Current status and future vision of retinal cell therapy

Masayo Takahashi MD, PhD

2019.8~ Vision Care Inc. (President)
Kobe Eye Center Hospital
RIKEN Center for Biosystems Dynamics Research
NPO, NEXT VISION
Kobe eye center total solutions for every patient

1. RIKEN, BDR → Eye Center Research Center
   - Basic research
   - Clinical Application
   - Treatment
   - Patient support
   - Low Vision Care

2. Eye Center Hospital

3. NPO Next Vision

4. Vision Care Inc.
   - VC Gene Therapy (VCGT)
   - VC Cell Therapy (VCCT)

- Working Opportunity
- Patient support
- Low Vision Care
- Treatment
- Clinical Application
- Basic research
- Eye Center Research Center
- RIKEN, BDR
Kobe Eye Center

(2) Ophthalmology hospital
Kobe Eye Hospital (KEC)

Regenerative medicine
RPE cells

Patients with retinal disease

Genetic diagnosis
Gene therapy

Genetic counseling

Automated driving

(3) Rehabilitation and social experiment
NPO NEXT VISION

(4) Vision Care. Inc

(1) Research
RIKEN & KEC research center

Retinal examination, imaging

Regenerative medicine
Photoreceptors

Patient iPSCs
Drug discovery/development

AI robotics

Visual rehabilitation development

Low vision care device development

Drug discovery/development

Regenerative medicine
Photoreceptors

Genetic diagnosis
Gene therapy

Genetic counseling

Automated driving

(4) Vision Care. Inc

(3) Rehabilitation and social experiment
NPO NEXT VISION

(2) Ophthalmology hospital
Kobe Eye Hospital (KEC)
Masayo Takahashi MD, PhD

**Academia**
2018 〜 USA NAM (National Academy of Medicine) member

**Board member**:
〜2018 ISSCR (International Society for Stem Cells and Regeneration)
2015〜 Japanese Society for Ophthalmology
2018〜 Japanese Vitreoretinal Society
2012〜 Japanese Society for Regenerative Medicine

**Ministry**
**Committee members of**
Ministry of Education, Culture, Sports, Science and Technology
Ministry of Health, Labor and Welfare
Ministry of Economy
PMDA (Japanese FDA) Board member (~2020)

**Company**
Board member : Sysmex, S’UIMIN
Advisor : IPGI Technologies
Founder : Healios, VC’ group
Masayo Takahashi MD, PhD

Two “first in the world” works @ the Salk Institute (1995-1996) in Fred Gage lab

Neural stem cells: Usage of the stem cell for retinal transplantation
M Takahashi et al. Molecular Cellular Neurosci. 1998

HIV vector: Animal experiments of the lentiviral vector
H Miyoshi, M Takahashi (Co-first) et al. PNAS 1998
M Takahashi, H Miyoshi et al. J Vil 1998

First in human

Retinal cell therapy using iPS cells

Gene therapy for Retinal degeneration
Retina

Modified from Nat. Rev. Genet. 11, 273-284 2010
Age related macular degeneration (AMD) & Current therapy

Normal

AMD

After treatment

Wet AMD

Neovascularization

Current therapy

Intraocular Anti-VEGF

Neural retina

Retinal pigment epithelium (RPE)

Inactive NV

recurrence
Stages of AMD & suitable treatment

- Neovascularization
  - Existing treatment: PDT, anti-VEGF drugs
  - CNV removal
- Fibrous membrane
- RPE damage
  - RPE transplantation
- Photoreceptor damage
- Choroidal damage
  - RPE + photoreceptor + choroid transplantation

Regenerative medicine

Wet type AMD

Dry type AMD
RPE transplantation: wet AMD

**Human embryo RPE**
- Algvere PV (1999)
- Allo - Rejection

**Auto RPE suspension**
- Cell suspension
  - Low survival ratio
  - Risk of cell harvest

**Auto RPE sheet**
- 2006〜7年4 report: effective for 58% patients (total 73 cases)
- Cell harvest High risk 40%

Peripheral RPE

Macula

Peripheral RPE

Macula
A Free Retinal Pigment Epithelium–Choroid Graft in Patients With Exudative Age-Related Macular Degeneration: Results up to 7 Years
ELSBETH J.T. VAN ZEEBURG, KRISTEL J. M. MAAIJWEE, TOM O. A.

