Request for Participation in Studies
Information Document
(Please read this document carefully before making your decision on participation.)

Study titles
R91: The Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis

- This document is to give you information to help you decide if you want to participate in these studies.
- Before you make your decision, please read this document carefully until you fully understand the information contained in this document. Please decide whether you agree or not agree to participate in the studies on the basis of your own free will.
- If you have any questions or concerns, please feel free to ask your study doctor.

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1. Introduction

In this hospital, we are conducting research to develop more effective treatments for patients who are having refractory diseases. The development of new treatments requires many studies to be conducted to discover more about the disease; for example, what causes the disease, what type of drug can cure the disease, and if such a drug is found, whether the drug is safe for use.

For these reasons, we need help from patients, their families, and healthy volunteers to conduct medical studies. A clinical study is a type of medical study that is performed to find the cause of a disease and ways to prevent, diagnose, and treat the disease more efficiently and to improve the quality of life of patients. Please note that a clinical study has an aspect that is different from regular medical care.

If you consent to participate in the present studies and change your mind later, you may withdraw your consent simply by writing to us. There is no penalty or loss of benefits if you decide to withdraw. If you withdraw your consent, the sample you have donated, the induced pluripotent stem cells (iPS cells) generated from your cells, and medical information associated with the donated sample and iPS cells derived from the sample will be destroyed after appropriate measures are taken so that you are not identified from them. They will not be used for research from that time on.

Note that, however, recovery and disposal of your samples and information may sometimes be difficult at the time when you withdraw your consent; for example, when the studies using your samples have made certain progress, a paper including data from the studies has been published, or data from the studies have been used by other institutions using the cell bank. (This will be described later in this document.) In such cases, use of your samples and/or the data obtained from your samples may continue despite your withdrawal of consent.

2. Purpose of the studies

These studies will be conducted in patients, their families, and healthy volunteers.

Many types of treatments and various combinations of treatments, such as a combination of medication and rehabilitation programs, have been used to improve the patient's medical condition. However, currently available treatments are not yet perfect. Researchers all around the world are working to develop better treatments. The development of new treatments requires many studies to be conducted to discover more about the disease; for example, what causes the disease, what type of drug can cure the disease, and if such a drug is found, whether the drug is safe for use. The ideal

way of studying the disease is to use an affected part (tissue) of the patient's body. However, the use of the affected tissue involves many issues; for example, sampling of the affected tissue may impose a severe burden on the patient or is sometimes technically impossible. In addition, because the amount of affected tissue that can be collected from the patient is limited, the affected tissue cannot be used repeatedly for research.

In 2007, Kyoto University developed an innovative technology that can reduce the burden on patients. This innovative technology enables skin cells to be converted into iPS cells, as you may have seen in newspapers and on TV. iPS cells are generated by introducing three or four types of genes into the cells extracted from skin tissue. As the name “pluripotent stem cell” indicates, iPS cells can differentiate into various tissues that comprise our body. This feature can be used to develop, for example, blood cells if a researcher wants to study blood disorders, liver cells if a researcher wants to study liver disease, or nerve cells to study neurological disease. Because all these specific cells can be developed from iPS cells in test tubes, there is no need to ask a patient to donate his/her tissue over and over again.

Meanwhile, researchers have also been working to generate iPS cells from various organ cells (stomach, liver, cheek, blood, and bone marrow cells) besides skin cells. It is now possible to generate iPS cells mainly from blood cells. We now know that the property of iPS cells is different depending on what type of body cell is used to generate iPS cells. Therefore, researchers are expected to use iPS cells of different origins depending on what type of treatment the researcher is trying to develop.
Because of this, it is expected that human iPS cells of different origins, including human cells extracted from the cheek, blood, bone marrow, stomach, and liver, would need to be generated.

We are asking you to participate in these studies because we want to generate iPS cells from the body cells of you and your family members and use them together with information such as your gender, age, and data from your medical records to discover more about the cause of the disease for which you are currently being treated and to develop new effective treatments.

To find the causes of diseases, understand the properties of disease-affected cells of patients, and conduct various studies, it is essential to compare affected cells with healthy cells (referred to as comparator cells in this document). Therefore, we are also asking healthy volunteers (including patients requiring treatment or undergoing surgery

as part of regular treatment unrelated to these studies at the department of plastic and reconstructive surgery or orthopedic surgery) to donate body tissue for the studies.

Please note that it will take more than several years to develop a new treatment based on data obtained in these studies. We do not use the human iPS cells generated in these studies for treatment; for example, the modified iPS cells will not be directly put back into the patient's body as treatment.

Also, one of the most important aspect of these studies is that the cells collected and information and data obtained in these studies will be used by a wide variety of research institutions (including laboratories inside pharmaceutical companies) in and outside Japan. (This will be discussed in more detail later.) This will help researchers working in various fields to bring together ideas and experiences in iPS cell research and facilitate the elucidation of the mechanisms of currently refractory diseases and the development of new treatments.

