# Social systems for healthcare in Japan

two stories on
1) whole-person screening in all 1.5 and 3-year-old children born in Japan
2) governmental approval system for pharmaceuticals and medical devices

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- I would like to introduce two examples in social systems for healthcare in Japan.
- One is 1.5-year-old and 3-year-old children screening programs which are based on Maternal and Child Health Act and have been conducted since 1961. All children's physical and mental health are examined by pediatricians and nurses at Heath Centers in each municipality. Children also undergo vision screening with Spot Vision Screener and visual acuity testing.
- The other is the governmental approval systems for new pharmaceuticals and medical devices based on Pharmaceuticals and Medical Devices Act which is in charge of Pharmaceuticals and Medical Devices Agency (PMDA). Three principles considered in the approval is safety, efficacy, and quality control. I show retinal prosthesis (OUReP) as an example to introduce good laboratory practice (GLP), good manufacturing practice (GMP) or quality management system (QMS), and good clinical practice (GCP).

# Vision screening program as part of whole-body examination system for children at 1.5 and 3.5 years in Japan

## History

- 1937- Maternal and Childhood Health Law
  →"Mother and Child Health Handbook"

  (1965- Current "Maternal and Childhood Health Law)
- 1961- Whole-body examination system for 3.5-year-old children including dental checkup
- 1978- Whole-body examination system for 1.5-year-old children
- 1981- Dental checkup added to 1.5-year-old examination system
- 1991- Vision and hearing examinations added to 1.5 and 3.5-year-old examination systems

## At present

**Examination of 1.5-year-old children and 3-year-old children**

According to Maternal and Childhood Health Law in Japan, all children at the age of 1.5 and 3 years have to undergo physical and developmental examinations including dental, eye, and hearing examinations.

Each municipality has responsibility for this examination system.

# Announcement for 3.5 and 1.5-year-old children examinations

## 3歳児健康診査

対象は、平成14年7月生まれの幼児です。健康診査票・目と耳のアンケート（事前に記入）、尿、親子手帳（母子健康手帳）、予防接種手帳を持参。1月末までに健康診査票が届かない人は保健所健康づくり課母子歯科保健係へご連絡ください。

| 月　日 | 受付時間 | 場　　所 |
|---|---|---|
| 2月21日 | 13:00～14:00 | 中央保健センター（岡山市保健福祉会館内） |
| 2月10日<br>2月24日 | 13:00～14:00 | 北保健センター<br>（北ふれあいセンター内） |
| 2月7日<br>2月15日 | 13:00～14:00 | 東保健センター<br>（岡山ふれあいセンター内） |
| 2月22日 | 13:00～14:00 | 西大寺保健センター（旧西大寺保健所） |
| 2月14日<br>2月28日 | 13:00～14:00 | 西保健センター<br>（西ふれあいセンター内） |
| 2月15日<br>2月22日 | 13:00～14:00 | 南保健センター<br>（南ふれあいセンター内） |

## 1歳6か月児健康診査

対象は、平成16年7月生まれの幼児です。健康診査票（事前に記入）、親子手帳（母子健康手帳）、予防接種手帳を持参。1月末までに健康診査票が届かない人は保健所健康づくり課母子歯科保健係へご連絡ください。

| 月　日 | 受付時間 | 場　　所 |
|---|---|---|
| 2月9日<br>2月16日 | 13:00～14:00 | 中央保健センター<br>（岡山市保健福祉会館内） |
| 2月1日 | 13:00～14:00 | 北保健センター（北ふれあいセンター内） |
| 2月1日<br>2月8日 | 13:00～14:00 | 東保健センター<br>（岡山ふれあいセンター内） |
| 2月23日 | 13:00～14:00 | 西大寺保健センター（旧西大寺保健所） |
| 2月16日<br>2月23日 | 13:00～14:00 | 西保健センター<br>（西ふれあいセンター内） |
| 2月2日<br>2月9日 | 13:00～14:00 | 南保健センター<br>（南ふれあいセンター内） |

# Flow of whole-body examinations for 1.5-year-old children at Health Centers

**Nurse interview**

- Check the Mother and Child Health Handbook
- Check the Questionnaires for vision and hearing
  filled in beforehand and brought by family members
- Ask about
  pregnancy and delivery history
  past history for diseases
  developmental milestones
  eating, sleeping, daily life habits
  vaccination
  dental habits
  hearing and vision
  housing and family members

**Examinations**

- Weight, Height, Chest, and Head circumference measurement by nurses
- Dentist examination
- Pediatrician or Medical Officer (MD) examinations

# Flow of whole-body examinations for 3.5-year-old children at Health Centers

**Nurse interview**

- Check the Mother and Child Health Handbook
- Check the Questionnaires for vision and hearing
  filled in beforehand and brought by family members
- Ask about
  pregnancy and delivery history
  past history for diseases
  developmental milestones
  eating, sleeping, daily life habits
  vaccination
  dental habits
  housing and family members

**Examinations**

- Urinalysis for protein and occult blood by nurses
- Weight, Height, Chest, and Head circumference measurement by nurses
- Dentist examination
- Visual acuity testing by nurses
- Hearing testing by nurses
- Pediatrician or Medical Officer (MD) examinations

# Summary Table for Flow of Vision Examination

| | 1.5 years old (1.5-2.0 years) | 3 years old (3.5-4.0 years) |
|---|---|---|
| **1st step** At home | | Questionnaire |
| | | Visual acuity testing |
| **2nd step** At Health Centers | Inspection by medical officers or pediatricians | |
| | | Visual acuity testing by nurses |
| **3rd step** by eye doctors | Ophthalmological examinations | |

# Summary Table for Flow of Hearing Examination

| | 1.5 years old (1.5-2.0 years) | 3 years old (3.5-4.0 years) |
|---|---|---|
| **1st step** At home | | Questionnaire |
| | | Hearing tests |
| **2nd step** At Health Centers | Inspection by medical officers or pediatricians | |
| | | Hearing tests by nurses |
| **3rd step** by ENT doctors | ENT examinations | |

# Flow of Vision Examination at 3.5 years old

**At first step:**

Questionnaires asking specific problems such as squint and printed Landolt-C in two different sizes for visual acuity testing at home are sent to families, and then families bring children to the regional Health Centers.

## Questionnaires for vision

- Whether or not the visual acuity testing was done at home
- Whether or not the child understood the test and passed the 0.5-equivalent visual acuity testing in both eyes and in each eye
- The presence or absence of eye-related conditions:
  - Convergent, divergent or vertical deviations,
  - Watching television at near distance,
  - Abnormal head postures (chin up or down, face turned, head tilted),
  - Winking at light,
  - Lid fissure narrowing,
  - Blepharoptosis,
  - Nystagmus,
  - Leukocoria, pupils of different sizes,
  - Slower mobility in the dark.
- If an ophthalmologist had diagnosed the child with any eye disease

# Visual acuity testing at home

- Instruction for measuring visual acuity and two 0.1-equivalent and 0.5-equivalent Landolt-C printed on a sheet of white paper are sent to families, together with questionnaire.
- Children learn visual acuity testing with Landolt-C at the distance of 1 m.
- Visual acuity with both eyes open and then in each eye with the other eye occluded is tested with a 0.5-equivalent Landolt-C at the distance of 2.5 m.
- Children are said to pass the test when they correctly recognize 3 of 4 directions (up, bottom, right, and left).

Instruction for visual acuity testing at home and a printed 0.5-equivalent Landolt-C sent to families

# Flow of Vision Examination at 3.5 years old

**At second step:**

Nurses at the Health Centers measure uncorrected visual acuity and medical officers or pediatricians inspect eye alignment.

In Okayama City, **orthoptists are not involved in this process.**

# Visual acuity testing at Health Centers

- The questionnaire asks 1) whether children understand visual acuity testing at home, and 2) whether children pass the test with a 0.5-equivalent Landolt-C at the distance of 2.5 m with both eyes open and also in each eye with the other eye occluded at home.
- Children who do not satisfy the above criteria undergo visual acuity testing by nurses at Health Centers.
- Visual acuity with both eyes open and then in each eye with the other eye occluded is tested with a 0.5-equivalent Landolt-C at the distance of 5 m.
- Children are said to pass the test when they correctly recognize 3 of 4 directions (up, bottom, right, and left).

**At third step:**

Children with suspected eye diseases are sent to ophthalmologists for the detailed examinations.

The final diagnoses are sent back to the Health Centers.

