EXPLANATION OF THE RESEARCH

AND PATIENT CONSENT FORM

Title of the Clinical Research:

Development of Corneal-Endothelial Regenerative Medicine Involving Cultivated Human Corneal Endothelial Cell Injection

Principal Investigator:

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Co-Investigators:

Dr. Chie Sotozono, Dr. Morio Ueno, Dr. Tsutomu Inatomi, Dr. Takahiro Nakamura, Dr. Hiroshi Tanaka, Dr. Yuji Yamamoto, Dr. Noriko Koizumi, Dr. Naoki Okumura, Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Dr. Kojiro Imai, Department for Medical Innovation and Translational Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

CONTENT

EXPLANATION OF THE CLINICAL RESEARCH

Dear Mr. / Mrs. / Ms. _____

1) Study Title:

Cultivated Corneal Endothelial Cell Injection Therapy for the Treatment of Bullous Keratoplasty

2) The Significance and Purpose of This Clinical Study – including the medical terms and explanation of the overview on this plan

In patients with severe vision loss due to a damaged or diseased cornea, corneal transplantation, also known as corneal grafting, is generally performed. There are two methods of corneal transplantation. The first method is known as 'penetrating keratoplasty', a surgical procedure in which the entire cornea is replaced. The second method is known as 'Corneal Endothelial keratoplasty', a surgical method in which only the posterior part of the cornea is replaced. In both methods, the patient's damaged or diseased corneal endothelial layer is surgically removed and replaced with a donor corneal graft obtained from an eye bank, thus leaving the patient with a transparent cornea and good vision post-surgery. Although both methods are well-tested and proven procedures for the restoration of vision, problems such as graft rejection, detachment, or displacement can arise post-surgery. In addition, the transplanted corneal graft can sometimes become dull or opaque over time due to a decrease in corneal endothelial cells (CECs), ultimately resulting in corneal endothelial dysfunction, so called bullous keratopathy, in which the patient experiences impaired, blurred vision. Moreover, the worldwide lack of donor corneas for these procedures is a constant problem.

We at the Department of Ophthalmology, Kyoto Prefectural University of Medicine, have been developing a new therapeutic modality using cultivated corneal endothelial cell injection therapy, and have confirmed the following two facts through our research using animal experiment models:

(A) A damaged or diseased cornea does not recover transparency via treatment using cultivated corneal endothelial cell injection alone.

(B) In cases of bullous keratopathy, it is possible for the cornea to recover transparency via the surgical injection of cultivated CECs in combination with a Rho-associated protein kinase (ROCK) inhibitor Y-27632, which helps injected cells adhere to the appropriate position. Although ROCK-inhibitor Y-27632 is not yet approved for use in the clinical setting and is currently only available as a reagent for laboratory research, a clinical study involving 31 subjects has shown it to be both safe and effective for human applications without any side effects.

Thus, the aim of this current clinical research is to recover corneal transparency in patients afflicted with bullous keratopathy via novel regenerative medicine involving the injection of cultivated human CECs (HCECs) in combination with ROCK-inhibitor Y-27632 to the patient's anterior chamber.

3) Study Protocol

In this study, we will transplant via cell injection cultivated human corneal endothelial cells in combination with ROCK-inhibitor Y-27632 into the anterior chamber of your eye for the treatment of bullous keratopathy. The human cultivated corneal endothelial cells used in this study are cultivated from a donor cornea obtained from SightLife™ Eye Bank, Seattle, WA, USA. After the cells are injected, you will be required to stay lying face-down for approximately 3 hours in order for the treatment to work correctly.

After the transplantation, we will strictly monitor your condition in order to avoid possible complications. Should a complication or any severe side effects develop, we will immediately terminate the procedure and provide you with our best medical treatment for the complication. You will be required to undergo the 24-week follow-up period of examinations on your condition in order to confirm the safety and efficacy of this procedure, which will be evaluated and judged by visual acuity, transparency of the treated cornea, and corneal endothelial cell density and corneal thickness.

4) Informed Consent Disclosure Statements

(A) Participation in this research is 100% voluntary.

Patient participation in this clinical research is 100% voluntary.

(B) Patients will receive identical clinical care regardless of participation.

Patients will not forfeit any benefits should they decide not to participate.

(C) Participation in the research can be canceled at any time without penalty, even if the patient has previously agreed to participate.