7 yrs after surgery: visual acuity 20/32 (= 0.6), fixation on the graft.

6 yrs and 7 mo after surgery: visual acuity 20/50 (= 0.4), fixation on the graft.
Retinal Cell Therapy

- **iPSC-RPE** (Phase 1,2)
  - RPE impairment diseases
- **iPSC-photoreceptor cells** (Phase 1)
  - Retinal degenerative diseases

Clinical study:
- #1 2013-15 (auto)
- #2 2017-18 (HLA matched)
- #3 2020 - (Allo)
Categories of Regenerative Medicine

Classification by **Action Mechanism**

1. **Endogenous stem cell activation**
   - Endogenous stem cell activation

2. **Cell Transplantation**
   - **Replacement therapy**
   - **Trophic effect**

Classification by **treatment method**

- **Regeneration promoters**
- **Cell therapy**
  - 1. **i.v.** Systemic
  - 2. **Surgery** Local

**Graft survival**

- **Short** Days~weeks
- **Long No division** Several division (mature cells)
- **Long Division** Continuous division (Stem/immature cells)

- **MSC**
- **RPE**
- **Neural retina**
Progress of retinal cell therapy

1. Auto RPE
   - 2013.8~
   - 2015.9

2. Allo RPE
   - 2017.3~
   - 2018.9

3. Photoreceptor
   - 2020.6~

4. RPE multicenter
   - 2020.1~

5. 2nd generation Retinal sheet
   - Now

Efficacy, System

Safety

1/50 cases
5 cases
2 cases
1 case

Now
The ideal state of regenerative medicine from the patients’ & doctors’ perspective

- Optimal treatment for each case
- Reconsideration of disease names
- Various forms (suspension & sheet)
- Reduce treatment costs
- Regulation, CPF
- Sustainable treatment as a medical system
- Consider hospitals profits (Japan)
- From cell products to therapy
- Surgery
- Around the treatment
- Evaluation tests
- QA of genetic diagnosis
Regulatory system in Japan

Reverse Translational research

Basic research → Preclinical research → Preclinical study → Clinical study (Act on the safety of regenerative medicine) → Clinical trial (revised Pharmaceutical affairs act) → Treatment

- Therapy at one's own expense
- Advanced therapy
- Covered by National Insurance

<Stage>
- Preclinical study
- Clinical study
- Treatment

<Clinical trial>
- Phase 1,2
- ≡Phase 3 ～7 years

Clinical Research
Clinical Trial (confirmation of probable benefit* and safety**)
Adaptive Licensing with condition (further confirmation of efficacy and safety)
Post Marketing Surveillance
Approval or Expiration
Marketing
Autologous iPSC-RPE transplantation
(1 case: 2013~2015)

1\textsuperscript{st} clinical research
using iPS cells

To show a safe way of clinical use

Mandai et al. New Engl J Med 2017
Autologous iPS-RPE transplantation to AMD patients

1st clinical research 2013〜2015

AMD patients

Skin fibroblasts

Reprogramming factors

4 months

iPS Cells

Differentiation

4 months

iPS-RPE cells

Transplantation

Kobe City Medical Center General Hospital

4 months

RPE cell sheet

2 months
• No report of metastatic tumor ever in the history
  Even in the familial tumor patients only hyperplasia of RPE occurs
  = with oncogene (ex. p53) mutations

• PEDF (pigment epithelial derived factor) = strong antitumor factor

• Eye ball is full of Retinoic Acid = strong inducing factor for differentiation
Why the RPE cell is the first one

Purification

Mature cells; less proliferation

Small amount of cells

PEDF; anti-tumor factor

OCT; fine examination

Safety

Kuroda et al. 2012 PlosONE

Kanemura et al. 2013 Scientific report
1st patient’s iPS cells

Feeder cells: the patient’s fibroblast

Karyotype: normal

<table>
<thead>
<tr>
<th>Target</th>
<th>Nanog</th>
<th>Oct3/4</th>
<th>SSEA4</th>
<th>Tra1-60</th>
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<tr>
<td>Merge</td>
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</table>
Function of RPE sheet → Quality Control (QC)
Quality of hiPSC-RPE cell-sheets