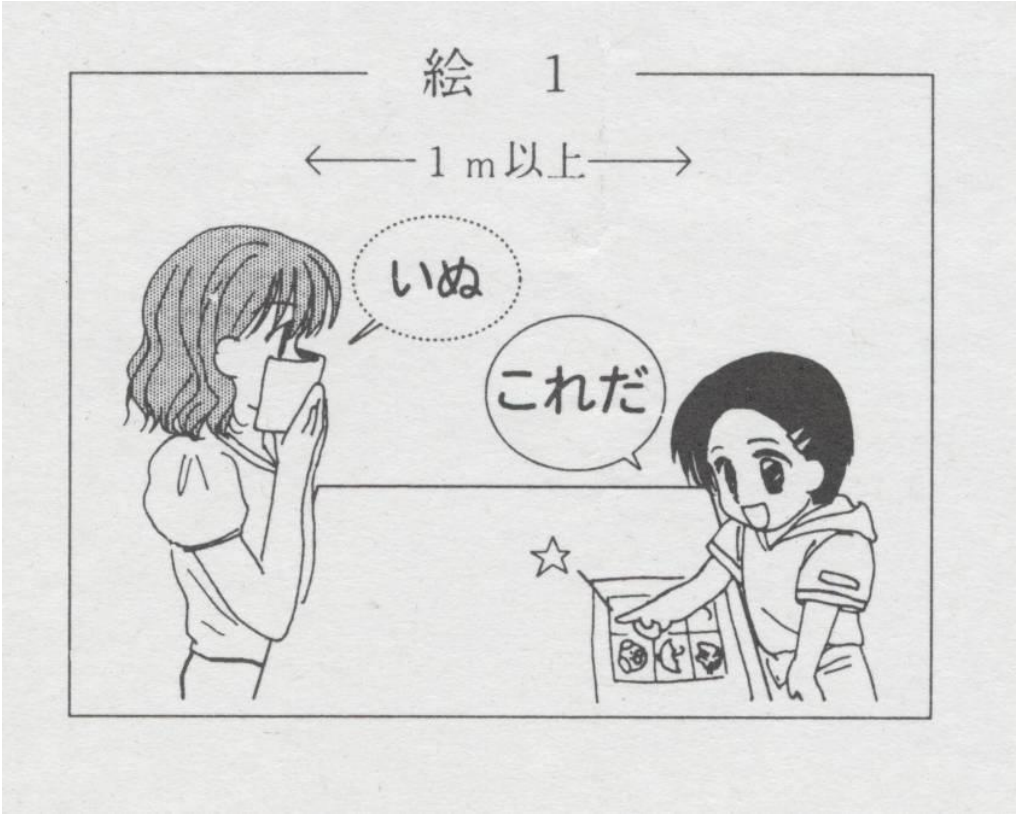
## Questionnaires for hearing

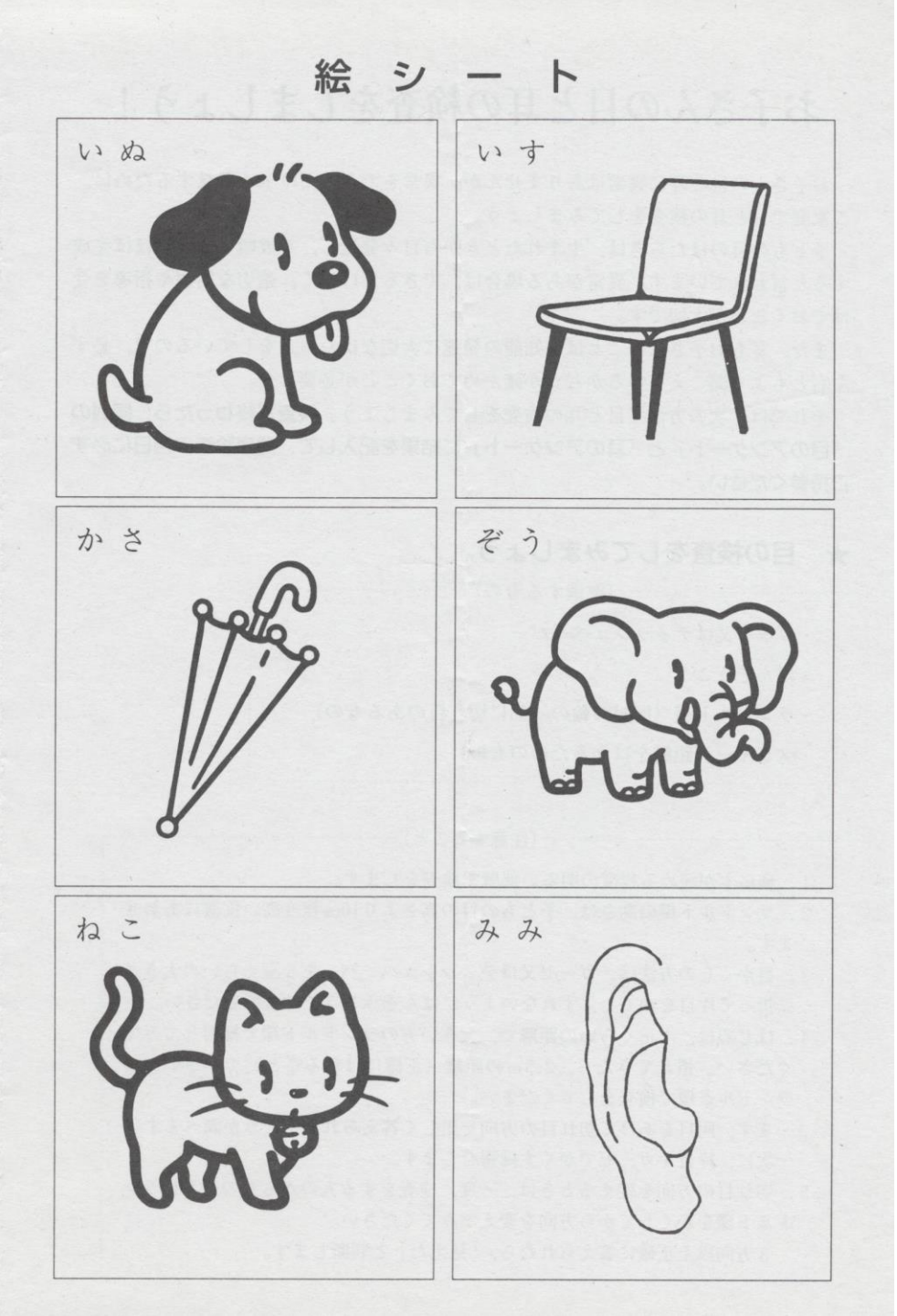
- Whether or not the hearing tests was done at home
- Whether or not the child understood the test and passed hearing tests
- The presence or absence of ENT-related conditions:
  - Nasal stuffiness, rhinorrhea, mouth breathing
  - Otitis media
  - No response to calling, tendency to reiterating or making a large volume of television
  - Delayed speech, aberrant pronunciation
  - Action required to convey message in addition to verbal sound
  - Family history of hearing problems from childhood
- If an ENT doctor had diagnosed the child with any disease
- Pointed out to have deafness by neonatal auditory brainstem response test

## Hearing tests at home

- Instruction for hearing tests and figures printed on a sheet of white paper are sent to families, together with questionnaire.
- Mother or other guardians whisper 6 words (dog, umbrella, chair, cat, elephant, and ear) with the mouth covered with a sheet of paper and a child is instructed to point to the corresponding figure. The distance between the child and the guardian is kept to be more than 1 m apart.
- Children are said to pass the test when they correctly points all the figures.

# Instruction for hearing tests at home and printed figures



# What can we learn from the children vision-screening program?

- To know the prevalence of strabismus and amblyopia at 1.5 and 3.5 years
- To study the feasibility of a new screening method, autorefraction, at 3.5 years old

## Prevalence Study Methods

The final diagnoses made by ophthalmologists and sent back to the Health Centers in Okayama City were summarized to elucidate the prevalence of strabismus and amblyopia in general as well as esotropia and exotropia in 1.5-year-old children and 3-year-old children in Okayama City in years from 2000 to 2004.

## Prevalence Study Results

| | At 1.5 years old | At 3 years old |
|---|---|---|
| Rate of health center visit | 83.7-86.8% | 77.8-81.9% |
| Rate of eye doctors' examination | 0.2-0.3% | 2.7-3.6% |
| Rate of strabismus | 0.01-0.09% | 0.20-0.34% |
| Rate of amblyopia | 0% | 0.13-0.18% |
| Rate of refractive errors | 0-0.03% | 1.06-1.75% |
| Rate of other diseases | 0.03-0.07% | 0.12-0.16% |

- The prevalence rates of strabismus at 1.5 years old and 3 years old in this population were 0.01-0.09% and 0.20-0.34%, respectively.
- The prevalence in this population is lower compared with the other populations.
- The number of intermittent exotropia in this population increased with the age.

## Autorefraction Study Purpose

- The role of autorefraction in preschool vision screening has been discussed over the years, however, no study has until now addressed whether autorefraction is superior, or at least equal to visual acuity testing.
- Furthermore, no study has shown the effectiveness of autorefraction in the current system of visual acuity testing at home and at the Public Health Centers.
- At present in Japan, some municipalities have introduced autorefraction and, in stead, abolished visual acuity testing as a screening method at the 3.5-year-old examination.
- In this study, we designed a prospective study to examine whether the introduction of autorefraction in addition to the current system including visual acuity testing would change the detection of eye diseases.