Patients can cancel their participation in the research at any time prior to surgery or after surgery by filling out the appropriate form. Upon request, a research team member will provide the patient with the appropriate form to fill out to cancel the participation agreement without the risk of penalty or any loss of benefits to which they are entitled.

NOTE: Should the patient decide to cancel their participation in the research after the surgery has been performed, the research team strongly recommends that the patient continues to adhere to the scheduled follow-up visits / examinations with the doctor to ensure safety.

(D) Should the patient decide to cancel their participation agreement, all associated samples, results, and records will be deleted and no personal information will be disclosed.

NOTE: If the results have already been made public (i.e., such as in the form of a published paper) prior to the patient requesting cancellation of the agreement, then the associated samples, results, and records will not be deleted

(E) Patient selection criteria.

The benefit of this novel treatment has already been proved via animal experiments and 31 Japanese cases of clinical research. Thus, patients with corneal endothelial dysfunction will be selected for participation in the research in order to examine its safety and efficacy in humans.

(F) Registration period for participation in the research.

From the day that the patient is admitted and agrees to participation in the research until March 31, 2018.

(G) Patient exclusion criteria.

Due to the limited number of patients needed for this research, any patient who requires the written consent of a parent or legal guardian will be excluded from the research.

(H) The expected results of this research and risk and disadvantage would occur to a patient

The benefit of this treatment has already been proven in animal studies and limited cases of previously-performed clinical research. The symptoms caused by bullous keratopathy, such as loss of visual acuity, corneal stromal edema, and corneal epithelial edema, are expected to be improved via this novel treatment. However, in cases where the symptoms are not be improved sufficiently post treatment, a general corneal transplantation may be required. In such cases, the patient will be required to pay all fees associated with the cost of the additional treatment (i.e., the general corneal transplantation and all associated hospital care) that are not covered by this research group's liability insurance.

The known risks and possible disadvantages associated with this treatment are as follows:

(1) All risks and disadvantages equal to that of a general corneal transplantation.
(2) All risks and disadvantages associated with the injection of cells into the human body.
(3) All risks and disadvantages associated with the use of cultivated cells.

The research team is prepared to appropriately treat all of the following possible intraoperative and postoperative problems:

(1) Postoperative inflammation, any drug-induced liver or kidney dysfunction, any allergic reaction, and any eye infection such as endophthalmitis.
(2) Any increase of intraocular pressure resulting from cell accumulation and/or endothelial rejection caused by the cell injection therapy.

IMPORTANT NOTE: This research involves the use of bovine serum albumin and/or gentamicin in the transplanted cells which are essential for cell cultivation. However, the residues of the bovine serum albumin and/or gentamicin may cause an allergy or a virus that result in inflammation. All cultivated HCECs are diligently checked at two weeks prior to transplantation to insure that they are not infected with a virus, as it takes one to two weeks for a virus to be detected. Those cells are checked for viruses once again on the day of transplantation, however, the results of that test are not available until one or two weeks after the transplantation.

NOTE: Cases in which severe intra- or postoperative health damage and/or unexpected problems such as severe inflammation, increased intraocular pressure, an allergic reaction to the medicine or the transplanted cultivated HCECs, or the development of a malignant tumor arises as a result of the cell-injection therapy, medical care will be provided, with the cost of that care covered by the research group's liability insurance.

5) Stock of research protocol.

All details of the research protocol, including how personal information will be collected, stored, and securely protected, both during and after the research period, will be made available for review upon request.

6) Protection of personal information.

Dr. Norihiko Yokoi, Department of Ophthalmology Kyoto Prefectural University of Medicine, will be solely in charge of the safe and secure protection and administration of all personal information. The computer used to analyze the data, including all personal information, will be isolated and secure, and will never be connected to any inter-institution network or the Internet.

7) Research-associated intellectual property and patent rights.

All intellectual data and patent rights that result from this research study will be the sole property of the primary investigatory team, the research institute, the collaborative research institutes, including those of the Country of Japan, and the associated private companies.

8) Monitoring of the obtained genetic samples and associated data provided to other institutes.

Monitoring of the obtained genetic samples and associated data will be the sole responsibility and custody of the officially certified Special Monitoring Committee for Regenerative Medicine of Kyoto Prefectural University of Medicine in order to protect, make anonymous, and avoid the leakage of the personal patient data.