(Kamao et al. Stem Cell Report 2014)
Monitoring points: RPE function

![Diagram](image)
<table>
<thead>
<tr>
<th>Quality/Function</th>
<th>methods</th>
<th>Case 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Appearance of sheets</td>
<td>Observation by eye and under microscopy</td>
<td>No cell defect No contamination of odd materials No discolor</td>
</tr>
<tr>
<td>2) Structure of sheets</td>
<td>Z-Stack observation of confocal microscopy</td>
<td></td>
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<tr>
<td>3) Live cell ratio &amp; density of cells</td>
<td>Toripane blue staining after trypsinization of sheet</td>
<td>&gt;= 70% &gt;= 4,500 cells/mm²</td>
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<tr>
<td>4) RPE specific gene</td>
<td>RT-PCR (RPE65, CRALBP, MERTK, BEST1)</td>
<td>Positive band</td>
</tr>
<tr>
<td>5) Purity</td>
<td>① immunocytochemistry &amp; pigmentation ② tight attachment cell</td>
<td>① &gt;= 95% ② &gt;= 99.9%</td>
</tr>
<tr>
<td>6) Stem or immature cell marker</td>
<td>qRT-PCR (Lin28)</td>
<td>Not detected (= less than 1/50000 cells)</td>
</tr>
<tr>
<td>7) Bacteria · Fungus</td>
<td>薬局方（membrane filter method）</td>
<td>none</td>
</tr>
<tr>
<td>8) Micoplasma</td>
<td>薬局方（PCR, immunostaining）</td>
<td>none</td>
</tr>
<tr>
<td>9) Endotoxin</td>
<td>薬局方</td>
<td>&lt;= 3EU</td>
</tr>
</tbody>
</table>

Case 1: Quality / function
- Good
- 96.8%
- 16,200

- Positive
- 100%
- >=99.9%
- None
- None
- None
- <=3EU
Heterogeneity of cells in the iPSC colonies

MCM: Master Cell Bank  WCB: Working Cell Bank

X gene mutation rate at 21.5%
Mutation 49.3%
Mutation 62.8%
Mutation 68.5%
Mutation rate 0.08%
Mutation rate 0.2%
Mutation rate 0.00%

Negative control
RPE signature genes

Human Molecular Genetics, 2010, Vol. 19, No. 12 2468–2486

Transcriptome analysis and molecular signature of human retinal pigment epithelium
N.V. Strunnikova¹,², A. Maminishkis²,³, J.J. Barb⁵, F. Wang²,³, C. Zhi²,³, Y. Sergeev¹,⁴, W. Chen⁶, A.O. Edwards⁷, D. Stambolian⁸, G. Abecasis⁶, A. Swaroop³,⁴, P.J. Munson⁵ and S.S. Miller²,⁴,*

Common among Adult native, fetal cultured, fetal native= 154 genes
Heatmaps by RPE signature genes

iPS-RPE, h-RPE, ARPE-19 (cell line)

NDC80, FOXD1, LHX2, SMAD6, BMP4, WC2
Microarray cluster analysis:

- cerebellum
- neural retina
- melanocyte

iPS

ARPE19

fibroblast

fetal RPE

iPS-RPE
<Robust protocol >  evaluation of purity and sameness

**Single cell RT-PCR**

**Microarray cluster analysis**

**RPE signature genes**

**Transcriptome analysis**

**cerebellum**

**neural retina**

**melanocyte**

**fibroblast**

**fetal RPE**

**IPS-RPE**

**ArPE19**

**marker**
## Genomic analysis

(@ CiRA, Prof. Yamanaka)

<table>
<thead>
<tr>
<th>Points</th>
<th>methods</th>
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<tbody>
<tr>
<td>a) Plasmid fragment remnant check</td>
<td>WGS, qRT-PCR, capture Sequence</td>
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<tr>
<td>b) Copy number variation (CNV)</td>
<td>SNP array</td>
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<tr>
<td>c) Mutations in the driver genes</td>
<td>WGS</td>
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<tr>
<td>d) Epigenetic analysis</td>
<td>Methylome analysis</td>
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<tr>
<td>e) Purity</td>
<td>single cell RT-PCR</td>
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</table>
The first-in-man application of iPS-derived cells (2014)

Wet AMD

Remove damaged RPE

Transplant iPS-RPE

Lens

Retina

iPS-RPE sheet
Fundus photos and visual acuity (4 years)

Visual acuity

Pre operation 1 month 12 months 48 months

Visual acuity

Intraocular Anti-VEGF

Week 168
OCT (Transvers section of the retina)
Choroidal thickness

Reduction rate (%) of choroidal thickness over time post-operation.