3. Administrative organization of studies

Shinya Yamanaka (Professor at the Center for iPS Cell Research and Application, Kyoto University) will conduct these studies as collaborative research with the hospital departments at Kyoto University Hospital and Institute for Life and Medical Sciences, Kyoto University. Megumu Saito (Professor at the Center for iPS Cell Research and Application) will supervise the studies.

The subinvestigators of Kyoto University are listed in **Attachment 1**.

The collaborating institutions other than Kyoto University that cooperate for somatic cell collection and other study-related activities are listed in **Attachment 2**.

4. Study period

The intended study period is as shown as follows. However, depending on the progress of the studies, the study period may be extended after being approved by the Ethics Committee.

Study period: From the date of approval to March 31, 2028

5. Study procedures

As described in the next section, these studies involve obtaining a sample of your body tissue and extracting cells from the body tissue. (These cells are called “somatic cells”.)

The extracted cells will be then sent to the laboratory at the Kyoto University Graduate School of Medicine/Hospital, Institute for Life and Medical Sciences, Kyoto University or Center for iPS Cell Research and Application, where iPS cells will be generated.

If Kyoto University determines it necessary after ample consideration, somatic cell extraction and/or iPS cell generation may be conducted under contract with an entity in or outside Japan that is selected fairly and properly at Kyoto University. In this case, your body tissue or somatic cells will be transported from Kyoto University to the contractor by appropriate means. Before transportation, your personal information such as your name will be removed from your body tissue and somatic cells and will be replaced with a code. (This will be explained in detail later in this document.) Therefore, your body tissue and somatic cells, when transported to the contractor, will carry no personal information that can identify you personally. Such outsourcing will be conducted after we conclude an agreement with the contractor. The contractor will be required to be in compliance with matters specified in the agreement. Kyoto University will supervise the contractor appropriately as necessary.

iPS cells are currently generated by introducing genes using viral vectors. In the future, however, more effective and safer techniques may become available. We will use the most suitable method available at the time. Generated iPS cells will then be used for research to determine the causes of diseases and to develop new treatments.

6. What you are asked to do

(1) Screening tests for virus infection

Before the sampling procedure, we will collect approximately 7 mL of blood from you to determine if you are infected with certain viruses.

Information on virus fection may be comfirmed from your medical records. In such a case, you will not be asked to undergo screening tests for the virus infection.

We will generate iPS cells from your somatic cells only if you test negative for infection.

We will inform you of the test result only when knowledge of the result can be helpful to you (for example, positive test result). Results will not be disclosed if the result is

negative.

(2) Tissue sampling
A sample of one of the following tissue types will be taken from you. The sample will be used to extract cells.
The extracted cells will be used for generating iPS cells.
Please note that if tissue already collected in another study is used, no new tissue will be collected.

1) Skin
A piece of skin will be taken from an area where the scar will be minimally visible (e.g., inner thigh or inner upper arm). First, the area will be disinfected and then made numb using local anesthesia (injection). Then, a piece of skin will be taken from the area using a 3- to 5-mm metal punch (trepan). After a piece of skin is taken from the area, the wound is sutured with a single stitch, disinfected again, and a sterile dressing will be applied to the area. The suture can be removed after 1 week or so. The skin sample will be cultured in a laboratory to increase the number of skin cells by several hundredfolds and then used to generate iPS cells. Except for the discomfort related to the sampling procedure, there will be no serious risk associated with sampling of skin tissue. However, infants need to be held tight during the procedure, which may impose a psychological burden on the infants. The most practical risk is that if you scratch the wound later, some complications may occur; for example, bacteria may get into the wound causing pus, or the wound may reopen. However, because we are careful to keep the area of biopsy clean, the development of such a complication is extremely rare in our experience.

2) Cheek (buccal mucosa cells)
A sample of cells will be collected by scraping the inside of the cheek with a cotton swab.

3) Blood
A sample of blood will be collected using the same procedure as for standard blood tests. This will be the most common sampling procedure performed in these studies. Blood sampling for iPS generation and for the aforementioned screening tests for the virus infection may be performed simultaneously.

4) Bone marrow
A sample of bone marrow will be collected using either of the following two methods.

One method is to obtain a sample using the standard bone marrow biopsy procedure. After administering local anesthesia to reduce the pain, a sample will be taken from the sternum or ilium. A bone marrow aspiration needle will be inserted through the skin into the bone surface and then into the bone marrow, and a sample of bone marrow fluid will be aspirated using a syringe. The other method is to obtain a sample when a bone graft is taken from the ilium during orthopedic surgery. A sample of bone marrow cells will be taken from the site of the bone graft on the ilium using an aspiration needle. There will be no pain because these procedures are performed under systemic or lumbar anesthesia.

5) Stomach tissue (gastric mucosa)

A sample of stomach tissue can be obtained from a portion of the stomach removed via surgery, or a sample can be obtained during endoscopy. The patient will be given information about the donation of a tissue sample when he/she undergoes stomach surgery or endoscopy.

6) Liver tissue

A sample of liver tissue will be obtained from a portion of the liver removed via surgery. The patient will be given information about the donation of a tissue sample when he/she undergoes surgery.