NOTE: The protocols of this research have been approved by the Institutional Review Board of Kyoto Prefectural University of Medicine. All patient data will be made anonymous via substitution with specific "ID" numbers.

9) Publishing of the research findings.

All participating patients must agree that all findings associated with this research may be published in a conference presentation, a scientific journal, and/or on a database after complete removal of all personal patient data.

10) Preservation and use of the cell samples.

HCEC cultivation at the cell processing center of Kyoto Prefectural University of Medicine for transplantation, as well as the 30-year preservation of those cells, is conducted in compliance with all applicable laws and official guidelines. After the 30-year preservation period, all cell samples will be disposed in a safe and appropriate manner.

11) Funding and Support of the Research.

Funding and support of this research was provided by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, and Technology (MEXT), a Health Labour Sciences Research Grant from the Ministry of Health Labour and Welfare (MHLW), and/or a grant from the Japan Agency for Medical Research and Development (AMED). There will be no cost to you. The individual medical expenses for general practices, as well as transportation expenses, will be covered for all registered participants in this study.

12) Conflict of Interest Statement.

There are no conflicts of interest to report for all investigators, public and private institutions, and private corporations associated with this study.

13) Contact Information for Study-Related Questions and/or Claims.

Dr. Chie Sotozono or Dr. Morio Ueno
Department of Ophthalmology
Kyoto Prefectural University of Medicine
Kyoto, Japan
Tel: +81-75-251-5578.

14) Name, affiliation, and seal of the person explaining the study / Date and place where the explanation was given.

Name: _____

Affiliation: Department of Frontier Medical Science and Technology for Ophthalmology ・ Department of Ophthalmology

Date (MM/DD/YYYY): _____/_____/_____

Place: Department of Ophthalmology, Kyoto Prefectural University Hospital of Medicine

CONSENT FORM

To: Professor Shigeru Kinoshita, M.D., Ph.D.
Principal Investigator, Chairman
Department of Frontier Medical Science and Technology for Ophthalmology
Kyoto Prefectural University of Medicine

I, (name of subject) _____ was given a complete and detailed explanation, along with the explanation form, about "Cultivated Corneal Endothelial Cell Injection Therapy for the Treatment of Bullous Keratoplasty" (study title) by (Explainer's name) _____at the Department of Ophthalmology, Kyoto Prefectural University Hospital of Medicine, Kyoto, Japan on (Date) (MM/DD/YYYY):_____/_____/_____, and I hereby acknowledge that I thoroughly understand the significance, purpose, methods, and risks associated with the study, how my personal information will be collected, stored, and protected, and that I agree to participate in this research.

I hereby acknowledge that I was given explanations about, and that I understand, the following (boxes to be checked by the participant):

- ☐ The significance and purpose of this research
- ☐ The methods in which the study will be conducted
- ☐ The method in which the subjects will be selected
- ☐ That participation in this research project is 100% voluntary
- ☐ The explanation regarding the needed informed consent
- ☐ That I can cancel my agreement at any time by written form
- ☐ The expected results and possible associated risks
- ☐ How my personal information will be collected, stored, and protected
- ☐ The associated costs, and how the funding will be allocated
- ☐ The preservation of cell samples and how they will be used

Name of Participant: _____ Personal Seal: _____
Date of Birth (MM/DD/YYYY): _____/_____/_____
Address:_____
Date (MM/DD/YYYY): _____/_____/_____

CANCELLATION FORM

To: Professor Shigeru Kinoshita, M.D., Ph.D.
Principal Investigator, Chairman
Department of Frontier Medical Science and Technology for Ophthalmology
Kyoto Prefectural University of Medicine

I, (name of subject) _____ hereby cancel my agreement to participate in "Cultivated Corneal Endothelial Cell Injection Therapy for the Treatment of Bullous Keratoplasty" (study title), and have today announced my decision to retract to (name of investigator) _____ and submit this retraction form, even though I previously agreed to participate in this study and signed the consent form.

Name of Subject: _____ Personal Seal:_____
Date of Birth (MM/DD/YYYY): _____/_____/_____
Address:_____
_____
Phone Number: _____

Date (MM/DD/YYYY): _____/_____/_____

I hereby certify that I have received this official retraction form of this research.
Name of Investigator: _____ Personal Seal: _____
Affiliation: Department of Frontier Medical Science and Technology for Ophthalmology ・ Department of Ophthalmology