- **Pre-operation**
- **1 month**
- **3 months**
- **12 months**
- **24 months**
- **48 months**

The graphs show the reduction rate of choroidal thickness at the transplant site and outside the transplant site over months after surgery.
Risks of the cell therapy

1. **Cell risk** - gene mutation etc.
2. **Treatment risk** - Immune suppression
   - Surgery technique
3. **Disease’ risk (Risk of inaction)** - deterioration risk
Risk Matrix for complication of iPSC-RPE

- **Transformed Malignant tumor**
- **iPSC Benign tumor**
- **Immune suppression risk for elderly**
- **Surgery risk**
- **Deteriorate risk of RP**
- **Deteriorate risk of AMD**

**Cell risk**

- **Treatment risk**
- **Inaction risk**

2. Schwartz SD, et al. IOVS 2016

- Age-related macular degeneration
- Retinitis pigmentosa

**Frequency**

- **Severity**
  - high
  - low
2nd clinical research

**HLA matched Allogeneic** iPSC-RPE transplantation
(5 cases: 2017~2018)

To show the possibility of allogeneic transplantation
*without systemic immune suppression*
for elder patient
Allogeneic iPS-RPE transplantation (2017~)

Healthy HLA homozygous donor

iPS cell

Allogeneic iPS-RPE

6 loci homozygous “super donor” iPS cells

Sugita et al. submitted

(Modified from JMA J. 2018;1(1):6-14)
RPE cell suspension transplant

Wet AMD

Neovascularization (NV)

Sensory retina

RPE

iPS-RPE transplantation

Cell injection

iPS derived RPE suspension (end product)

100um

Age < 85
BCVA < 0.3
Anti-VEGF > 4 times

Suppress the NV

Non active

Cell injection
1. Diagnosis for immune rejection after RPE cell transplantation:

**LGIR Test (Lymphocytes-Grafts Immune Reaction test)**

- Blood (AMD patient) → PBMC
- Culture for 4-6 days
- PBMC: CD4 – Helper T cells (Th), CD8 – Cytotoxic T cells (CTL), CD11b – Monocytes, CD19 – B cells, CD56 – NK cells
- IPS-RPE cells (grafts) → Radiation
- Evaluation: Ki-67 FACS (Cell proliferation) & IFN-γ ELISA (Inflammatory cytokines)

**DSA Test (donor specific antibody)**

- Blood (AMD patient) → Serum
- IHC for RPE cells with serum or antibody
- Evaluation: Confocal microscopy (MFI)
Efficacy of LGIR test Case 1

5W

Subtle subretinal fluid
Immune rejection? or
Recurrence of disease?
→ LGIR test
→ slightly positive

8W

Local steroid injection

→ LGIR test  negative
Graft survival!

5W

8W
Monitoring of immune reaction by LGIR & DSA

**DSA (donor specific antibody); RPE specific antibody**

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<th>Case # \ DSA</th>
<th>非前</th>
<th>術目</th>
<th>4W</th>
<th>8W</th>
<th>12W</th>
<th>24W</th>
<th>52W</th>
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**LGIR; Lymphocyte graft immune reaction test**

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<th>Case # \ LGIR</th>
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**Case 2**

- **Pretreatment: 5 min**
- **1 Year: 5 min**

**Section**

- Autofluorescence
- Fluorescein angiography

**Swept source OCT**

- Front
- Section

**Transplantation:**
- IPS-RPE cell suspension
- + anti-VEGF (IVA)
- + local steroid (IVTA)

**Injection of grafted cells**
Regulatory system in Japan

Reverse Translational research

Basic research → Preclinical research → Clinical research (Act on the safety of regenerative medicine)

Clinical trial (revised Pharmaceutical affairs act)

Treatment

Therapy at one's own expense
Advanced therapy
Covered by National Insurance

<Stage>
Preclinical study

<Clinical trial>

Clinical research

Approval or Expiration
Marketing

Phase 1,2

Adaptive Licensing with condition

Post Marketing Surveillance (further confirmation of efficacy and safety)