7) Lung tissue

A sample of lung tissue will be obtained from a portion of the lung removed via surgery as treatment or for diagnosis. The patient will be given information about the donation of a tissue sample when he/she undergoes surgery.

8) Oral mucosa

A sample will be obtained during oral surgery. A piece of oral mucosa will be collected from the tissue excised from a surgical incision. No additional incision or invasive procedure is required for the donation of your sample.

9) Wisdom tooth germs, extracted tooth, and deciduous tooth pulp

Dental pulp will be collected from a tooth that needs to be extracted for medical treatments or a deciduous tooth that has fallen out. No additional invasive procedure is required for the donation of your sample.

10) Urogenital tissue

A sample of urogenital tissue will be collected from the kidney removed from the

patient undergoing a kidney transplant. Tumor and healthy tissues excised during surgery for a urogenital tumor will also be used. No additional incision or invasive procedure is required for the donation of your sample.

11) Heart tissue

A sample of heart tissue will be collected from a surgical incision in the heart or from partial heart resection. The patient will be given information about the donation of a tissue sample when he/she undergoes surgery.

12) Urine

A method of creating iPS cells from urine has been reported as a less invasive method compared to blood collection. 20 mL of urine is collected for iPS cell generation. You will be required to collect urine by yourself. If it is difficult for you to collect urine by yourself, for example, if you are physically disabled or if you are a child, a family member will help you to collect urine.

(3) Use of your medical information

Concerning the following information on your health condition (including your past condition and condition to be recorded in the future), we would like to use a part of your medical records, which is considered necessary in performing these studies. We may also ask you about your health condition that has not been entered in your medical records. If you are a healthy volunteer, we will ask you to fill in a separate interview form for information such as your age, gender, current health condition, and, in some cases, medical history of yourself and your family members and medications you have taken. The information recorded in the interview form will be stored together with your cells and your results of tests for the virus infection.

Diagnosis; age; gender; medical, treatment, family, and medication histories; and results of tests (genetic tests, infection tests, imaging tests, etc.)

You will be asked to provide us with the aforementioned information, because such valuable information on changes in your health condition or on your clinical course of treatment can be helpful to our research when combined with information obtained from your cells to discover mechanisms of diseases and to develop new treatments.
However, except for age and gender, the required information will vary depending on a type of study. At this stage, therefore, we cannot tell you what part of the aforementioned information will be used in these studies.

Your valuable information will be used only for these studies.
However, as we explain later, your cells may be transported to other institutions in and outside Japan, your cells may be deposited in cell banks, or your information may be registered in data banks. In such occasions, before the provision of your cells and data to third party institutions, your personal information will be removed from your cells and data and will be replaced with a code. Therefore, the confidentiality of your personal information will be strictly protected.

7. Handling of iPS cells

Using iPS cells generated in these studies, researchers will work to identify the causes of diseases or to develop new treatments. Please understand that we will use iPS cells that are generated from cells collected from the patient's healthy blood relatives as comparator cells in studies of various diseases. Diseases to be studied cannot be specified in advance.
However, iPS cells generated in these studies will not be used as an actual treatment. Researchers may make iPS cells differentiate into various tissues and cells that make up the human body, such as tissues and cells exhibiting diseases, (this process is called “differentiation induction”) or administer candidate drugs or substances to such tissues or cells to examine their responses to drugs or substances. Currently, the following uses of iPS cells are prohibited by law in Japan:

1) Generation of whole bodies from human iPS cells by transplantation of the embryo (the embryo acts similarly to the fertilized egg), which has been developed from human iPS cells, into a human or animal uterus, or any other means. However, human–animal chimeric embryo research, which is permitted by government guidelines, is not subjected to this rule.
2) Introduction of human iPS cells into human embryos
3) Introduction of human iPS cells into human fetuses
4) If germ cells (sperms and eggs) are developed from human iPS cells, the use of such germ cells to develop human embryos.

These four rules will be strictly applied to the use of iPS cells generated on the basis of the protocols of these studies.
If your cells or information is desired to be used in the aforementioned human–animal chimeric embryo research 1) or germ cell research 4), we will first give you an explanation about the research using a separately prepared information document. If you consent to participate in the research as well, your cells and information will be

used in the research.

In the future, the laws and guidelines may be revised or deregulated. If the laws and guidelines are revised in the future, we will use iPS cells in compliance with the revised laws and guidelines and follow necessary steps accordingly, which might include revisiting your consent decision.

8. Genetic analysis

iPS cells are currently generated by introducing genes into cells using viral vectors. To assess the safety of the generated iPS cells, we must determine where in the cells the genes have been inserted.

In addition, by comparing genes in iPS cells generated from patients' cells and those in iPS cells generated from healthy volunteers' cells, we may be able to obtain data that will provide new findings on the disease or lead to the development of new treatments for the disease. For many diseases, the causative genes are completely unknown. Even when some genes are suspected of causing a disease, we often have no clear picture of the onset mechanisms and how the abnormality in the genes is causing the disease. In such cases, we may analyze all the genes. To obtain new findings on the disease and find new treatments for the disease, we would like to analyze genes in iPS cells generated from your sample.