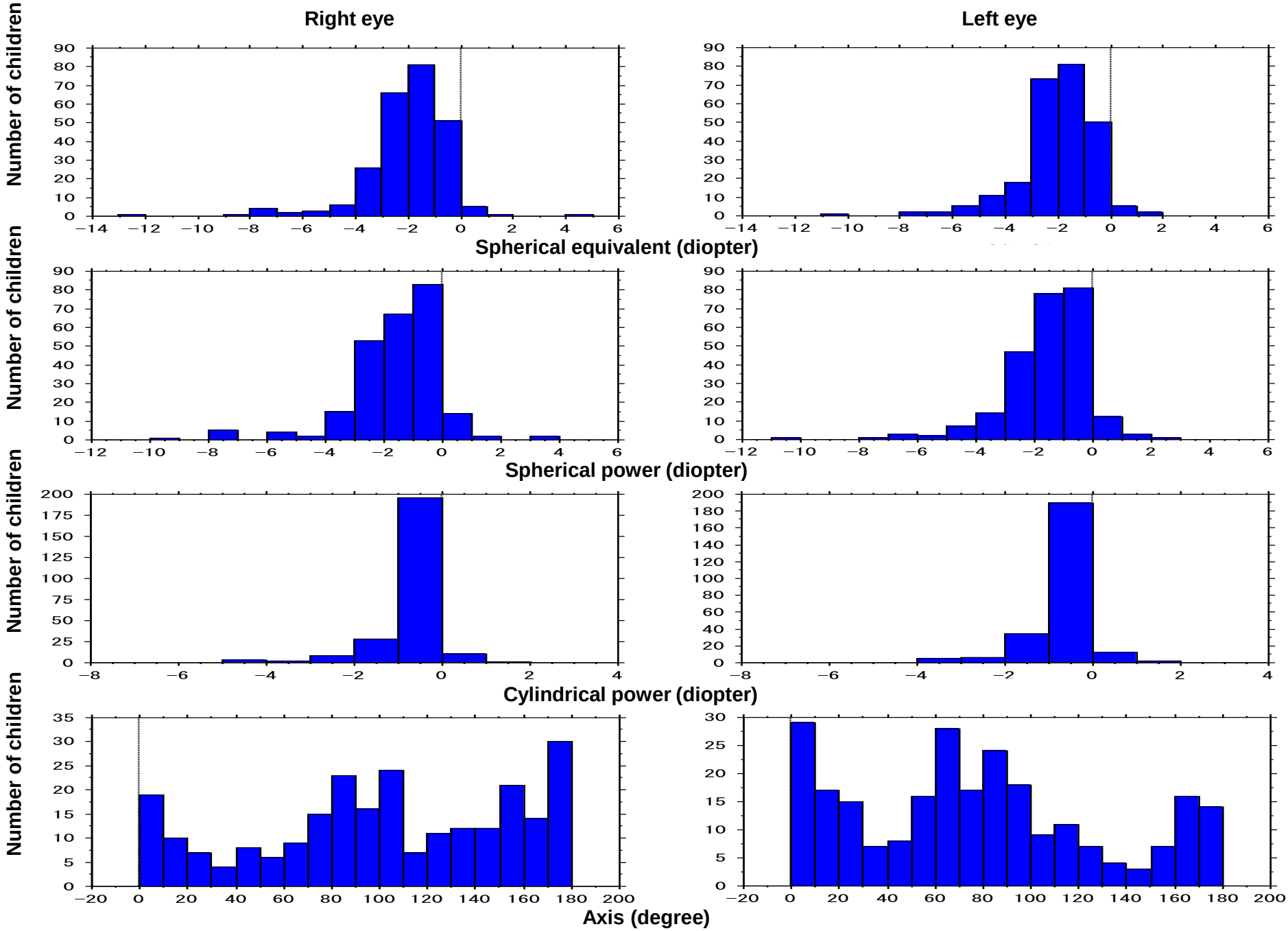
## Autorefraction Study Participants

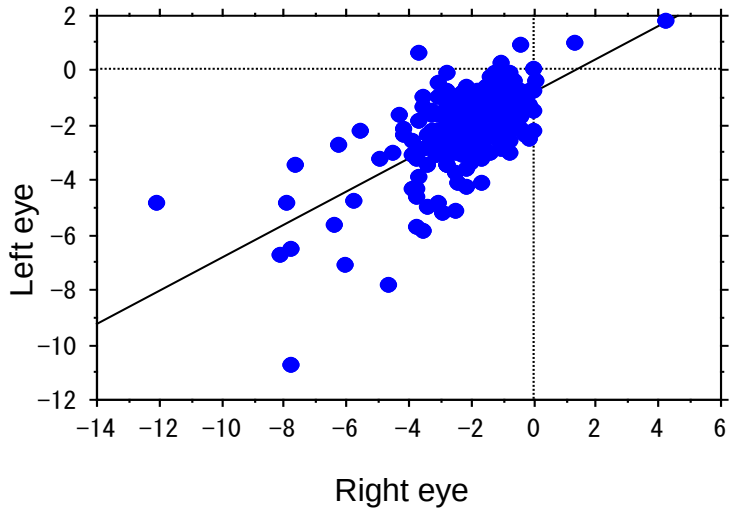
- The population in Okayama City was about 700 thousands, and the Okayama City Government Public Health Centers consisted of 6 Regional Public Health Centers.
- The 3 regional centers had one day in a month and the other 3 centers had two days in a month for the examination of children who became just over 3 years and 6 months of the age.
- <u>The East Regional Public Health Center with two days in a month for the examination was chosen and all 265 children who visited the Center on 6 consecutive days during November 2007 to February 2008 were enrolled in this study.</u>

# Results of visual acuity testing by nurses in 48 of 265 children at the regional Public Health Center

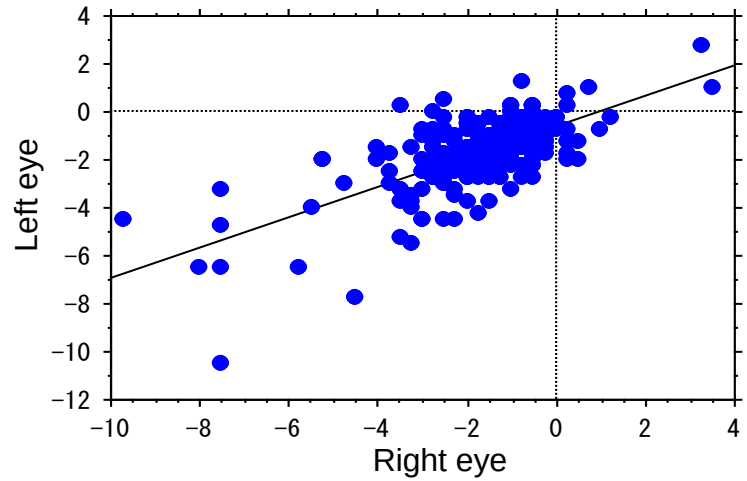
| Visual acuity testing results | The number of children |
|---|---|
| 0.5 in both eyes | 24 |
| 0.5 in the right eye, 0.1 in the left eye | 7 |
| 0.1 in the right eye, 0.5 in the left eye | 1 |
| 0.1 in both eyes | 7 |
| Un-measurable in both eyes | 8 |
| 0.5 in the right eye, un-measurable in the left eye | 1 |
| In total | 48 |

The children except for those who have passed 0.5 visual acuity in both eyes are sent to detailed examinations by ophthalmologists as the third step. Visual acuity is tested with Landolt-C cards and expressed as decimals.

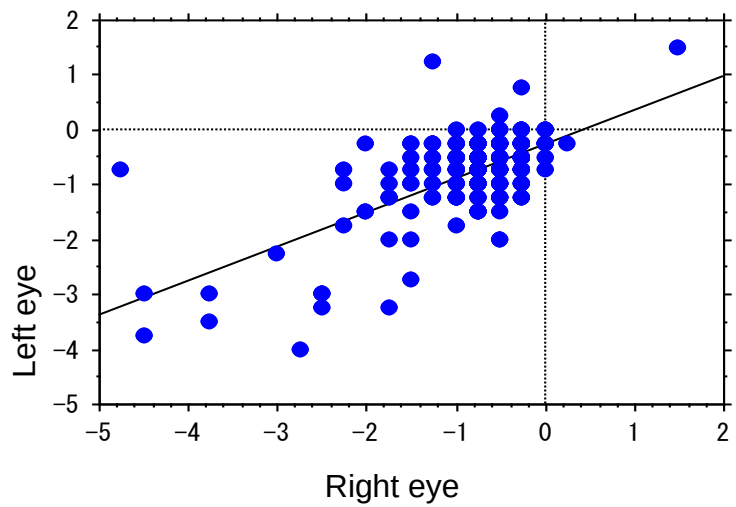

Right eye
Left eye
Number of children
Spherical equivalent (diopter)
Spherical power (diopter)
Cylindrical power (diopter)
Axis (degree)



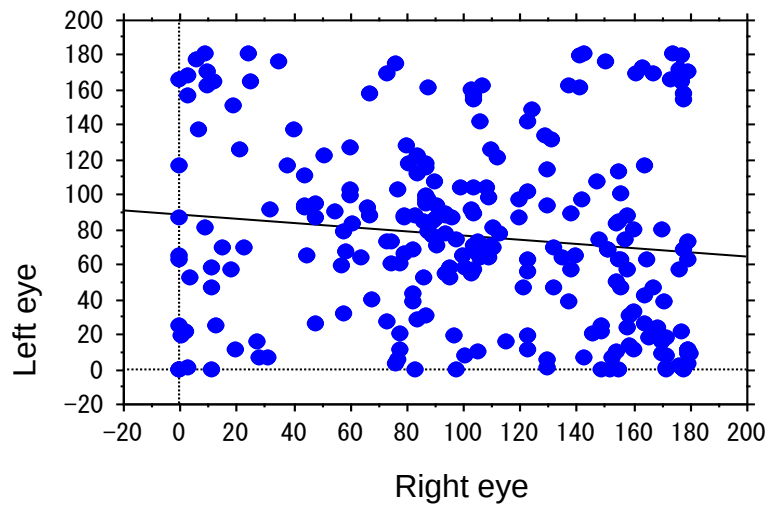

Spherical equivalent (diopter)




Spherical power (diopter)




Cylindrial power (diopter)




Axis (degree)

**Statistically significant correlation between both eyes (Spearman correlation coefficient by rank)**
***P*<0.0001 for spherical equivalents, *P*<0.0001 for spherical powers,**
***P*<0.0001 for cylindrical powers, and *P*<0.0301 for axes**

# Autorefraction Study Methods -Autorefraction

- Refraction with a hand-held autorefractometer (Autorefractometer AR-20 type R, Nidek, Japan) was done in all children by a single well-trained examiner who was masked to their visual acuity test results and questionnaire answers.
- Cycloplegics were not used, and the measurements were done first in the right eye and then in the left eye at a preset distance of the appliance.
- Five measurements for each eye on a quick mode were automatically processed to get representative values for spherical power, cylindrical power and axis.

