Impact Objectives

- Expand investigations into Muse cells through clinical application, based on the intravenous drip of donor-derived Muse cells
- Clarify the mechanism for how Muse cells accumulate to damaged tissue and how they receive signals from their microenvironment

Muse cell offer new hope for 'reparative medicine'

*Researchers at **Tohoku University** in Japan have discovered the potential of Muse cells to be the new tool of reparative medicine in the 21st century*

Up to now, embryonic (ES) and induced pluripotent stem (iPS) cells were considered the gold-standard pluripotent stem cells for regenerative medicine. These are highly pluripotent and are able to generate all kinds of cells. On the other hand, there are several problems that need to be overcome for the use of these cells in clinical application; the risk of tumorigenesis; time and cost for the preparation and differentiation of cells prior to transplantation; ethical issues with the use of fertilised eggs in ES cells; and the necessity of surgical operations for transplantation. Since Muse cells are non-tumorigenic and are able to repair damaged tissues through an intravenous drip of donor-derived cells, they may resolve many of the current problems in regenerative medicine.

Can you talk briefly about what you hope to learn from your work?

I would like to learn the mechanism of how our body maintains tissue homeostasis throughout our life. The concept of repair seems too ordinary and we tend to take it for granted. However, the mechanism of the innate repair system is not well known. Muse cells are one of the explanations for how we maintain our body through daily minute repairs.

You are investigating endogenous non-tumorigenic pluripotent Muse cells, how are you building on existing stem cell research?

Furthermore, full utilisation of the innate reparative system is safe and thus may provide medical care compatible with that of nature. Muse cells may open a door to a 'Next-Generation Medical Care' compatible with the body's natural repair system, which does not rely on artificial gene introduction or manipulation. In this sense, the medical care provided by Muse cells is 'reparative medicine' rather than regenerative medicine.

What type of research work are you currently involved in?

We are propelling the Muse cell project in the two major streams; clinical application and basic research. The study for clinical application is conducted by Life Science Institute, Inc. (LSII) and clinical doctors. LSII succeeded in generating clinical-grade Muse cell preparation. After approval from the Japanese regulatory organisation, LSII started clinical study in acute myocardial infarction and stroke in 2018, based on the intravenous drip of donor-derived Muse cells. After evaluating safety of Muse cell, LSII will expand target diseases for clinical trial. The basic research is mainly conducted by our laboratory and other independent laboratories. In our lab, we aim to unveil the dynamics of Muse cells *in vivo*, both at steady and diseased states. We are also attempting to clarify the mechanism for how Muse cells accumulate to damaged tissue and how they receive signals from their microenvironment to spontaneously differentiate into tissue-compatible cells after homing.

Can you explain the Reparative Medicine approach you are working on?

Muse cell treatment is performed through an intravenous drip of donor-derived Muse cells. This is innovative compared to other stem cell types in regenerative medicine because Muse cell treatment does not require a surgical approach for delivering cells to the target organ. Therefore, generalisation of regenerative medicine to general city hospitals and clinics is possible. In addition to this, Muse cells also have other strengths mentioned above. In summary, Muse cells do not require the introduction of new genes, nor differentiation prior to transplantation. Cells from the patient themselves are also not required as donors are compatible, and there are not any ethical complications. We like to call our approach 'reparative medicine' rather than regenerative medicine because we like to emphasise the original function of Muse cells *in vivo* and how we are trying to amplify their effect.

You have been working on a text book on Muse cell, how will this build understanding about this topic?

This should have a wide impact because a broad spectrum of readers is expected to recognise Muse cells. The book, which will be published by Springer, is targeting not only clinical doctors and stem cell researchers, but also PhD students, undergraduate students, industries and so on. ●

A new candidate for next-door generation medical care

*Researchers at **Tohoku University**, Japan have discovered the potential of Muse cells to be the new tool of reparative medicine in the 21st century*

The future of medicine in the 21st century is rooted in the development of several key tools and techniques. Acquisition and analysis of large amounts of medical data will allow healthcare providers to understand the trends and causes of disease like never before. Greater ability to analyse an individual's health will also allow for the tailoring and personalisation of medical treatment to the individual. Finally, a key improvement in healthcare will be in regenerative medicine. The aim of such medicine is to repair the damage done by disease and accidents in such a way as to essential regenerate the area as new. Such an approach would lead to fewer complications from an injury or disease, less pain and better long-term recovery.

The torch-bearer for regenerative medicine has long been stem cell technology. Stem cells are cells that are capable of differentiating into a wide range of different cell-types. This is known as the potency of the stem cell. Professor Mari Dezawa, a researcher at Tohoku University in Japan, is an expert in this field. She explains that there are various different levels in stem cell potency, but where regenerative medicine is concerned, pluripotent stem cells capable of becoming almost any kind of cell are most desired. 'For just over a decade, the two candidates for stem cell medicine have been embryonic stem cells (ES) and induced pluripotent stem cells (iPS),' outlines Dezawa. 'ES cells are derived from the fertilised embryos and are thus both extremely potent and ethically questionable. iPS cells are generated from adult cells by introducing several genes, reverted to a pluripotent state and re-differentiated before being grafted onto the site of regeneration.' This is a lengthy and costly process that involves invasive and sometimes risky surgery, and as a result neither solution is currently ideal.