◆ **Gene (acting as a blueprint for the body)**

Your body consists of numerous cells. Each cell contains all the genes needed to make up your entire body, and only the genes needed for the cell to function are active. If any change occurs to a gene, the activity of the changed part of the gene is affected and resulting symptoms may occur. Everyone has genetic variations. Certain types of genetic changes have little effect on our daily activities; they produce only minor differences among individuals such as differences in facial appearance, physical attributes, and constitution. However, there are other types of genetic changes that are associated with diseases. Such genetic changes associated with diseases are further classified into various types; some types cause few symptoms, whereas some other types cause severe symptoms. Tens of thousands of genes are scattered in each cell. All the genetic information is collectively referred to as “genome.” The human body is made up of approximately 60 trillion cells, and each cell contains all the genes.

First, DNA and RNA will be extracted from your somatic and iPS cells generated from your somatic cells. Extracted DNA and RNA will then be analyzed in detail to determine candidate genes that may be related to the onset of disease or a difference in

the degree of the patient's response to certain drugs. We will analyze the structures and functions of the candidate genes and examine whether they are actually related to the onset of disease or response to drugs.

As a rule, the results of genetic analyses performed in these studies will not be disclosed to you, because the significance of such data in terms of a relationship to diseases is usually unclear at the time. The results could be used to determine the presence of certain genetic polymorphisms in your blood relatives. This might raise psychological concerns within the family.
Our hospital offers a genetic counseling service to help relieve the anxiety you may feel and address other issues. Please tell your study doctor if you want to talk to the genetic counselor. In the counseling session, how you or your family think or feel about the genetic analysis, your lifestyle, and your social background will be respected. You may discuss anything related to genetic issues until you are satisfied with the information you have received. We support study participants through genetic counseling to ensure that they obtain the best emotional result.

Kyoto University Hospital, Clinical Genetics Unit:
Appointment required, TEL: 075-751-4350 (Weekdays: 13:00–16:30)

9. Personal information

Your somatic and iPS cells generated from the somatic cells in these studies; your medical information, DNA, and RNA; and your results of genetic analysis will be given a code name after removing the personal information (name, address, etc.) that can identify you. This procedure is called anonymization. A list will be prepared to link the code with your personal information. This list is called the link table. The link table will be strictly managed by a personal information custodian.

Personal information custodian: Isao Asaka, Professor at the Center for iPS Cell Research and Application, Kyoto University

10. Provision of samples to external research institutions

Collaborating research institutions participating in these studies and other research institutions in and outside Japan may request the use of your somatic and iPS cells generated from your somatic cells, and iPS cell-derived differentiated cells.
If we receive such a request, we would like to supply the cells and medical information

associated with the cells (diagnosis; age; gender; medical, treatment, family, and medication histories; and results of tests such as genetic, infection, and imaging tests) to external research institutions provided they meet the following criteria:

* For institutions to which we are currently planning to provide the cells and information, please see **Attachment 3**.

1) The plans of the study in which your cells and information will be used have been reviewed and approved by the Ethics Committee or equivalent of the external research institution (unless the Ethics Committee or equivalent decides such review or approval is not required according to the applicable rules or guidelines).
2) The study plan, including the purpose and content of the research and how the study was reviewed by the external research institution or how the institution determined it may proceed with the study, is considered appropriate by researchers who have been involved in the generation of iPS cells.

* To effectively use iPS cells to develop new treatments, it is important to facilitate medical/pharmaceutical research conducted by commercial companies including pharmaceutical companies. Thus, we would like to supply your somatic cells; iPS cells; and your information such as gender and age; and, if needed, your health condition and medical history to companies if their research plan is appropriate and approved by an Ethics Committee or equivalent. Please note that the provision of the cells derived from your sample and medical information associated with the cells may be done through a for-profit entity that will be selected at Center for iPS Cell Research and Application, Kyoto University after confirming that the entity has met relevant requirements. This may lead to the development and eventual marketing of new effective drugs that may be beneficial to patients by pharmaceutical companies.

We may outsource examination and analysis of cells to other institutions in and outside Japan. In such occasions, sufficient measures will be taken to protect your personal information before the transportation of your cells to these institutions.

11. iPS cell banking and database registration

RIKEN Bioresource Research Center (hereafter abbreviated as RIKEN BRC) organizes an iPS cell bank to help studies on iPS cell be conducted and help researchers conduct research using various iPS cells.

RIKEN BRC has received support from the national government (from the Ministry of Education, Culture, Sports, Science and Technology [MEXT]) and has gathered and

distributed a large number of iPS cells from and to researchers in and outside Japan.
RIKEN BRC has ample resources for preservation of iPS cells and gives lectures on the techniques for handling iPS cells. We would like to consider registration and deposition of your somatic and iPS cells generated from your somatic cells, your medical information associated with your somatic and iPS cells generated from such cells, and analysis information of such cells with RIKEN BRC so that many researchers can use them. In such cases, iPS cells will be anonymized so that your personal information cannot be linked to iPS cells at RIKEN BRC, and then, the cells will be sent to RIKEN BRC. This will protect your privacy. RIKEN BRC will distribute your somatic and iPS cells generated from your somatic cells to researchers and institutions (including pharmaceutical companies) in and outside Japan together with data such as your medical records in accordance with proper procedures and the rules established by the Japanese government. The cells will then be used in various studies to elucidate the mechanisms of diseases and assist in the development of new treatments.
Neither RIKEN BRC nor we will contact you upon the distribution of your somatic and iPS cells, and medical information associated with such cells, but RIKEN BRC will release the cells only to research judged to be appropriate by the specialist committee (Ethics Committee) of the institution to which the individual researchers requesting the cells belong.

