

## **Explanation of Regenerative Medicine Treatment**

### Regenerative Medicine Treatment Name

Ligament and Tendon Injury Treatment Using Adipose-Derived  
Mesenchymal Stem Cells

This document is intended to help you understand the details of the regenerative medicine treatment and make an informed decision about whether or not you wish to receive it based on your free will.

Please read this document carefully and, after listening to the explanation from the attending physician, take time to consider whether or not to proceed with the treatment. If you have any questions, feel free to ask.

This treatment will be conducted in compliance with the "Act on Ensuring the Safety of Regenerative Medicine, etc." (enacted on November 25, 2014). Furthermore, based on this law, after obtaining the opinions of the designated Regenerative Medicine Review Committee (Regenerative Medicine Review Committee, R.M.C. Certification Number NA8190011), a regenerative medicine plan (Plan Number: [ ]) has been submitted to the Minister of Health, Labour and Welfare.

This treatment is provided to patients who have not seen improvement with conservative therapy but do not wish to undergo surgery or who are considered unlikely to achieve improvement with conventional therapies.

### **1. Purpose and Content of the Regenerative Medicine Treatment**

This treatment involves injecting adipose tissue-derived mesenchymal stem cells, which are harvested from the patient's own fat and cultured, into the affected area to suppress inflammation and improve symptoms such as pain, joint instability, and decreased function caused by soft tissue injuries in the limbs, such as ligaments, tendons, and muscles.

The procedure begins with a small incision (approximately 5mm, in an inconspicuous area) in the patient's abdominal area to extract around 0.5g of fat tissue. The extracted fat will then be cultured for a period of about 2 weeks to 1 month at the cell culture facility at Osaka Iseikai Cancer & Neurology Clinic, in order to increase the number of mesenchymal stem cells. Once the required number of cells is reached, they will be injected into the affected area.

Please note that the following patients are not eligible for this treatment:

- ① Patients with hypersensitivity to anesthesia or substances used during the manufacturing process.

- ②Patients who have experienced allergic reactions to penicillin, streptomycin, or amphotericin B used during culturing.
- ③Patients with a positive test result for viruses or bacteria (e.g., HIV, syphilis).
- ④Minors.
- ⑤Pregnant or breastfeeding women.
- ⑥Patients with cancer (due to the potential for stimulating cancer cell growth).
- ⑦Obese patients with a BMI of 40 or higher.
- ⑧Patients with abnormal coagulation test results as determined by the physician.
- ⑨Other patients deemed unsuitable by the physician.

## **2. Cells Used in Regenerative Medicine**

This treatment uses mesenchymal stem cells, which are derived from the patient's own fat tissue. Mesenchymal stem cells are found in both bone marrow and subcutaneous fat.

These cells can differentiate into a variety of cell types, including those of ligaments and tendons, and promote the repair and regeneration of damaged soft tissue. Additionally, adipose-derived stem cells secrete anti-inflammatory substances, which can help alleviate pain by reducing inflammation.

## **3. Treatment Process (From Fat Extraction to Injection)**

### 1. Pre-Treatment Tests

Before the procedure, blood tests will be conducted to check for viruses and infections. The tests include:

- a) HIV (antigen-antibody test)
- b) HCV antibodies (CLIA method)
- c) HBs antigen (CLIA method)
- d) HBe antigen (CLIA method)
- e) HTLV-I antibodies (CLEIA method)
- f) Syphilis (RPR method, TPHA method)
- g) Mycoplasma (PA method)
- h) Blood cell count, blood coagulation tests, biochemical tests, etc.

### 2. Fat Extraction Day

- Fat Extraction (in the operating room, typically takes 10 minutes) Fat will be extracted from the abdominal area, usually near the navel, using local anesthesia. A small incision (about 5mm) will be made along natural skin folds, which will be almost invisible after healing. Approximately 0.5g of fat will be extracted. Stitches

may be applied with absorbable sutures if needed, but no removal of stitches will be necessary.

- Blood Sampling (in the procedure room) Approximately 40cc of blood will be collected for the purpose of cell culturing. This amount is not expected to cause anemia, but you are advised to drink plenty of fluids after the procedure. Please refrain from alcohol consumption, and limit bathing to a shower.

### 3. Culturing Period

After the fat is extracted, it will be transported to the Osaka Iseikai Cancer & Neurology Clinic's cell culture facility for processing. Culturing typically takes about 1 month, during which the cells will be grown under sterile conditions. If culturing progresses as planned, you will be informed of the expected date for cell injection after about 2 weeks. Once the injection date is set, it cannot be changed. If culturing is unsuccessful, the process may be discontinued, and a new fat extraction will be necessary (at no additional cost).