ⅡPhase 3 〜7 years

Clinical Trial

Clinically covered by National Insurance

Physician

Mainly Company

Clinical research

(Act on the safety of regenerative medicine)

Mainly Company
3rd clinical research (phase 2)

**HLA matched & unmatched Allogeneic**

iPSC-RPE transplantation

(50 cases: 2021.1~2016)

To evaluate the efficacy of iPS-RPE treatment

How to access the efficacy

What kind of cases are suitable
Retinal degenerative diseases

Disease name | Cause, Pathogenesis | Cell therapy
---|---|---
Cone dystrophy | Cone gene mutation, Rod gene mutation, Rod & Cone gene mutation | Photoreceptor
Retinitis pigmentosa | RPE gene mutation, RPE & photoreceptor, RPE senescence (& gene) | RPE
Choroideremia etc | | |
AMD | | |
RPE impairment diseases

- Crystallin retinopathy
- Dry type AMD
- High Myopia
- Stargardt disease
- Best disease
- APMPPE
Progress of retinal cell therapy

Safety

Allo RPE (Phase 2, Multicenter)

Photoreceptor

Auto RPE

Change the concept of diseases
How to evaluate efficacy

HLA-KO iPS cells & autologous
**Direct Reprogramming**

**Induced RPE (iRPE) ~40-60 Days**

**iPS-RPE ~150-200 Days**

Patient-specific iRPE will be faster, easier, and cheaper than iPS-RPE
iRPE From Human Skin

*Best1::EGFP* Reporter Indicates RPE Maturation

Early Reprogramming iRPE Colony

Expanded iRPE Colony
Progress of retinal cell therapy

- Auto RPE
- Allo RPE
  - (Phase 2, Multicenter)

Efficacy System

Photoreceptor

Change the concept of diseases
How to evaluate efficacy

HLA-KO iPS cells & autologous
Retinal Cell Therapy

- **iPSC-RPE** (Phase 1,2)
  - RPE impairment diseases
- **iPSC-photoreceptor cells** (Phase 1)
  - Retinal degenerative diseases

Clinical study

#1 2013-15 (auto)
#2 2017-18 (HLA matched)
#3 2020 - (Allo)
Next project: 1\textsuperscript{st} clinical research

**HLA unmatched Allogeneic**

iPSC-photoreceptor transplantation
(2020~)

To show the organoid transplantation
To reconstruct neural network in the CNS
Retinitis pigmentosa
Photoreceptor degeneration

After birth

Visual field constriction

Photoreceptor degeneration
Photoreceptor transplantation

ES/iPS cells → differentiation → Immature retina → Transplantation → Grafted retina

Normal retina → Degenerated retina → Grafted retina

Synapse

RPE

PR

Inner cells
Start of Organoid Research

Self-organizing optic-cup morphogenesis in three-dimensional culture

April 7, 2011

Mototsugu Eiraku, Nozomu Takata, Hiroki Ishibashi, Masako Kawada, Eriko Sakakura, Satoru Okuda, Kiyotoshi Sekiguchi, Taiji Adachi, Yoshiki Sasai (CDB, RIKEN)

Prof. Eiraku

Prof. Sasai
iPS / ES cell-derived retinal organoids (Embryonic retina)

iPS / ES cell aggregates (embryoid bodies)

Self-organizing retinal morphogenesis

Retinal organoid

Fully layered retina

(Eiraku et al. Nature 2011)

12,000 iPS cells

Photoreceptors

Cell biology
Animal experiment
Organizer clinical study
QA, QC Clinical trial

Eiraku MD, PhD
Mandai MD, PhD
Takahashi MD, PhD

Sumitomo Dainippon Pharma

Eiraku et al. Nature 2011
Nakano et al. Cell Stem Cell 2012
Kuwahara et al. Nature Communications 2015
Kuwahara, Yamasaki et al. Scientific Reports in press
iPS-photoreceptor transplantation preclinical study

4 steps of Proof of Concept

1. Survival of grafted cells
2. Synapse formation
3. Electrophysiological study
4. Behavior test

Mouse

Host retinal inner layer

Graft: photoreceptor

QIPUPSFDFQUPSUSBOTQMBOUBUJPOQSFDMJOJDBMTUVEZ
1. Survival of grafted cells

Assawachananont et al, Stem Cell Reports, 2014
2. Synapse formation between the host and graft