If you want to learn more about RIKEN BRC, please contact the following:

Cell Engineering Division, RIKEN Bioresource Research Center
Address: 3-1-1 Koyadai, Tsukuba-shi, Ibaraki 305-0074, Japan
URL: http://cell.brc.riken.jp/ja/hps/hps_diseaselist_index
Fax: 029-836-9130
E-mail: cellips.brc@riken.jp

Various types of data generated in these studies, including genetic information, will also be useful for other medical research. Data obtained from you will be, after anonymization (removal of the information including your name and address that can be used to identify you), registered in publicly funded academic databases so that researchers can access the data.
Data registered in some databases are made accessible to researchers. We plan to register data from these studies in the database of the National Bioscience Database Center (NBDC) of the Japan Science and Technology Agency (JST). JST is an agency under MEXT and promotes and funds scientific research projects in Japan. NBDC was

founded in 2011. Data registered in the NBDC will be made accessible through databases in and outside Japan to researchers from various fields and will help in the development of new technologies, elucidation of the mechanisms of currently incurable diseases, and discovery of new treatments and prophylactic therapies.
If you want to know more about NBDC, please contact the following:

National Bioscience Database Center, Japan Science and Technology Agency
Address: 5-3, Yonbancho, Chiyoda-ku, Tokyo 102-8666, Japan
URL: http://biosciencedbc.jp/
Tel: 03-5214-8491
E-mail: office@biosciencedbc.jp

12. If you want to know more about the study plans
If you want to learn more about the study plans, we can show you the study protocols, excluding the portions of the protocols where information is confidential because of intellectual property rights (patent), etc.

13. Publication of study data
Data obtained from these studies may be presented at academic conferences or published in academic journals or databases in and outside Japan. However, we will take appropriate measures to ensure that the patient's personal information is protected. No data will be published before we confirm that the personal information of the patient will not be released to any third party and will not appear in any presentations or publications.

If you withdraw your consent during the studies, iPS cells generated from your sample will not be used for research from that time on, and thus, no new data will be published. However, the data published (in reports, journals, etc.) before withdrawal of your consent will not be retractable.

14. Expected benefits and risks of participating in the studies
Note that you will not receive immediate therapeutic benefits because of your

participation in these studies. Because research on iPS cells began recently, it is uncertain if we can obtain useful research findings that can contribute positively to your actual treatment. Nevertheless, if the cause of your disease is discovered or a new drug or therapy is developed through participation in the studies, you and others who have the same disease as you could receive benefits in terms of disease diagnosis and treatment in the future. The expected risks are 1) the risks related to sampling of your tissue and 2) invasion of privacy due to leakage of personal information. Concerning risk 1), we can reduce the risk by choosing the least invasive sampling method and perform the sampling procedure for each tissue sample with care. Concerning risk 2), we will do everything we can do to protect the confidentiality of your personal information; this includes anonymization. Your personal information will be kept under strict security. However, if your disease is rare and there are few patients with the same disease in Japan, there is a possibility that you might be identified from the cells you donated.

These clinical studies are not covered by the clinical research liability insurance policy. Thus, if study-related injury occurs, you will be promptly provided with appropriate diagnostic and medical care using health insurance. There will be no cost to you regarding your treatment of study-related injury.

15. Preservation of cells and information after completion of the studies

As explained, your somatic and iPS cells generated from the somatic cells, iPS cell-derived differentiated cells, and your medical information associated with such cells are precious. Therefore, these cells and information along with your genetic information, DNA, and RNA will be strictly preserved at Kyoto University and at the repositories if the cells are deposited and/or the information is registered for research use. The preservation period might be a long time even after the completion of these studies because such cells and information could lead to new research findings in the future. In the case of cells or information that yields evidence of certain research results published by academic papers, we will keep the cells or information for at least 10 years after the publication of the research results.

16. Intellectual property generated from these studies

Intellectual property (e.g., patents) and intellectual property rights may be generated from the outcomes of studies conducted using iPS cells generated from your tissue and medical information associated with the donated tissue. Such intellectual property

rights are not given to the donated sample itself or the information associated with the sample, but to the value generated by the work of researchers (research, the use of research outcomes, etc.). Thus, the donor or affiliates of the donor cannot claim the rights by saying, “Because the donor is the one who donated the sample and information, the intellectual property rights related to the sample and information should be given to the donor.” For the same reason, if monetary profit is obtained from the intellectual property, the donor cannot claim the right to receive such profit. As a rule, all of the intellectual property is managed by Kyoto University.

