PRESS RELEASE

October 11, 2016

To whom it may concern:

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British multidisciplinary scientific journal *Nature* publishes the result of a study on a myocardial infarction treatment using iPS cells

With the goal of developing a new treatment for myocardial infarction, Ina Research has been pursuing a joint research project with a research team led by Associate Professor Yuji Shiba of the Institute for Biomedical Sciences (Director: Naoto Saito), Interdisciplinary Cluster for Cutting Edge Research at Shinshu University (hereinafter referred to as the "Shiba research team") (as reported in a press release dated August 17, 2015).

Today, I am pleased to inform you that the project's achievements have been recognized and an article written by Associate Professor Yuji Shiba as lead author, and an employee of Ina Research as coauthor, will be published in the British multidisciplinary scientific journal *Nature* (publication date: October 10).

1. Background and future prospects of the research

Ina Research has provided the Shiba research team with major histocompatibility complex (MHC)-matched cynomolgus monkeys that are unsusceptible to rejection (note), along with a dedicated test facility, the latest equipment, and engineers with extensive experience in testing, as part of the joint research agreement with Shinshu University School of Medicine on "iPS cell-derived cardiomyocyte transplant therapy for myocardial infarction."

The Shiba research team worked to restore heat function by transplanting iPS cell-derived cardiomyocytes to the site of myocardial infarction using resources provided by Ina Research, and

has confirmed engraftment of transplanted cells and improvement of cardiac function with support from Assistant Professor Itsunari Minami of the Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University. Because the research results can lead to a breakthrough procedure for patients with risk of heart failure due to, for example, the aftereffects of myocardial infarction, it is expected to be developed into a medical technology as early as possible.

2. Influence on business performance

The usefulness of the MHC-matched cynomolgus monkey has been mentioned not only by Shinshu University but also by organizations including the Center for iPS Cell Research and Application, Kyoto University, RIKEN, and Osaka University at a conference of the Japanese Society for Regenerative Medicine and other occasions. The publication in this journal is expected to enhance awareness among engineers of transplantation/regenerative medicine technologies working at Western research institutes and global pharmaceutical companies in addition to those working at Japanese research institutes, and thereby increase demand at various stages of regenerative medicine research in the future.

Expected contributions to the business performance of the Ina Research group include an increase in the number of various entrusted tests, an improvement in the rental laboratory utilization rate, and the commercialization of intellectual property obtained from joint research.

The influence on the Ina Research group's future business performance is being determined.

Explanation of the term

(Note) MHC-matched cynomolgus monkey

The iPS cell stock project, which was proposed by Professor Shinya Yamanaka of the Center for iPS Cell Research and Application (CiRA), Kyoto University is underway with the intention of performing allogeneic transplantation using the same human leukocyte antigen (HLA) genotype. The MHC-matched cynomolgus monkeys refer to the cynomolgus monkeys with the immune-related genotype that has been matched using a gene analysis technique jointly developed by Ina Research, Tokai University, and Shiga University of Medical Science. Its usefulness has been recognized as a test system that is suitable for iPS research under the aforementioned project. It is closest to human test system, and is useful for the development of drugs related to immune reactions and new transplantation technologies. Currently, Ina Research, together with Tokai University, Shiga University of Medical Science, and Keio University, is pursuing research and planned production as

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a A-STEP project of the Japan Agency for Medical Research and Development (AMED).

Attachment

A press release jointly issued by Shinshu University and Kyoto University

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October 11, 2016

Institute for Biomedical Sciences, Interdisciplinary Cluster for Cutting Edge Research, Shinshu University

Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University

Ina Research Inc.

A new heart disease treatment developed with iPS cells

A research team, led by Associate Professor Yuji Shiba of the Institute for Biomedical Sciences at Shinshu University/Department of Cardiovascular Medicine, Shinshu University Hospital, developed in August 2016 a myocardial regeneration therapy using iPS cells as a new regenerative medicine for patients with severe heart disease.

The research team produced iPS cells from special cynomolgus monkeys that are unsusceptible to immunorejection, transplanted iPS cell-derived cardiomyocytes into normal cynomolgus monkeys that had developed myocardial infarction. The engraftment of the cells was confirmed, and the results showed improved heart function. This research was published in the British science journal *Nature* on Monday, October 10, 2016 at 16:00 London time (Tuesday, October 11, at 12:00 midnight Japan time).

<Points of the release>

1. A myocardial regeneration therapy using iPS cells was developed as a new regenerative treatment for patients with severe heart disease. The research was published in the British science journal *Nature* on October 10, 2016.
2. The therapeutic effect was confirmed using cynomolgus monkeys[*1] that are close to humans.
3. The research was conducted using both special cynomolgus monkeys supplied by Ina Research Inc. through an established system, which are unsusceptible to immunorejection, and normal cynomolgus monkeys.
4. The research team produced iPS cells from special cynomolgus monkeys that are unsusceptible to immunorejection, transplanted iPS cell-derived cardiomyocytes into normal cynomolgus monkeys that had developed myocardial infarction, and confirmed engraftment of the cells and improved heart function.