### 4. Injection (in the procedure room, takes about 30 minutes)

On the confirmed injection day, you will arrive at the clinic. After confirming you have no fever or other signs of illness, mesenchymal stem cells will be injected into the target area. You will need to rest in the same position for about 15 minutes after the injection. Please refrain from alcohol consumption and limit bathing to a shower on the day of the procedure.

### **4. Cell Storage and Disposal**

The cells will be injected within 12 hours of culturing completion. If the cells are not used within this period, they will be disposed of properly. During the culturing process, some of the cells and serum will be stored in a freezer ( $-80 \pm 5^{\circ}\text{C}$ ) for future use.

### **5. Potential Benefits and Risks**

**Expected Benefits:** The use of adipose-derived mesenchymal stem cells is expected to reduce inflammation and promote healing and repair of damaged tissues in the ligaments, tendons, and other soft tissues. Because the stem cells come from your own body, there is no risk of rejection.

**Risks:** Like any medical procedure, there are potential risks, including complications from fat extraction or stem cell injection. Minor side effects such as infection or injection site pain have been reported, but there have been no reports of severe adverse events. If you experience any complications, they will be managed by the physician, and costs for necessary treatments will be covered by insurance or our malpractice insurance if severe. The procedure may be

halted at the physician's discretion if complications arise.

## **6. Alternative Treatments**

There are two main treatment options for soft tissue injuries: conservative treatment and surgical treatment.

**Conservative Treatment:** This involves immobilization using casts or braces to support self-healing of the ligaments or tendons. However, immobilization can lead to joint stiffness, and rehabilitation may cause pain after the cast is removed. In some cases, the ligament may not heal properly.

**Surgical Treatment:** Surgery involves suturing the torn ligament or tendon or reconstructing it using another ligament or synthetic material. These procedures usually require general anesthesia and hospitalization. Post-surgery, the area may need to be immobilized for weeks.

Stem cell therapy is considered a middle ground between conservative and surgical treatments. It uses your own cells, which avoids the risks of rejection, and can potentially promote tissue repair. The recovery time is typically shorter, and the need for immobilization is usually about a week.

If you wish to explore other options, please feel free to let us know. We can provide explanations or refer you to another facility.

## **7. Handling of Important Findings from Health or Genetic Testing**

If any important findings (e.g., medical conditions or abnormal test results) are detected during the pre-treatment blood tests, we will inform you. In some cases, these findings may prevent you from undergoing the treatment.

## **8. Use of Samples and Results**

Any cells or samples obtained during this treatment will only be used for your own treatment. They will not be shared with other medical institutions or used for research purposes. However, anonymized data may be published in academic journals or at conferences to contribute to the advancement of medical knowledge.

## **9. Consent for Receiving Regenerative Medicine**

You are not obligated to undergo this treatment. If, after receiving the explanation, you decide that you do not wish to proceed, you have the right to refuse the treatment.

## **10. Withdrawal of Consent**

If you withdraw your consent at any time before the stem cell injection, you will not face any

disadvantages in future medical treatment or care.

### **11. Withdrawal of Consent and Related Costs**

You may withdraw your consent before receiving the treatment. If costs have been incurred up to that point (e.g., for cell culturing), you will be responsible for paying those costs.

### **12. Compensation for Health Damage**

If you experience any health damage due to this treatment, the physician will provide appropriate care. For any medical costs related to this, insurance may cover the treatment. If the damage exceeds normal expectations, our malpractice insurance (with a coverage limit of 200 million yen per incident) will apply. However, if the cause of the damage is unrelated to the treatment, compensation may not be provided, or it may be limited.

### **13. Protection of Personal Information**

We adhere to the "Personal Information Protection Act" and have strict policies in place to protect your privacy. Any personal information or medical records will be kept confidential.

### **14. Retention of Medical Records**

Medical records related to this treatment will be kept for 10 years after the final treatment date, as this treatment uses your own cells.

### **15. Treatment Costs**

This treatment is not covered by insurance, so patient will be responsible for the entire cost of the treatment. The cost, including blood tests and fat collection costs for stem cell treatment, is 1.1 million yen (tax included) per area to be treated. The payment have to be made at the date the treatment started. In addition, you will be responsible for travel expenses, transportation costs, etc. required to receive this treatment.

If the examination before the fat collection shows that you are not a candidate for this treatment, you will be responsible for the costs associated with the examination, and if you withdraw your consent for the cell processing process, you will be responsible for the costs up to the point at which you withdrew your consent. Any remaining fees will be refunded. Please note that we cannot offer refunds if you cancel on the day of the procedure.

