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# Development of Muse cell therapy for KAITEKI society

Clio is a regenerative medicine company that focuses on the research and development of Multilineage-differentiating stress-enduring (Muse) cells. Clio, which was founded in 2009 and is based in Japan, has a worldwide exclusive license to use Muse cells. Clio was acquired by Life Science Institute, Inc. in 2015 and the firm is committed to enhancing and expanding the healthcare business element of its parent company, Mitsubishi Chemical Holdings Corporation Group. Since the outset, researchers at Clio have been developing manufacturing processes and quality control measures for Muse cell preparations, and are continuing nonclinical research and development so they can start clinical trials.

Muse cells are naturally existing non-tumorigenic pluripotent stem cells that are found in the connective tissue of nearly every organ and in the bone marrow. Sources of Muse cells are mesenchymal tissues of the body, such as the bone marrow, adipose tissue and umbilical cord[1], but they can also be obtained from commercially available cultured mesenchymal cells such as fibroblasts and bone marrow mesenchymal stem cells (MSCs). Muse cells can be selected by the expression of a surface marker, stage-specific embryonic antigen-3 (SSEA-3), which is expressed in cells at the pluripotent stage of early embryonic development as well as in embryonic stem cells. Muse cells can be separated either from mesenchymal tissue sources or from cultured mesenchymal cells by SSEA-3-based cell sorting. Alternatively, they can be selectively enriched from cultured mesenchymal cells by stress conditions. When MSC are cultured under stress conditions such as long-term protease incubation, the ratio of Muse cells will be increased because Muse cells are stress tolerant and proliferate as usual whereas non-Muse cells cannot proliferate or proliferate more slowly. Because Muse cells are pluripotent and have the ability to differentiate into mesodermal- (which includes osteocytes, adipose cells, skeletal muscle cells and endothelial cells), endodermal- (hepatocytes, cholangiocytes, islet β cells) and ectodermal- (neuronal and glial cells, melanocytes)-lineage cells and self-renew, they can potentially be used to treat various types of intractable diseases such as myocardial infarction and stroke.

Muse cells have unique features that make them suitable for regenerative stem cell therapy. First, they have receptor(s) to perceive signal(s) from damaged tissue and can selectively migrate to and integrate into damaged tissue by intravenous injection. Second, they have the ability to perceive the microenvironment and will spontaneously differentiate into tissue-compatible cells to replenish damaged cells, leading to efficient tissue repair. Because of Muse cells' ability to repair tissue, *in vitro* induction into purposive cells prior to transplantation is unnecessary. In the laboratory, intravenously injected human Muse cells migrated to the damaged liver and reconstructed the liver tissue by spontaneous differentiation into liver components[2]. Human Muse cells supplied to a rat stroke model integrated into the cortex and spontaneously differentiated into functional neuronal cells whose axons contributed to reconstruction of the pyramidal tract and sensory circuit, leading to long-lasting functional recovery[3]. Similarly, locally injected adipose tissue-derived Muse cells accelerate robust tissue reconstruction in skin ulcers of a diabetes mellitus model by newly replenishing dermal and epidermal cells[4].

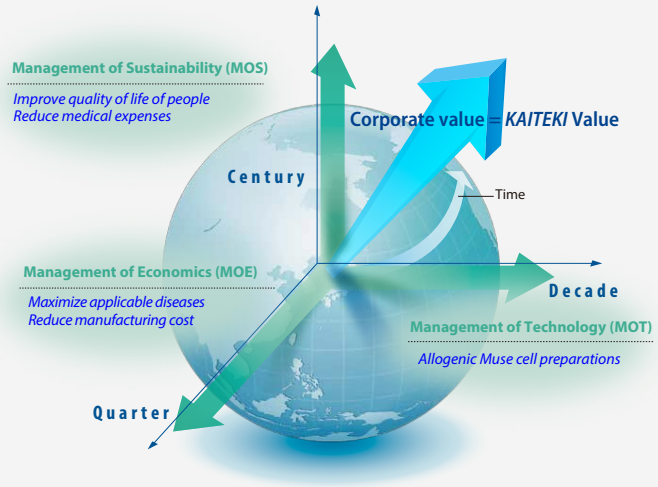


***Figure 1. Clio's mission to realize the KAITEKI society.*** *Clio will be managed to improve the sustainability of our society as well as pursue economic interests and create technological innovations.*

Another advantage of Muse cells in regenerative medicine is their suggested safety, which is indicated by their use in clinical situations. Muse cells, which comprise approximately 0.03 % of mononucleated cells in the bone marrow, are administered to people with leukaemia as part of bone marrow transplants. Muse cells are contained in MSCs, as mentioned above. MSCs are already applied to clinical studies to treat diseases such as stroke and heart disease and were recently approved in Japan for graft versus host disease. Muse cells have low telomerase activity that is comparable to that of somatic cells such as fibroblasts, and do not form tumours when injected *in vivo* for up to six months.

The Mitsubishi Chemical Holdings Corporation Group aims for 'a sustainable condition that is comfortable for people, society and the Earth, transcending time and generations'. This condition is expressed by the original concept 'KAITEKI', under which companies in the group are required to be managed to improve the sustainability of the society (management of sustainability) as well as pursue profits for future activity (management of economics) and create technological innovation (management of technology) (Fig. 1). As society is experiencing an increase in the aging population and a decline in the birthrate, extending healthy life expectancy and curbing medical expenses has become a social and political issue. Clio will contribute to the management of sustainability axis by providing therapies to treat diseases that currently lack effective treatments, and will take cost into consideration with respect to health economics.

Clio has established a cell-processing procedure that is compliant with the Japansese Good Manufacturing Practice (GMP) and Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP) regulation. The Muse cell preparation is currently being tested in nonclinical toxicity studies. Clio plans to conduct the first clinical trial in patients with acute myocardial infarction in 2017. After confirming the safety of the products in patients, the application of the Muse cells will be expanded to other disease areas.

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