<Background of the research >

Pluripotent stem cells[*2] (ES cells[*3] or iPS cells[*4]), which have an almost infinite ability to proliferate as well as an ability to differentiate into many cells, are expected to be applied to regenerative medicine. Meanwhile, heart disease such as myocardial infarction has high morbidity and mortality rates, and a new treatment is expected to be developed for the disease.

Shinshu University produced cells constituting the heart muscle (i.e., cardiomyocytes) from ES cells, transplanted them into a guinea pig myocardial infarction model, and confirmed improved heart function after myocardial infarction. This was reported in British science journal *Nature* in 2012. In addition to this research, previous research studied "heterologous transplantation," in which cardiomyocytes produced from humans (human-derived cardiomyocytes) were transplanted into different animals. However, it was impossible to evaluate immunorejection after transplantation by studying heterologous transplantation because the cells were transplanted into a host from a different animal species.

<Summary of the research result>

In this research, cynomolgus monkeys that are less likely to show rejection were identified and used to produce iPS cells. Then, normal cynomolgus monkeys were subjected to myocardial infarction, and cardiomyocytes were transplanted between cynomolgus monkeys (allogeneic transplantation) (Figure 1). As a result, most of the cardiomyocytes transplanted were engrafted without the complication of rejection, and restoration of heart function after myocardial infarction was confirmed. However, animals that received a cardiomyocyte transplant showed a transient increase in arrhythmia as a side effect. Therefore, it will be necessary in the future to conduct research to reduce this side effect.

This research was conducted as part of the "Development of a myocardial regeneration therapy using iPS cells in a transplantation immunity tolerance primate model" (Grant-in-Aid for Scientific Research of the Japan Society for the Promotion of Science) and "Development of a production system for regenerative medicinal cells from human induced pluripotent stem cells (cardiomyocytes and nerve cells) under the Project Focused on Developing Key Evaluation Technology: Manufacturing Technology for Industrialization in the Field of Regenerative Medicine (Japan Agency for Medical Research and Development (AMED)). The Institute for Biomedical Sciences, Interdisciplinary Cluster for Cutting Edge Research, Shinshu University (research leader: Yuji Shiba) played a leading role in the research; the Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University (Itsunari Minami) conducted experiments to assess cell function; and Ina Research Inc. provided special cynomolgus monkeys that are less likely to show rejection than existing supply channels.

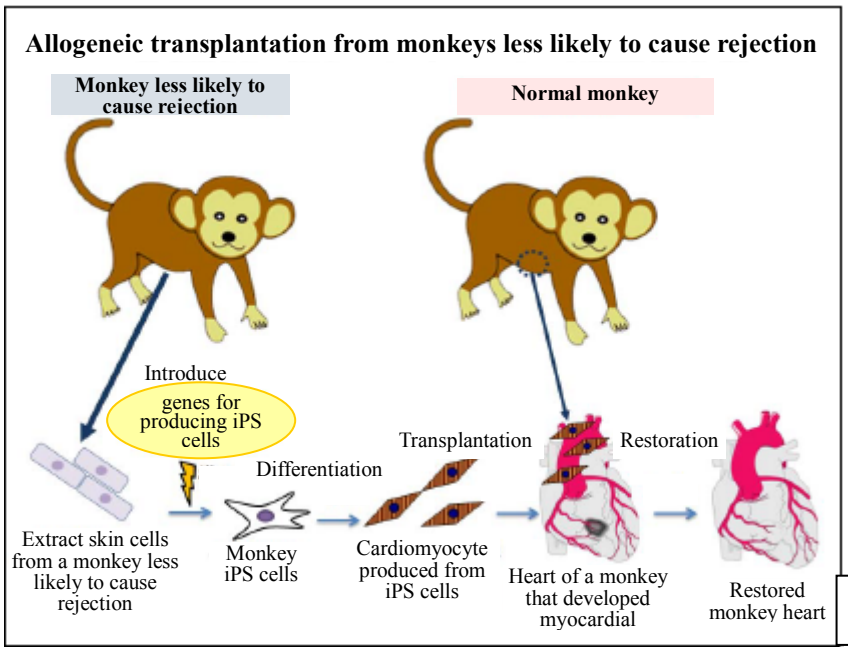

Figure 1

<Glossary>

*1 Cynomolgus monkey: A medium-sized monkey that is found mainly in Southeast Asia. It is often used as an experimental animal.

*2 Pluripotent stem cell: A cell having an ability to differentiate into various tissues of the body.

*3 ES cell: It is also called an embryonic stem cell and one of the pluripotent stem cells. It is produced from a part of the embryo, an early stage of animal life.

*4 iPS cell: It is also called an induced pluripotent stem cell. It was presented by Yamanaka of Kyoto University and another professor as a cell with characteristics equivalent to an ES cell, which is produced by introducing several kinds of initialization genes into a somatic cell.

<Article information>

Title: “Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts”

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