### **16. Conflicts of Interest**

Patents, copyrights, other property rights, and economic interests newly arising from regenerative medicine using cells donated by patients belong to our hospital.

## **17. Other Important Notes**

To ensure the safety and effectiveness of this treatment and to monitor the patient's health condition, please cooperate with regular visits and examinations after 1, 3 and 6 months after receiving this treatment. If regular visits are difficult, please let us know and we will monitor your condition by phone.

Those who have had allergies to anesthetics or antibiotics cannot receive this treatment.

If the implementation of treatment for the patient is delayed or difficult due to reasons beyond the control of our hospital, such as natural disasters such as earthquakes and typhoons, wars, riots, civil unrest, amendments or abolition of laws, orders or dispositions by public authorities, strikes, other labor disputes, transportation accidents, equipment malfunctions, or third-party actions (theft by third parties, traffic accidents, etc.), our hospital will not be liable for any damages resulting from this.

## **18. Implementation system for this treatment**

The implementation system for this treatment is as follows.

[Medical institution that performs adipose tissue collection]

Medical institution name: Iseikai International General Hospital

Address: 4-14 Minami Ogimachi, Kita-ku, Osaka City, Osaka Prefecture

TEL: 0570-099-166 (Reception)

Administrator: Kazuo Minematu, MD

person in charge: Minoru Yoneda, MD

Doctor that performs adipose tissue collection: Minoru Yoneda, MD

[Specific cell processing product manufacturing company]

Business name: Isekai Medical corporation

Address: 2-9-15 Higashinakajima, Higashiyodogawa-ku, Osaka City, Osaka Prefecture, 8th floor, Nihon Yamatosei Building

TEL: 06-6323-6355 (Reception)

Administrator: Hideya Ohnishi, MD

[Medical institution that performs stem cell administration]

Medical institution name: Iseikai International General Hospital

Address: 4-14 Minami Ogimachi, Kita-ku, Osaka City, Osaka Prefecture

TEL: 0570-099-166 (Reception)

Administrator: Kazuo Minematu, MD

person in charge: Minoru Yoneda, MD

Doctor that performs adipose tissue collection: Minoru Yoneda, MD

### **19. Treatment Inquiries**

We have a dedicated contact point for this treatment. If you have any questions, please feel free to contact your doctor or the following phone number at any time. When you contact the call center, please let us know the details of your inquiry and we will respond to you from the department that handles complaints.

TEL: 0570-099-166 (Call Center)

### **20. Committee that reviewed this regenerative medicine treatment plan**

Reiwa Regenerative Medicine Committee Secretariat

Website: <https://saiseiiryoinfo/>

TEL: 050-5373-5627

## Consent Form

Iseikai International General Hospital

Director: Minematsu Kazuo, MD

I have received the following explanation regarding the provision of regenerative medicine (titled "Treatment of ligament and tendon injuries using autologous adipose-derived mesenchymal stem cells") in accordance with the "Explanation of Regenerative Medicine Treatment"

- About the purpose and contents of regenerative medicine, etc.
- About the cells used in regenerative medicine, etc.
- About the flow of treatment (from fat collection to administration)
- About the storage method and disposal of cells
- About the effects and risks of receiving regenerative medicine, etc.
- About other treatment methods
- About handling when important findings on health, genetic characteristics, etc. are obtained
- About samples obtained through regenerative medicine, etc.
- About consent to receiving regenerative medicine, etc.
- You will not be treated disadvantageously for refusing to receive regenerative medicine, etc. or withdrawing consent
- About withdrawal of consent
- About compensation for health damage
- About protection of personal information
- About storage of medical records
- About costs
- Other special notes
- About the implementation system of this treatment
- Contact for treatment, etc.
- Committee that reviewed this regenerative medicine treatment plan



I explained the provision of regenerative medicine, etc. mentioned above.

Explanation date                      Year      Month      Day

Person in charge of explanation

I fully understand the explanation above and agree to receive regenerative medicine, etc.

I have confirmed that this consent can be withdrawn at any time up until the administration of stem cells.

Date of consent:                      Year      Month      Day

Patient signature

Date of consent:                      Year      Month      Day

Signature of legal representative

Relationship to the patient

## Withdrawal of Consent Form

Iseikai International General Hospital

Director: Kazuo Minematsu

I have consented to receiving regenerative medicine (titled "treatment of ligament and tendon injuries using autologous adipose-derived mesenchymal stem cells"), but I would like to withdraw this consent.

I have no objection to bearing the medical expenses and other costs incurred up until the time of withdrawal of consent.

Date of withdrawal:            Year    Month    Day

Patient signature

Date of withdrawal:            Year    Month    Day

Signature of legal representative

Relationship to the patient