# Autorefraction Study -Criteria-

- The current criteria: (any of the following)
  - Failure in visual acuity testing at home or at the Public Health Center
  - Problem(s) raised by questionnaires
  - Problem(s) pointed out by medical officers' or pediatricians' inspection
- The refractive error criteria: (any of the following)
  - Greater than 3-diopter spherical powers for myopia
  - Greater than 1-diopter spherical powers for hyperopia
  - Greater than 2-diopter cylindrical powers for astigmatism
- "The current criteria only"
  - children detected by the current criteria but not detected by the refractive error criteria
- "The current criteria plus refractive error criteria"
  - children detected by the current criteria and also by the refractive error criteria
- "Refractive error criteria only"
  - children detected by refractive error criteria but not by the current criteria

# Autorefraction Study Results
# Notice for third step examination by eye doctors

- Notice to visit ophthalmologists for the detailed examination as the third step was issued for 64 (24%) of 265 children, and 37 children (58%) of those did so to make documents with final diagnoses sent back to the Public Health Office.
- Of the 64 children, 12 was sent to ophthalmologists based on the current criteria only, 10 based on both the current criteria and the refractive error criteria, and 42 based on the refractive error criteria only.
- The rates of children who visited ophthalmologists and had their final diagnoses sent back to the Public Health Office were 50% (6 of 12 children) in the current criteria only, 70% (7 of 10 children) in both the current criteria and the refractive error criteria, and 57% (24 of 42 children) in the refractive error criteria only. The rates were not significantly different among the three groups ($P$=0.6322, chi-square test).

# The number of children sent to ophthalmologists' examination and their diagnoses, based on the current criteria and/or the refractive error criteria in 265 children

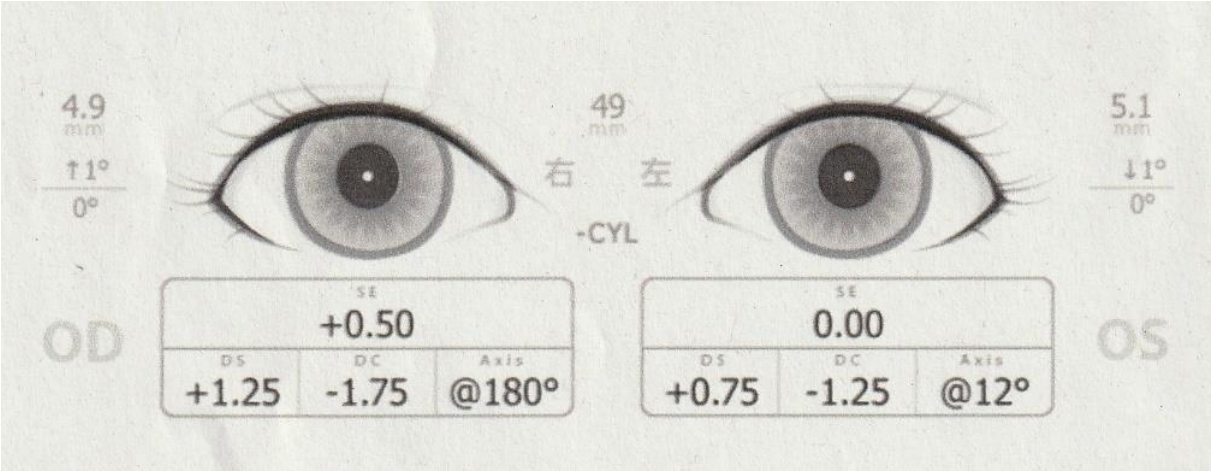
| Criteria | The number of children recommended for ophthalmologists' examination | The number of children visiting ophthalmologists and with final diagnoses sent back to Public Health Office | The number of children diagnosed as abnormal | The number of children with diagnoses |
|---|---|---|---|---|
| The current criteria only | 12 | 6 | 5 | Myopia/myopic astigmatism 3<br>Intermittent exotropia 1<br>Esotropia 1 |
| The current criteria plus refractive error criteria | 10 | 7 | 7 | Hyperopic astigmatism 1<br>Mixed astigmatism 2<br>Intermittent exotropia 2<br>Ametropic amblyopia 1<br>Congenital blepharoptosis 1 |
| The current criteria in total | 22 | 13 | 12 | |
| Refractive error criteria only | 42 | 24 | 15 | Myopia 9<br>Hyperopia 1<br>Mixed astigmatism 1<br>Exophoria 2<br>Ametropic amblyopia 1<br>Poor visual acuity 1 |
| Grand total | 64 (24% of 265 children) | 37 (14% of 265 children) | 27 (10% of 265 children) | |

# Autorefraction Study Results and Conclusion
# **current versus refractive error criteria**

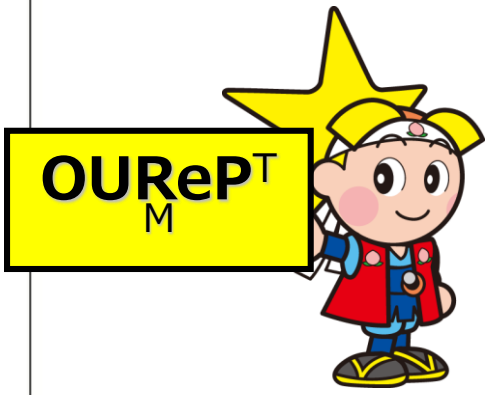
- Twelve of 13 children visiting ophthalmologists by the current criteria had diagnoses such as amblyopia and strabismus: one child with esotropia, three children with intermittent exotropia, one child with ametropic amblyopia, and one child with congenital blepharoptosis.
- In contrast, 15 of 24 children visiting ophthalmologists by the refractive error criteria only had mainly diagnoses of refractive errors with no serious problems. However, it should be noted that one child with ametropic amblyopia was detected by the refractive error criteria only.
- The rate of children with abnormalities was higher in the current criteria (12/13=92%) than in the refractive error criteria only (15/24=63%), but the difference between the two groups was not statistically significant ($P$=0.0655, Fisher exact probability test).
- The present study is the first to address the role of autorefraction in the current vision-screening program for 3.5-year-old children as part of systemic examinations including physical, mental, developmental, dental, hearing, and vision checkups.
- The autorefraction in addition to the questionnaire, visual acuity testing at home or at the office, and medical officers' or pediatricians' inspection in the current standard system, led to about 3-fold increase in the number of children sent to the third step examinations by ophthalmologists.
- Of these, only one additional child was diagnosed as amblyopia.
- Autorefraction is not recommended as an additional test from the viewpoint of cost-effectiveness as far as the current system was conducted appropriately.

Matsuo T, Matsuo C, Matsuoka H, Kio K. Detection of strabismus and amblyopia in 1.5-and 3-year-old children by a preschool vision-screening program in Japan. Acta Medica Okayama 2007;61:9-16.
Matsuo T, Matsuo C, Kio K, Ichiba N, Matsuoka H. Is refraction with a hand-held autorefractometer useful in addition to visual acuity testing and questionnaires in preschool vision screening at 3.5 years in Japan? Acta Medica Okayama 2009;63:195-202.

# From April 2021, spot vision screeners are used for screening in 3.5-year-old children




# Photoelectric dye-coupled thin film as retinal prosthesis for the blind to gain the sight again


岡山県マスコット ももっち

Okayama
University
Retinal Prosthesis

Toshihiko Matsuo, MD, PhD
Ophthalmology, Okayama University Hospital
Graduate School of Interdisciplinary Science and Engineering in Health Systems
Tetsuya Uchida, PhD
Polymer Materials Science, Graduate School of Natural Science and Technology

## *Today's story*

***How to develop a medical device like retinal prosthesis?***

Three ***nonclinical (preclinical)*** requirements for medical devices

- Safety biological safety tests →standardized
- Efficacy preclinical tests: animal model and *in vitro* test
- Quality manufacturing in quality management system (QMS)

→ Negotiation with government authority
PMDA (Pharmaceuticals and Medical Devices Agency) in Japan

★***We are here.*** →

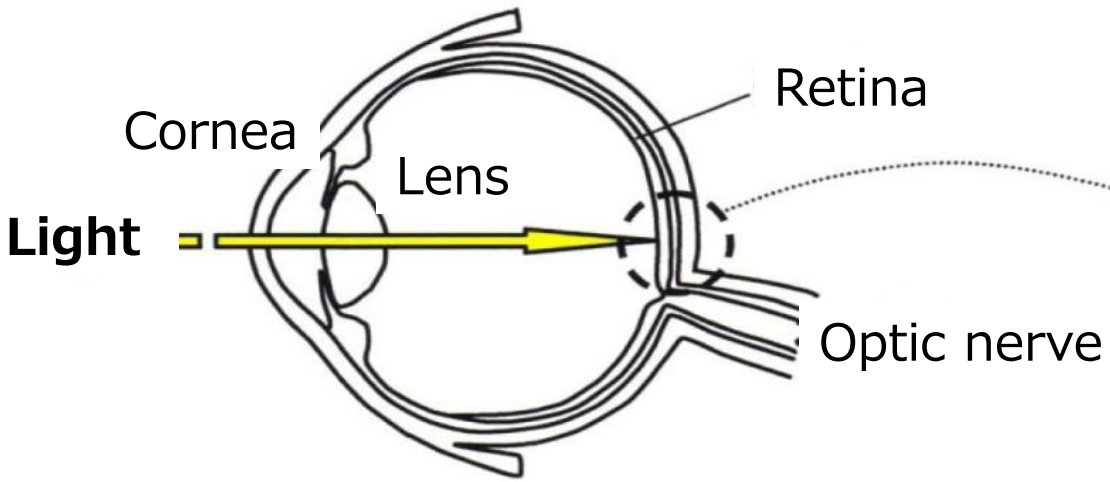
***Clinical trial***
based on GCP (Good Clinical Practice)
(Ministerial Ordinance in 1997, 2012)