(Assawachananont et al. Stem Cell Report 2014)
3. Electrophysiological study

Med probe (MED-P5155)

Electrode size: 50x50µm
Post-grafting maturation and response to light in a mouse model of end-stage retinal degeneration

(Iraha and Tu et al Stem Cell reports 2018)
4. Behavior test: shuttle avoidance test

Effect of transplantation confirmed by behavioral analysis of the mouse model

Counts of escape responses to light signals

Normal mouse

Mouse with retinal degeneration

Counts of random movements made in the dark irrespective of a signal

Untrained mouse (control)

Behavioral pattern similar to that of normal mice (escape responses to light signals) shown immediately after grafting

miPSC-derived photoreceptor grafting in a mouse model of retinal degeneration

Mice were trained to learn that an electric shock would follow a light stimulus
Long-term survival of hiPSC-retina was also confirmed (2 years)
Clinical study of allogeneic iPS cell-derived retinal sheet transplantation for retinitis pigmentosa

• To evaluate the safety and efficacy
• Target number of subjects: 2 cases
• Eligible criteria:
  ➢ retinitis pigmentosa, age 20 years and older
  ➢ corrected visual acuity less than 0.2
  ➢ MD less than -30dB on Humphrey's visual field test (10-2)
• 6 months registration and 1 year observation period
Organoid research
The ideal state of regenerative medicine from the patients’ & doctors’ perspective

- Optimal treatment for each case
- Reconsideration of disease names
- Various forms (suspension & sheet)

- Reduce treatment costs
- Regulation, CPF

- Sustainable treatment as a medical system
- Consider hospitals profits (Japan)

- From cell products to therapy
  - Surgery
  - Evaluation tests
  - QA of genetic diagnosis

- Around the treatment
RPE impairment diseases

- Crystallin retinopathy
- Dry type AMD
- High Myopia
- Stargardt disease
- Best disease
- APMPPE
Progress of retinal cell therapy

Efficacy System

Safety

Allo RPE (Phase2, Multicenter)

Change the concept of diseases
How to evaluate efficacy

HLA-KO iPS cells & autologous
Stages of AMD & suitable treatment

1. Neovascularization
2. Fibrous membrane
3. RPE damage
4. Photoreceptor damage
5. Choroidal damage

Existing treatment
- PDT, anti-VEGF drugs
- CNV removal
- RPE transplantation
- RPE + photoreceptor transplantation
- RPE + photoreceptor + Choroid transplantation

Wet type AMD
Dry type AMD

Regenerative medicine
Robotic Biology
LabDroid - Mahoro

Dr. Natsume at AIST
Half open booth for CPF

DAIDAN

semiconductor
With Kobe Eye Center Hospital

1. RIKEN, BDR
   Eye Center Research Center

2. Eye Center Hospital
   Clinical Application

3. NPO Next Vision
   Patient Care

4. Vision Care. Inc

With the hospital

- Cell manipulation room (Thawing)
- Genetic diagnosis, counseling
- Immunological test (LGIR, DSA)
- Surgical technique, devise
- Ophthalmology test
  - Adaptive Optics camera
  - Polarized light OCT
- Low Vision Care (mental care)
Clinical imaging of iPS-RPE using adaptive optics

rtx1 AO camera (Imagine Eyes, FR)

Adaptive optics image

ROI - cell detection

Voronoi analysis

Detection by 5 evaluators

Co-localization with color fundus image

Co-localization with OCT image

Quantification

Densities (neutrophils) 6.94 × 10^6 mm^-3
Densities (lymphocytes) 3.11 × 10^6 mm^-3
Distance (neutrophils) 10.48 microns
Distance (lymphocytes) 2.98 microns

Hematology: 10.2 ± 2.5
Hemoglobin: 8.5
White blood cells: 4.5 ± 0.5
Red blood cells: 4.2 ± 0.4
Platelets: 0.4 ± 0.1

Total analyzed 32
Regenerative medicine

Start up

Pharmaceutical company

Clinical trial

Approval

B to B

B to C

RPE suspension

RPE sheet

Parkinson’s disease

20 years of history

RCT
Masayo Takahashi Lab. → Vision Care Inc.
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“Any approaches to restore lost vision”