quality of therapeutic products are the critical steps. The isolator technology is the alternative system which can enable cell processing to be conducted in a closed aseptic environment, which may reduce equipment and maintenance/operation costs while providing a reliable aseptic environment which reduces product losses and helps ensure patient safety. The comparison of management between cell processing facilities with safety cabinet and with the isolator system reveals that isolator technology leads to reductions of the running cost as well as operational laboriousness in the small production, compared to the conventional cell processing facilities (CPF) with safety cabinet. Especially, in case of autologous cell processing, the CPFs are expected to handle cells collected from a large number of patients, and some believe that isolators with a function to prevent cross-contamination may be advantageous in providing a more reliable aseptic environment compared with open operation in manned CPFs.
In our current study (3), a novel design of manufacturing facility based on a flexible Modular Platform (fMP) has been proposed to realize that the individual modules can connect and disconnect flexibly with keeping the aseptic environment as well as biological containment in each module, leading to the compactness of aseptic processing area and quick change-over for multi-purposes and patients. This technology will make cost-saving with safety and security. As a model case of cell processing, the fMP was applied for the preparation of myoblast cell sheet. The cell processing of cell isolation from muscle tissue, primary culture, expansion culture, and cell sheet assembly was successfully performed, and the stable process was recognized through the several runs, suggesting the broad versatility for the production in other types of cells as well as multilayered sheets.

As it is known that the serial processes for cell processing, influence the quality of the cells, automation of the processes is expected not only to maintain an aseptic environment but also to lead to stable processing in CPF. It can be said in regenerative medicine that “the process is the product. Consequently, development and operational testing of automation equipment form one of the key issues in effective industrialization. Thus, our attempts are concluded to build an advanced culture system employing isolator technology. In addition, the adaptation of the fMP in CPF will lead to easy installation of the new modules for production line addition and/or revision through the clinical phases as well as commercial production, which contributes to the reduction of production costs.

Acknowledgments

This study was supported by the Japan Society for the Promotion of Science (JSPS) through the “Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program),” initiated by the Council for Science and Technology Policy (CSTP) and by Industrial Technology Research Grant Program in 2014 from New Energy and Industrial Technology Development Organization (NEDO) of Japan.

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