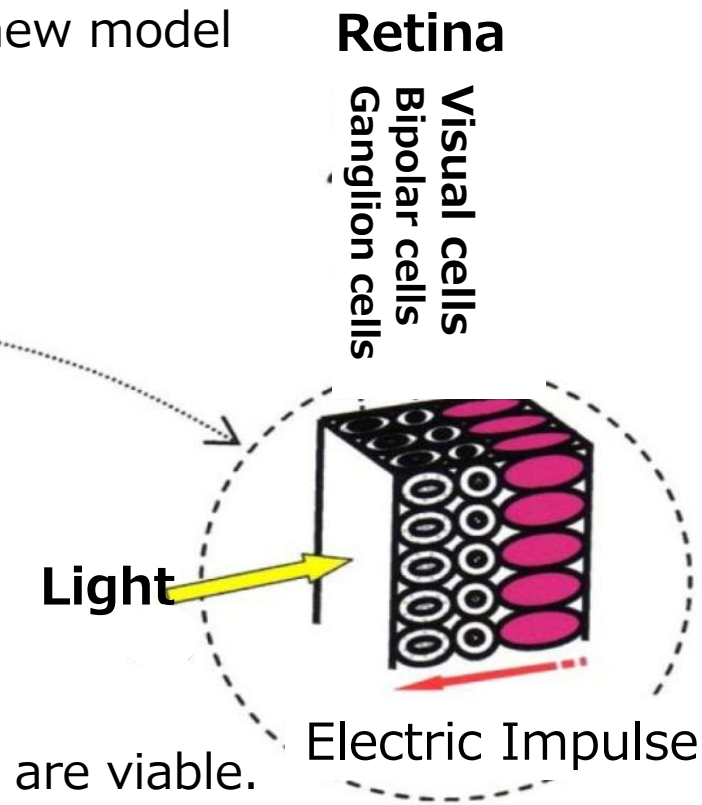
Biological safety tests for medical devices (ISO 10993)
Guidance (March 1, 2012) from Ministry of Health, Labor, and Welfare of Japan
GLP (Good Laboratory Practice) (Ministerial ordinance in 1997, 2008)

- Tests for *in vitro* cytotoxicity
- Tests for eye irritation and skin sensitization
- Tests for genotoxicity and carcinogenicity
  - Ames test (E. coli)
  - Chromosomal aberration test
- Tests for local effects after implantation
- Tests for systemic toxicity, acute and subacute (28-day repeat application)

# Background

- No therapy at moment for loss of vision caused by retinitis pigmentosa
- Retinal prosthesis as a most promising candidate for regaining vision
- Camera image-capture and electrode-array-output as a standard model
- Photoelectric dye-based retinal prosthesis as a new model




Retinitis pigmentosa

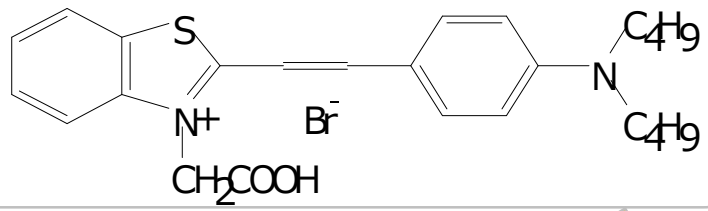
- Photoreceptor (visual) cells are lost.
- Retinal ganglion cells, sending axons to brain, are viable.

**Vision can be restored by something artificial to replace the function of photoreceptor cells.**

# World-first "dye-coupled thin film retinal prosthesis"

## Photoelectric dye→electric potential !

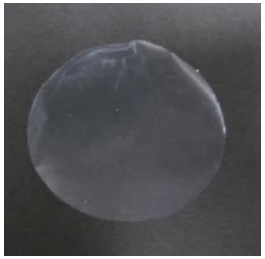
**(Absorb light and generate potential)**




**Chemical coupling**

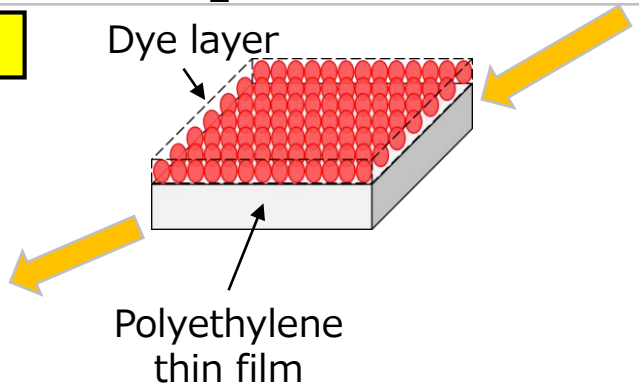
**Polyethylene thin film**

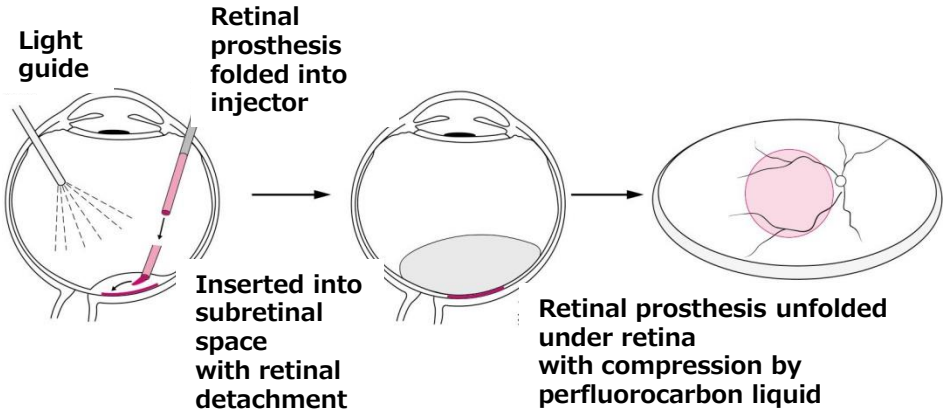
$$-(CH_2CH_2-)_n$$



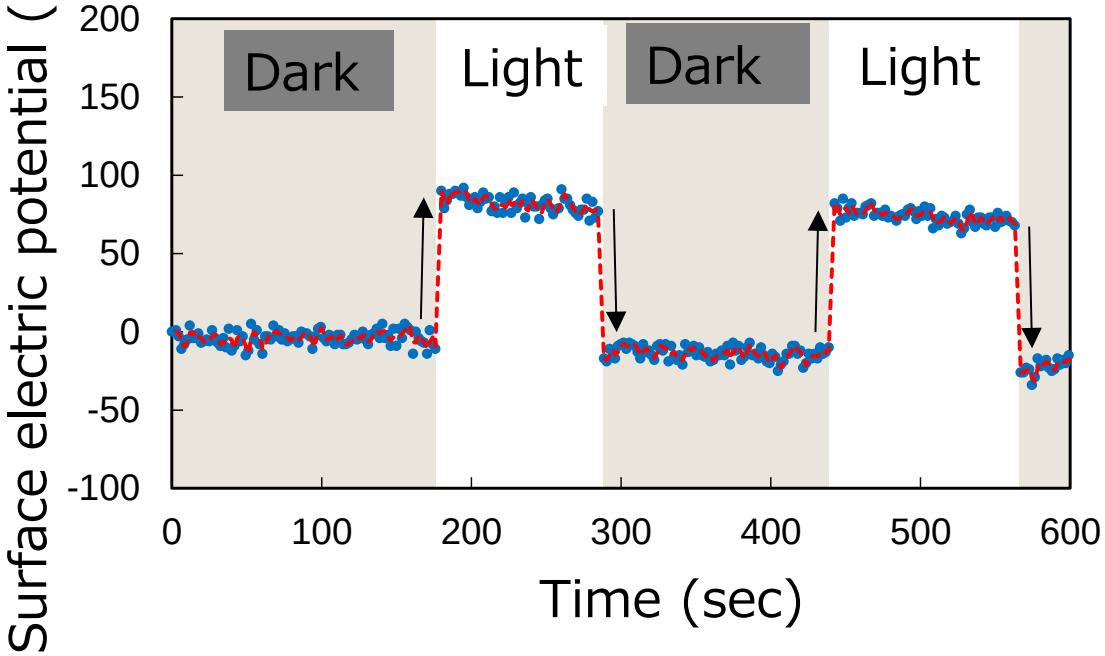
- chemically and biologically stable
- with physical strength