17. Costs

All necessary research-related expenses will be paid through our research funds (government grants from the Ministry of Health, Labour, and Welfare [MHLW] and MEXT or research funds provided through industry–university collaboration). There will be no cost to you. Moreover, you will not be paid for taking part in these studies.

18. Funding sources and conflict of interest

Conflict of interest in research refers to situations in which financial, material, or other personal considerations may affect the research results. These studies are conducted basically through public funds such as Grants-in-Aid for Scientific Research and commissioned research project funds from MEXT and MHLW. Researchers conducted at the Medical Innovation Center, Translational Research Department for Skin and Brain Diseases, and Department of Drug Discovery for Lung Diseases, in Graduate School of Medicine, Kyoto University are collaboration projects between the University and companies, and the departments' financial source is the collaborative research expenses paid by the cooperating companies. In addition, some research activities including these studies are financed through competitive research funds from external sources. Each project is operated by a committee consisting of the same number of members from Kyoto University and the collaborating company, and supervised by a professor at Kyoto University’s Graduate School of Medicine as the leader and a researcher from the company as the sub-leader. Under the guidance of both parties, each group led by several principal investigators employed by Kyoto University conducts research in Kyoto University. Whether or not these studies have conflicts of interest is appropriately reviewed and managed by the Kyoto University Conflicts of Interest Review Committee for Clnical Research in accordance with the Kyoto University Conflicts of Interest Policy and Kyoto University Conflicts of Interest Management Regulations.

19. Review by the Ethics Committee

The protocols of these studies have been reviewed by the Ethics Committee at Graduate School of Medicine and Faculty of Medicine, Kyoto University as well as Kyoto University Hospital and approved by the Dean of Graduate School of Medicine and Faculty of Medicine, Kyoto University and the Director of Kyoto University Hospital.

20. Your participation is voluntary, and you are free to withdraw your consent at any time

You are free to choose to participate or not participate in these studies. If you change your mind later, you may withdraw your consent at any time. Your participation is voluntary. If you are not of legal age but are 16 years or older, both you and your legal representative are responsible for deciding whether or not to participate. If you are younger than 16 years, your legal representative is responsible for deciding whether you should participate or not. If you are an adult patient and it is difficult to confirm your understanding and intention to participate in this research, we may ask your legal representative to decide. You have no obligation to participate in these studies. Your decision to participate or not participate will have no influence on your current and future relationship with our hospital. We will always provide you with the treatment that is in your best interests.

If you consent to participate in these studies and change your mind later, you may withdraw your consent by writing to us. There is no penalty or loss of benefits if you decide to leave the studies. If you withdraw your consent, the sample you have donated, iPS cells generated from your cells, and medical information associated with the donated sample and iPS cells will be destroyed after appropriate measures are taken so that you are not identified from them. They will not be used for research from that time on.

Note that, however, recovery and disposal of your samples may sometimes be difficult at the time when you withdraw your consent; for example, when the study using your samples has made certain progress, a paper including data from the study has been published, or iPS cells generated from your sample have been distributed to other institutions from a cell bank. In such cases, use of your sample and iPS cells derived from the sample and/or the data obtained from these samples may continue despite your withdrawal of consent.

21. Contact information

If you have questions or concerns about your participation in these studies, please feel free to call your study doctor.

Your study doctor:
TEL:

If you hesitate to ask your study doctor or you wish to ask someone else, please contact the following:

Clinical Research Consultation Service, Kyoto University Hospital
(Tel) 075-751-4748
(E-mail) ctsodan@kuhp.kyoto-u.ac.jp

Informed Consent Form

(Name of the head of the medical institution, etc., if the informed consent discussion is held in any institution listed in Attachment 2, outside Kyoto University)
Dean of Graduate School of Medicine, Kyoto University
Director of Kyoto University Hospital
Director of Center for iPS Cell Research and Application, Kyoto University

Study titles
R91: Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis

I have been given information about the aforementioned studies verbally and in writing. The following items regarding the studies have been explained to me by the study doctor using the information document, and I fully understand the explanation. I volunteer to take part in these studies. I hereby sign the informed consent form and receive the information document and a copy of the signed informed consent form.

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17. Costs
18. Funding sources and conflict of interest
19. Review by the Ethics Committee
20. Your participation is voluntary, and you are free to withdraw your consent at any time
21. Contact information

[Donor] Date of consent MM/DD/YYYY

Study participant (signature) _____

Legal representative of the participant (Signature) _____
(Relationship of the legal representative to the participant)_____

[Doctor who has conducted the informed consent discussion] Date of informed consent discussion MM/DD/YYYY

I confirm that I have given the participant detailed information about these studies and that the donor has consented to participate voluntarily in the studies.

Institution (Name)/Department (Name): _____
Doctor who has conducted the informed consent discussion: (Signature)_____
(*should be a doctor for obtainment of IC listed in Attachment 1)

The hospital will keep the original copy of the signed informed consent form, and a copy will be given to the donor.

Request for Participation in the Research on Germ Cell Production

- This form is for volunteers who have already consented to participate in the following studies.

  “Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis”
  “Genetic Analysis Study Using Human Disease-Specific iPS Cells”

- iPS cells generated in these studies through your consent have the potential to be important and valuable in other studies.