Dezawa and her team have discovered a novel stem cell type that is ideal candidate for regenerative medicine. Known as Multilineage-differentiating stress enduring cells (Muse cells), these are a type of stem cell that is essential in day-to-day repairs in the body. They reside all over the body, including in the bone marrow, peripheral blood and connective tissues. 'The natural role of Muse cells is that they function as endogenous reparative stem cells in our body, contributing to minute reparative maintenance,' Dezawa outlines. 'Therefore, they are able to differentiate into the broad spectrum of cell-types that comprise our body. They accumulate to damaged tissue either through blood stream or local migration, spontaneously differentiate into tissue-compatible cell and repair the tissue.'

CAREFUL OBSERVATION

Dezawa has long-studied mesenchymal stem cells (MSCs) and had suspected for many years that these cells must harbour a small subpopulation of genuinely pluripotent stem cells. When one of her technicians observed unusual cell clusters in some cultured MSCs, they decided to investigate further. Dezawa noticed that these clusters bore a strong resemblance to embryoid bodies and displayed biochemical markers that suggested pluripotency. 'However, these cells did not show exponential proliferation which meant they may be extremely useful, non-tumorigenic regenerative candidates,' she highlights. But after four years of struggling to isolate and study these cells in-depth Dezawa was no closer to isolating them. It was only through serendipity that she was able to finally make a breakthrough. 'I was doing a subculture of skeletal muscle cells induced from MSCs. The cells were about to be re-plated for expansion when I received a phone call from my collaborator, Professor Fujiyoshi. He was calling to invite colleagues to a wine party that evening. It was a hot summer afternoon, and a wine party sounded very appealing! I hurried to finish my work so that I could get to the wine party, and because of this, I made a simple mistake that I didn't notice until next day.'

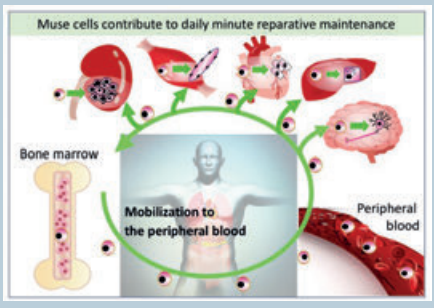
The mistake was that, in a rush to get to the party, Dezawa had forgotten to plate the cells in the culture medium and they had thus been stuck in the harsh protease media of the day before. Consequently, nearly all the cells died. Another scientist might have thrown the apparently empty flasks away and started afresh, however Dezawa has the excellent habit of thoroughly checking over her mistakes before discarding them. In this case she observed the media under the microscope. 'After observing the empty dishes for more than 30 minutes, and then noticing that something was floating on the surface of the medium,' she says. 'I adjusted the microscope focus to the surface and found that a small number of cells were still alive.' Further observations showed that these cells were not muscle cells but rather stem cells.' She then applied the same harsh protease stress to MSCs and succeeded in isolating the hypothetical stem cells she had suspected of existing for some time. ▶

'The natural role of Muse cells is that they function as endogenous reparative stem cells in our body, contributing to minute reparative maintenance'

REMARKABLE PROPERTIES

Since discovering the cells in 2007, Dezawa and her team have spent years honing the understanding of Muse cells. This included many of the very basics, such as the best way to consistently isolate and culture them and their basic role in nature. Once they begun to understand more about the cells, their potential for use in regenerative medicine appeared clear. 'Not only are Muse cells capable of repairing tissues all across the body, but they do so in a non-tumorigenic way,' confirms Dezawa. 'This is in contrast to ES and iPS cells which proliferate extremely quickly and can stray from the site of repair causing an unwanted tumour.' She also found that Muse cells naturally migrate to the site of injury. This means that they need only be injected into the patient and they should find their own way to the site of injury.

Muse cells also have specific systems to modulate immunoreactions. For example, HLA-G is one of the factors expressed in fetal cells in placenta that strongly suppress immunological attack from maternal immune system. Thus, fetal cells are protected from maternal immunological attack. Since Muse cells also express HLA-G, allogenic Muse cells can escape from immunorejection after systemic administration to patients. Through various tests Dezawa's team found that the allogenic Muse cells appeared to have no harmful effects and should therefore prove safe for general use. 'As Muse cells need only be grown to create more of them, there is no need to work out how best to differentiate them *in vitro*,' she points out. As a result of their huge potential, Dezawa has teamed up with Life Science Institute. Inc., a healthcare and medicine provider, to begin trials and, hopefully, distribution of the treatment.



Daily reparative tissue maintenance by Muse cells

FUTURE POTENTIAL

The future of Muse cells is extremely promising. Human trials are beginning for their use in acute myocardial infarction and stroke patients. The range of potential uses is almost limitless if these trials are successful. For Dezawa and her team this is culmination of many years of work, however, there is still much to find out. 'Muse cells are still a very interesting target from a biological point of view,' she confirms. 'We are now planning to expand our study of their biology in order to compare the endogenous reparative systems of human against those of lower animals such as amphibians and fishes.' Further foundational work such as this will continue to shed light on the clinical applications which Dezawa and her team will also remain heavily involved with.

Project Insights

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BIO

Professor Mari Dezawa graduated Chiba University School of Medicine, she was awarded the degree of MD in 1989, and her PhD in 1995. She then became a research associate in Chiba University Graduate School of Medicine. After moving to Kyoto University Graduate School of Medicine in 2003, Dezawa found methods to induce neurons and skeletal muscle cells from human MSCs. In 2008, she was appointed as Professor and Chair of Department of Stem Cell Biology and Histology in Tohoku University Graduate School of Medicine. She reported the discovery of Muse cells in 2010.

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