**OUReP™**



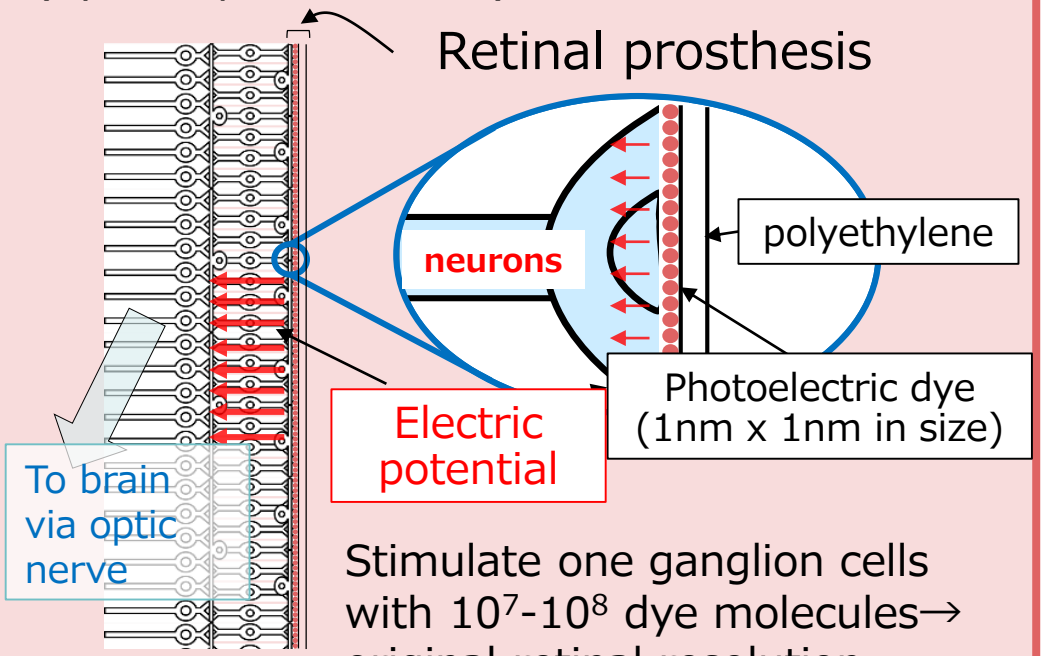

Electric potentials generated by light stimulation (300 lux) in *in-vitro* study



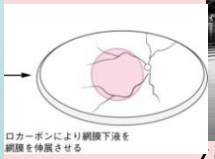
# Existing electrode array device → Photoelectric dye-based device

## Okayama Univ — OUReP ®

(dye-coupled thin film)




Stimulate one ganglion cells with $10^7$-$10^8$ dye molecules→ original retinal resolution

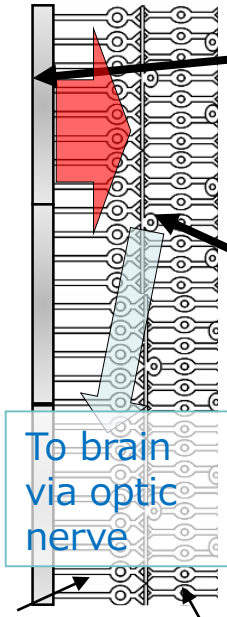



〈theoretical resolution〉
Defects by dead ganglion cells and axons

## American — Argus Ⅱ ®

Approved by FDA in 2013

(camera capture electrode array)



Retinal prosthesis

Each electrode
1mm x 1mm in size

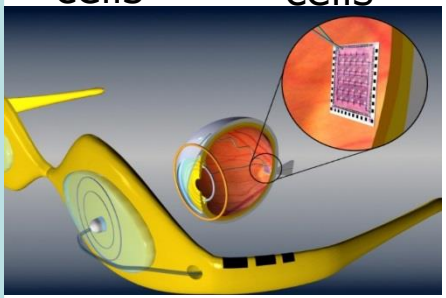
Electric current

To brain via optic nerve

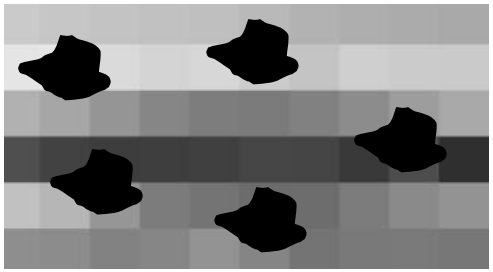
Stimulate 100-10000 ganglion cells with one electrode
60 electrodes→60 pixels

Ganglion cells

Bipolar cells

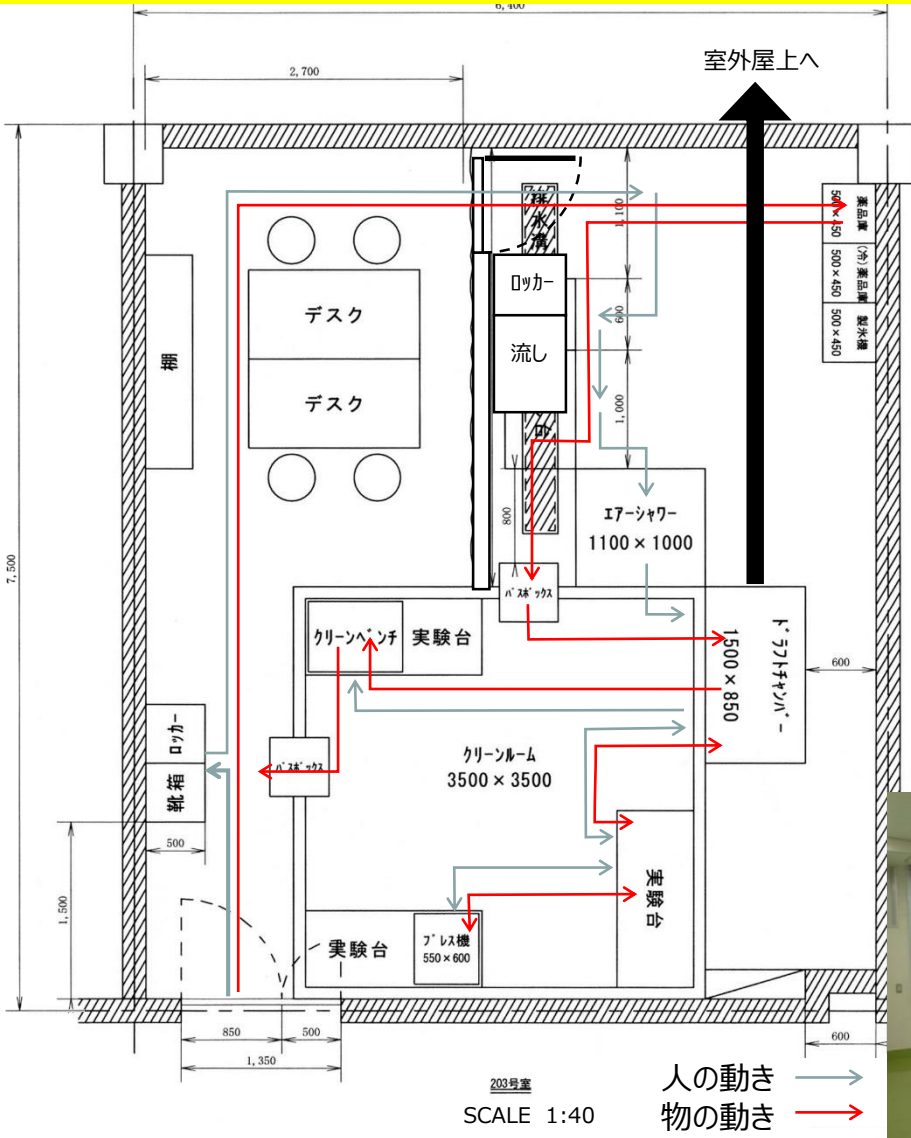


Homepage,
Second Sight, Inc.



〈theoretical resolution〉
Defects by dead ganglion cells and axons

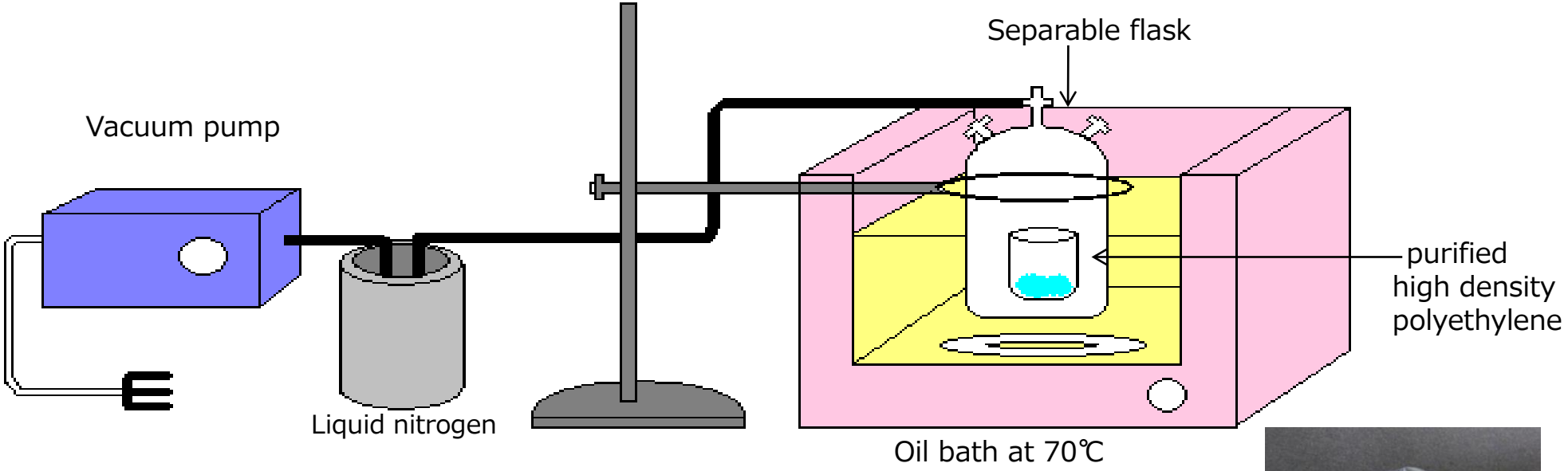
# Clean room facility at Okayama Univ. Incubation Center for Small Business