- For example, research on differentiation into germ cells, such as eggs and sperm, using iPS cells has the potential to help clarify causes of infertility and congenital diseases that originate in germ cells and could lead to the establishment of innovative treatment methods. This document explains the research on germ cell production.

- Your cooperation in the research is voluntary. You are free to decide whether you consent or not consent to the use of iPS cells generated from your tissue in the research on the induction of differentiation into germ cells. If you choose not to consent, there will be no penalty or loss of benefits to which you are otherwise entitled.

1. What is the research on germ cell production?

It has been years since we started the studies on differentiating iPS cells to various tissues and cells that make up our bodies (this process is called differentiation induction) as explained in the separate information document.
Germ cells (sperm, eggs, and their precursor cells) take over a dozen years to mature through complex processes including meiosis in the body. Therefore, complex differentiation, which is not seen in other somatic cells, is necessary. Little advancement has been made in such research on humans due to the difficulty in obtaining germ cells from people compared with animals.

In Japan, producing germ cells from human iPS cells and other pluripotent stem cells had previously been prohibited, but now it is allowed on the basis of the policy set forth in the "Production of germ cells from human ES cells and their use" (2009, Bioethics and Biosafety Commission under the Council for Science and Technology).
The policy said germ cell production would allow investigation of the mechanisms of maturation and differentiation of sperm and eggs in the human body, which had been difficult to investigate before, and can help clarify the causes of infertility and congenital diseases/syndromes that originate in germ cells and could lead to the establishment of innovative methods of diagnosis and treatment. Therefore, they concluded study of the processes up to germ cell production in basic research should be permitted as long as such research will not be applied to human bodies. It requires further careful discussion whether such germ cells are used for human embryo production. As a result, in 2010, the "Guidelines on the Research on Producing Germ Cells from Human iPS Cells or Human Tissue Stem Cells" were newly established.

2. Purpose and method of the research

On the basis of the guidelines, we are currently conducting the research on germ cell production at Kyoto University under a separate study protocol for germ cell production, which has been reviewed and approved by the Ethics Committee and notified to the MEXT. The goal of the germ cell research using iPS cells is the same as that of other disease studies; the research is being conducted to acquire new knowledge through the production and analysis of cells of tissues, which are otherwise difficult to obtain.

By developing a method to induce differentiation into germ cells using human iPS cells, we might be able to acquire knowledge on germ cell development, which has been difficult so far. The investigation on the differentiation process is expected to help clarify causes of infertility that originate in germ cells and develop innovative treatment methods.

This research aims to develop a method to induce differentiation of human iPS cells into germ cells based on the findings from germ cell differentiation studies in mice and monkeys. In this research, we will closely analyze the effects of genes on the structures and functions of germ cells and compare the results with those in mice and monkeys to gain a better understanding of the characteristics of the mechanism of human germ cell formation.

3. Provision of cells to external institutions (nonprofit or for-profit institutions)

Other researchers and companies (hereafter referred to as "external institutions") outside Kyoto University may request the use of iPS cells generated from your somatic cells in their research on germ cell production. If we receive such requests, we would like to supply iPS cells to these external institutions provided the researcher(s) who has been involved in the generation (establishment) of iPS cells from your somatic cells and researcher(s) who has been involved in the research on germ cell production confirm that the research meets the following criteria:

1) External institutions in Japan: The study protocol for germ cell production using iPS cells generated from your somatic cells has been reviewed and approved by the Ethics Committee and notified to the MEXT.
2) External institutions outside Japan: The study protocol complies with the applicable laws, regulations, and guidelines of the country and region and meets the following conditions:
   a) The study is a basic research (e.g., clarification of human development, differentiation, and regeneration functions or development of innovative diagnostic, preventative, and treatment methods or pharmaceuticals).
   b) Human embryos will not be produced.
   c) The study results shall be disclosed in principle.

Note: The aforementioned conditions a)–c) are included in the conditions in the guidelines on producing germ cells that are stipulated by the Japanese government.

3) The researcher(s) who has been involved in the generation (establishment) of iPS cells from your somatic cells and researcher(s) who is responsible for the research on germ cell production in Kyoto University judge that the research objectives and contents are appropriate.

The separate information document explains that iPS cells derived from you will be registered and stored in a cell bank so that many researchers can gain access to the cells. The cell bank may be used for the said provision of the cells derived from you for research on germ cell production at external institutions.

4. What we want you to understand if you decide to give consent

(1) Germ cells generated in the study will not be used for the production of human embryos or be put back into human bodies.

(2) As explained in the separate information document, your personal information will be managed by a personal information custodian of the study, and iPS cells generated from your tissue will be anonymized and used for the research on germ cell production.

(3) Genetic analysis of donated cells will also be performed in the research on germ cell production. However, the genetic analysis is not intended to identify specific individuals, as explained in the separate information document on genetic analysis.

(4) You will receive no reward from cooperating in the research on germ cell production.

