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Life Science Institute, Inc. initiates clinical trials of Muse-cell product CL2020 to treat acute respiratory distress syndrome (ARDS) related to novel coronavirus (SARS-CoV-2) infection

Life Science Institute, Inc.

Life Science Institute, Inc. (Headquarters: Chiyoda-ku, Tokyo, President: Seiichi Kiso, hereafter LSII) is pleased to announce that clinical trials of the Muse cell-based product CL2020 for the treatment of ARDS related to the novel coronavirus (SARS-CoV-2) infection have commenced in Japan.

The rapid global spread of the infectious disease caused by SARS-CoV-2 (COVID-19), which was first reported in Wuhan, China, in December 2019, poses a serious threat to the world population and has intensified the urgent search for effective treatments of acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 infection, including countermeasures against its aggravation and sequelae. Managing patients with COVID-19-related ARDS has recently overwhelmed medical systems throughout the world.

ARDS is a general term for symptoms that cause severe respiratory failure due to a rapid decrease in the blood oxygen levels and pulmonary edema. ARDS is very difficult to treat and has a high mortality rate. There is currently no reliable cure and no established drug therapy for ARDS, making the development of an effective treatment for ARDS a high priority.

Muse cells (Multilineage-differentiating Stress Enduring cells) are non-tumorigenic endogenous pluripotent reparative stem cells that normally accumulate in injured organs where they replace and replenish injured cells by differentiating into the damaged cell type. They also exert anti-inflammatory, anti-apoptotic, anti-fibrosis actions, and vascular protection over an extended period of time because they survive in the injured organs for a longer period. There is no need to use gene transfer to induce pluripotency or to induce cell differentiation to specific cell types before administration. Furthermore, Muse cells are unique compared with other stem cells in that they have a placenta-like immunomodulatory function (HLA-G expression) that eliminates the need for leukocyte-type testing or matching (HLA-testing or matching)

and long-term immunosuppressive drug administration. Thus, donor Muse cells can be administered by intravenous drip without modification and do not induce serious immune reactions. Importantly, they have a very low risk of tumorigenesis. Clinical trials using donor-derived Muse cell products to treat acute myocardial infarction, cerebral infarction, epidermolysis bullosa, spinal cord injury, neonatal hypoxic-ischemic encephalopathy (investigator-initiated trial), and amyotrophic lateral sclerosis are in progress, all by intravenous drip.

In a mouse infection model, intravenous administration of human Muse cells suppressed cytokine storms and rescued the mice from a normally fatal acute encephalopathy caused by the infection (Ozuru et al., Molecular Therapy 2020;28(1):100-118). In addition, intravenous administration of human Muse cells in a rat pulmonary ischemia/reperfusion injury model improved lung function to a significantly greater degree than intravenous administration of human mesenchymal stem cells (Yabuki et al., Cell Transplantation 2018;27(6):979-993). Muse cells accumulate in greater quantities than human mesenchymal stem cells in the injured lung tissue, where they secrete various substances that protect against inflammation and cell death, and promote cell growth and division. The effects of Muse cells have been shown to contribute to the reduction of pulmonary edema. The administration of Muse cells is thus expected to be a highly effective treatment for ARDS.

LSII is developing a new CL2020-based treatment for ARDS on the basis of knowledge obtained from currently available data. This clinical trial will evaluate the seventh indication for CL2020-based therapy, following acute myocardial infarction, cerebral infarction, epidermolysis bullosa, spinal cord injury, neonatal hypoxic-ischemic encephalopathy, and amyotrophic lateral sclerosis.

The mission of LSII is to contribute to the health and medical care of people around the world by developing healthcare businesses for the next generation, including Muse cell-based products, with the aim of realizing a healthy and secure society for people, KAITEKI.

Muse cells

Muse cells (Multilineage-differentiating Stress Enduring cells) are endogenous pluripotent repair stem cells discovered in 2010 by a group of scientists led by Professor Mari Dezawa of Tohoku University. Muse cells are naturally present in the bone marrow, peripheral blood, and connective tissues of all body organs. They normally accumulate in injured organs where they replace and replenish injured cells by differentiating into the damaged cell type, and exert pleiotropic effects including

anti-inflammatory actions and vascular protection over an extended period of time, without the need for HLA-matching test or long-term immunosuppressive drug administration for the use of donor Muse cells. Donor Muse cells, administered by simple intravenous drip, accumulate in the injured tissue to exert their tissue repair effects by spontaneously differentiating into healthy cells corresponding to the damaged tissue. Because the donor Muse cells that engraft into the injured tissue are maintained as living, functional cells over an extended period of time, the anti-inflammatory, vascular-protective, tissue protective, and anti-cell-death effects continue to be exerted for a long time. Administration of Muse cells is significantly more effective than administration of another type of stem cell, human mesenchymal stem cells, for the repair of damaged tissue. Owing to these properties, Muse cells are expected to enable regenerative medicine by a simple infusion of donor-derived cells.

Acute Respiratory Distress Syndrome (ARDS) associated with the novel coronavirus (SARS-CoV-2)

ARDS is a serious syndrome that includes severe pneumonia, sepsis (a severe systemic reaction that develops from the growth of bacteria in the blood), and trauma, leading to the activation of inflammatory cells that damage the lung tissue, alveoli, and capillaries. As a result, fluid seeps into the lungs, causing severe respiratory failure. ARDS has a very poor prognosis with a mortality rate as high as 58%.

The rapid global spread of the infectious disease caused by SARS-CoV-2 (COVID-19) poses a serious threat to the world population, and has intensified the urgent search for effective treatments of ARDS and its sequelae caused by SARS-CoV-2 infections. In most affected people, COVID-19 infection causes mild symptoms, including fever, respiratory symptoms (cough, sore throat, runny nose, stuffy nose), headache, malaise, and olfactory/taste abnormalities. Some patients, however, develop breathing difficulties and severe pneumonia, which may lead to death. In the initial case group of the new coronavirus in Wuhan, published data (Zhou F, et al. *Lancet* 2020;395:1054-1062; Wu C, et al. *JAMA Intern Med*. 2020;180(7):934-943) indicate that 31% to 41.8% of patients hospitalized with COVID-19 developed ARDS. Further, 54% to 93% of deaths from COVID-19 occurred in patients that were confirmed to have developed ARDS. Intensive care departments around the world have been overwhelmed by patients with ARDS resulting from these infections. The development of an effective ARDS treatment for critically ill patients is crucial and a high priority.