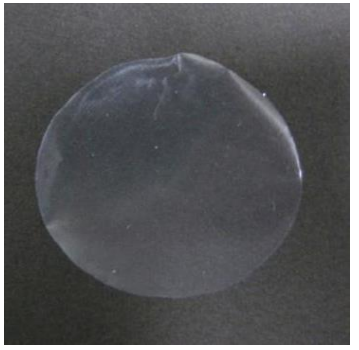




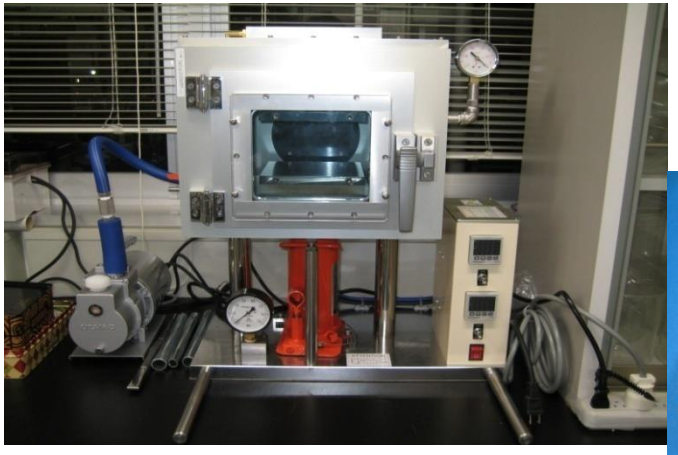
# Manufacturing

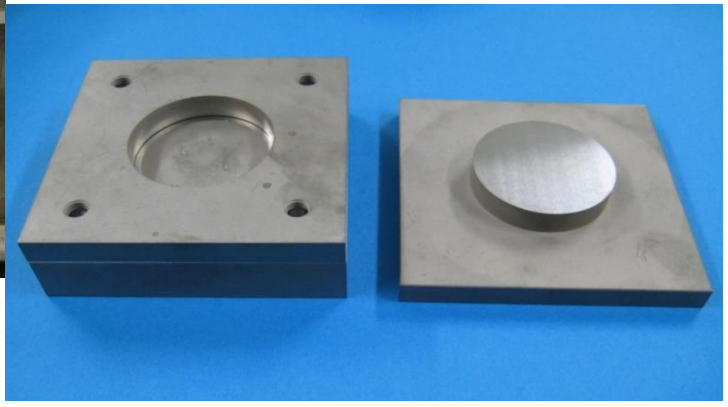
## 1. Purification of high density polyethylene



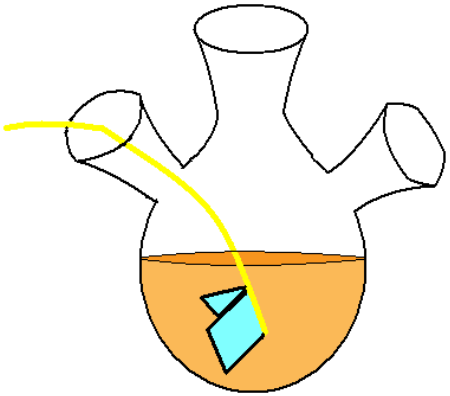



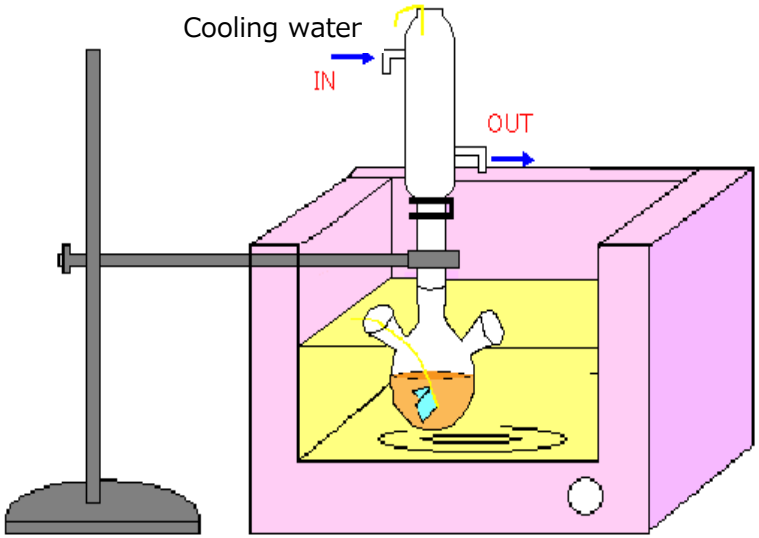
## 2. Polyethylene film preparation



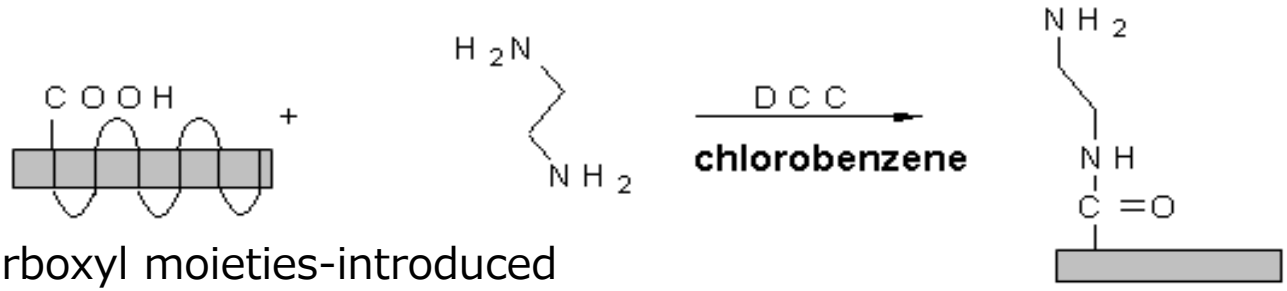


## 3. Fuming nitric acid treatment of polyethylene film





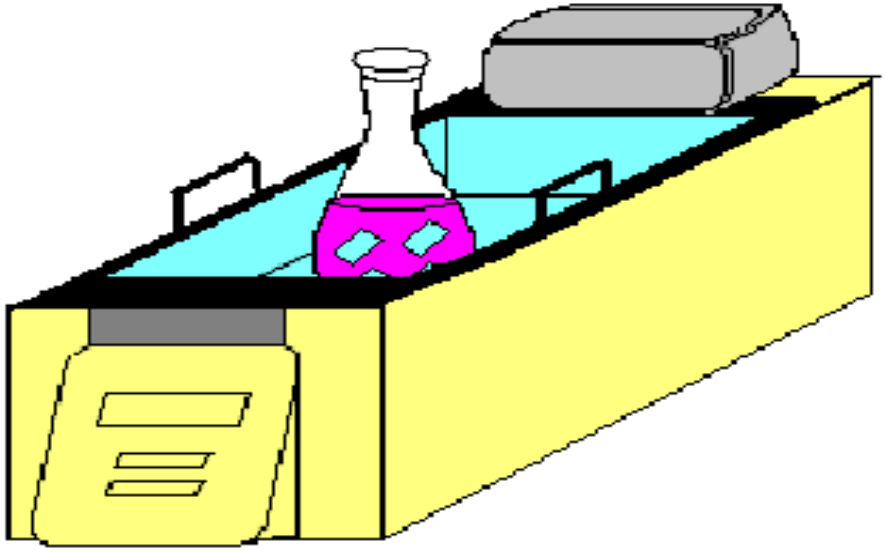

## 4. Ethylenediamine coupling to polyethylene film surface



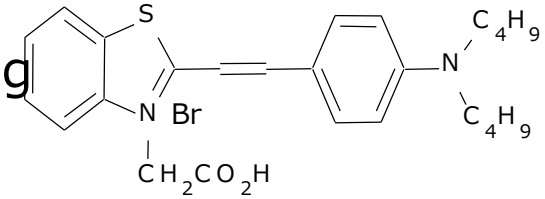

Carboxyl moieties-introduced polyethylene film

**Manufacturing**

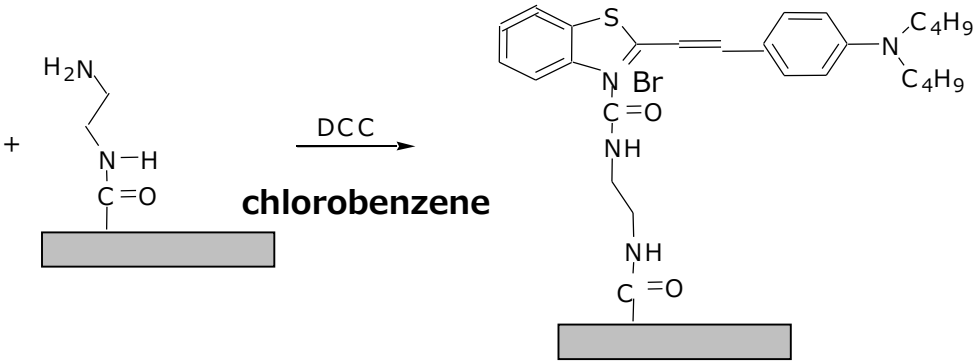
# 5. Dye-coupling to polyethylene film surface