(5) Data obtained from the research on germ cell production using iPS cells generated from your tissues may be presented at academic conferences, etc. Intellectual property rights (patent, copyright, etc.) or economic benefits may be generated from the useful outcomes of the research. Nevertheless, these rights or benefits will not belong to you.

(6) iPS cells, their differentiated cells, and analysis information used in the research on germ cell production will be carefully managed by the Center for iPS Cell Research and Application, Kyoto University, as well as external institutions to which these cells and information have been supplied (recipient institutions). Their property rights will belong to Kyoto University or recipient institutions (if approved by Kyoto University), depending on which institution has generated such iPS cells, differentiated cells, or analysis information.

(7) There are no direct benefits, penalty, or loss of benefits if you decide to participate or not participate in this research. If you consent to participate in the research and change your mind later, you may withdraw your consent anytime simply by writing to us. If you withdraw your consent, iPS cells generated from your sample and their differentiated cells produced in the research on germ cell production and your information associated with these iPS cells and their differentiated cells will be destroyed and will not be used for research from that time on. Note that, however, recovery and disposal of iPS cells generated from your sample may sometimes be difficult at the time of your withdrawal of consent; for example, when a paper including data from the research has been published, or iPS cells generated from your sample have been distributed to other institutions from a cell bank. In such cases, use of iPS cells, their differentiated cells, and/or information associated with these cells may continue despite your withdrawal of consent. There is no penalty or loss of benefits if you decide to leave the study.

After reading and fully understand this document, if you consent to the use of iPS cells generated from your tissues in the research on germ cell production, please sign and date the separate consent form and give the signed and dated consent form to your study doctor. The original copy of the signed informed consent form of the present research will be kept by the hospital, and a copy of the signed informed consent form will be given to you.

Date MM/DD/YYYY Doctor who has conducted the informed consent discussion (Signature)

Informed Consent Form for the Research on Germ Cell Production

_____

(Name of the head of the medical institution, etc., if the informed consent discussion is held in any institution listed in Attachment 2, outside Kyoto University)
Dean of Graduate School of Medicine, Kyoto University
Director of Kyoto University Hospital
Director of Center for iPS Cell Research and Application, Kyoto University

Study titles
R91: Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis

I have been given information that iPS cells generated from my body tissue in the aforementioned studies will be used in the research on germ cell production. The following items regarding the research have been explained to me by the study doctor using the information document, and I fully understand the explanation. I consent to take part in this research.

1. What is the research on germ cell production? 2. Purpose and method of the research
3. Provision of cells to external institutions (nonprofit or for-profit institutions)
4. What we want you to understand if you decide to give consent

(1) Germ cells generated in the study will not be used for the production of human embryos or be put back into human bodies.
(2) Procedure for protecting personal information of the donor (Details are explained in the information document for Study Title 1.)
(3) Genetic analysis may be performed. Genetic analysis is not intended to identify individuals. (Details are explained in the information document for Study title 2.)
(4) The donor will receive no reward.
(5) The study outcome may be presented or published at academic conferences, etc. Patent, copyright, other intangible property rights, and economic benefits may be generated from the study outcome. Nevertheless, these rights or benefits will not belong to the donor.
(6) Cells and associated information remain the property of Kyoto University (or external institutions accredited by Kyoto University).
(7) There are no direct benefits, penalty, or loss of benefits to the donor if the donor decides to participate or not participate in this research. About withdrawal of consent.

Date of consent MM/DD/YYYY
Donor (Signature) _____
Legal representative (Signature)_____
(Relationship of the legal representative to the donor)_____
I confirm that I have given the participant detailed information about the research and that the donor has consented to participate voluntarily in the research.
Date of informed consent discussion: MM/DD/YYYY
Institution (Name)/Department (Name):_____
Doctor who has conducted the informed consent discussion(Signature):_____
*The hospital will keep the original copy of the signed informed consent form, and a copy will be given to the donor.

Consent Withdrawal Notification

Dean of Graduate School of Medicine, Kyoto University
Director of Kyoto University Hospital
Director of Center for iPS Cell Research and Application, Kyoto University

I withdraw my consent to participate in the study using iPS cells generated from a part of tissue collected from my body. (**Please check ☑ 1 or 2**)

□ 1. I withdraw my consent to participate in the following studies and request that my donated tissue and information associated with the tissue be destroyed and not be used from this time on.
Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis
Genetic Analysis Study Using Human Disease-Specific iPS Cells

□ 2. **(Only for those who consented to cooperate in the research on germ cell production)**

I withdraw my consent to the use of iPS cells generated from my tissue in the research on germ cell production and request that all cells derived from my sample and information associated with the cells, which have been used in this research, be destroyed and not be used in the research from this time on. I shall continue to take part in the following studies:

R91: Generation of Human Disease-Specific iPS Cells and the Use of Such iPS Cells for Disease Analysis

Donor (Signature)	Date of notification MM/DD/YYYY
Legal representative (Signature) (relationship of the legal representative to the donor:)	

Receipt of Consent Withdrawal Notification

We have received the notification for withdrawing your consent to the participation in the studies/research using iPS cells.

Person in charge	Date of receipt MM/DD/YYYY
Remarks: Check 1 or 2. □ 1. □ 2.	