Dye coupling



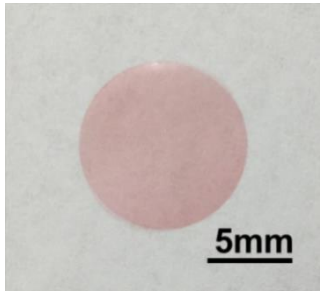

Photoelectric dye ( NK-5962)

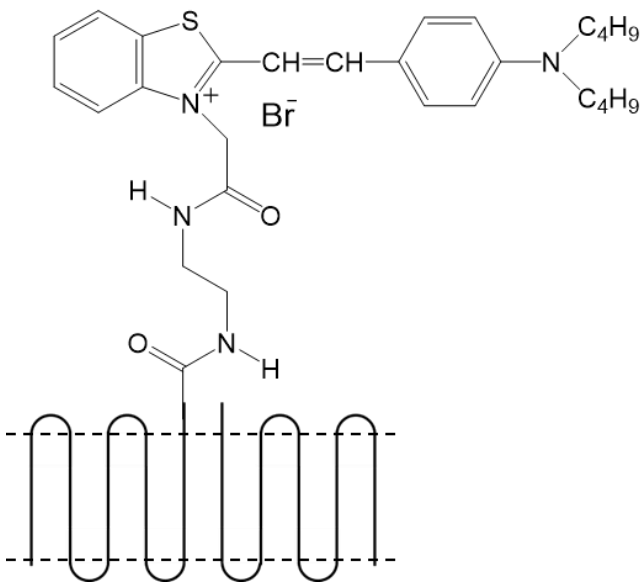


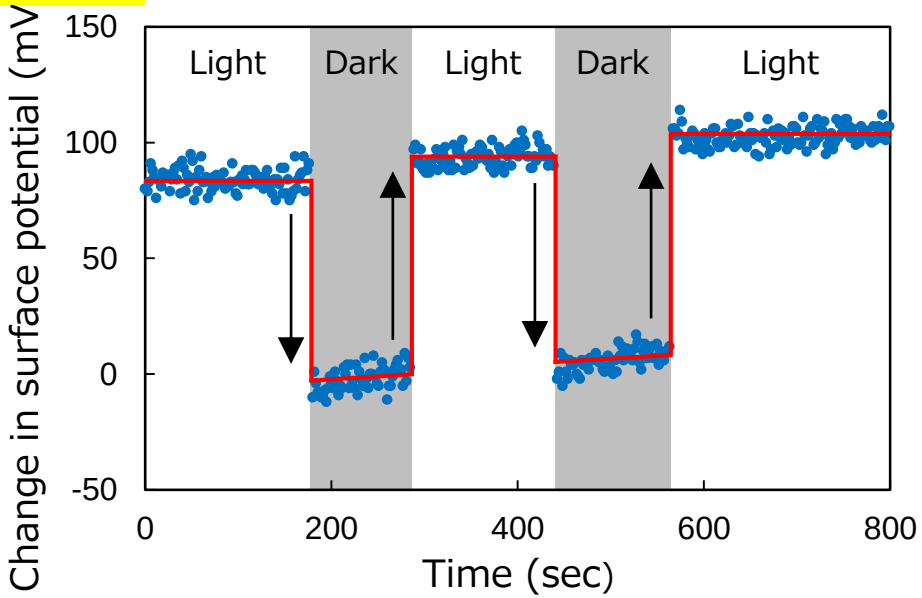

Dye-coupled polyethylene film

**Manufacturing**

# Kelvin probe surface potential measurement

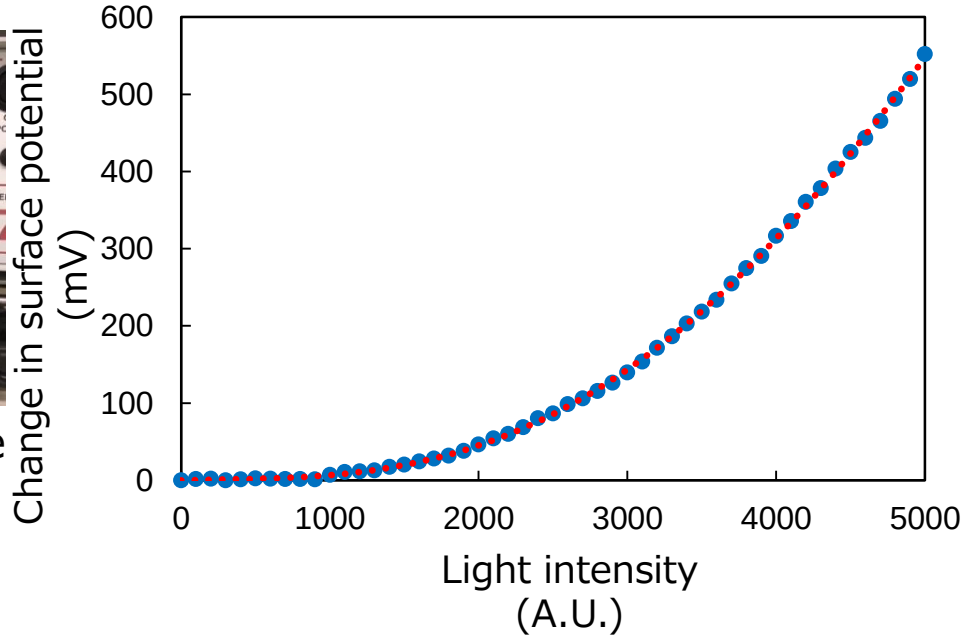


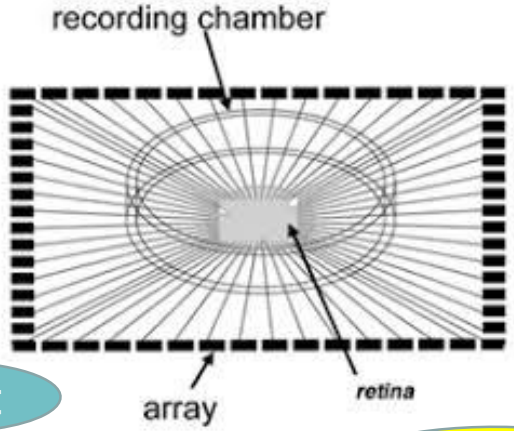

Humidity-controlling box

Dew point temperature




# Quality Control

# Light-evoked action potential spike response in isolated degenerative retinal tissue placed on multielectrode array dish




Retinal dystrophic mice (rd1) at 8 weeks of the age

Light

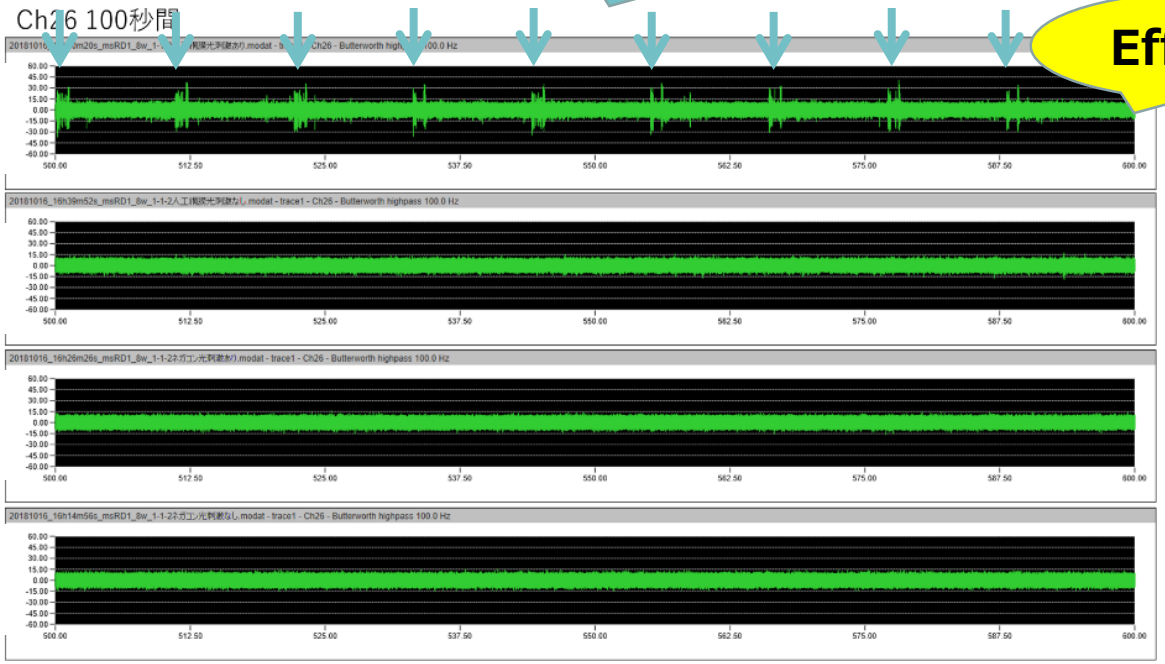
Efficacy

***Light flashing*** to **dye-coupled film**
layered on degenerative retinal tissue

***No Light*** to **dye-coupled film**
layered on degenerative retinal tissue

***Light flashing*** to **plain film**
layered on degenerative retinal tissue

***No Light*** to **plain film**
layered on degenerative retinal tissue

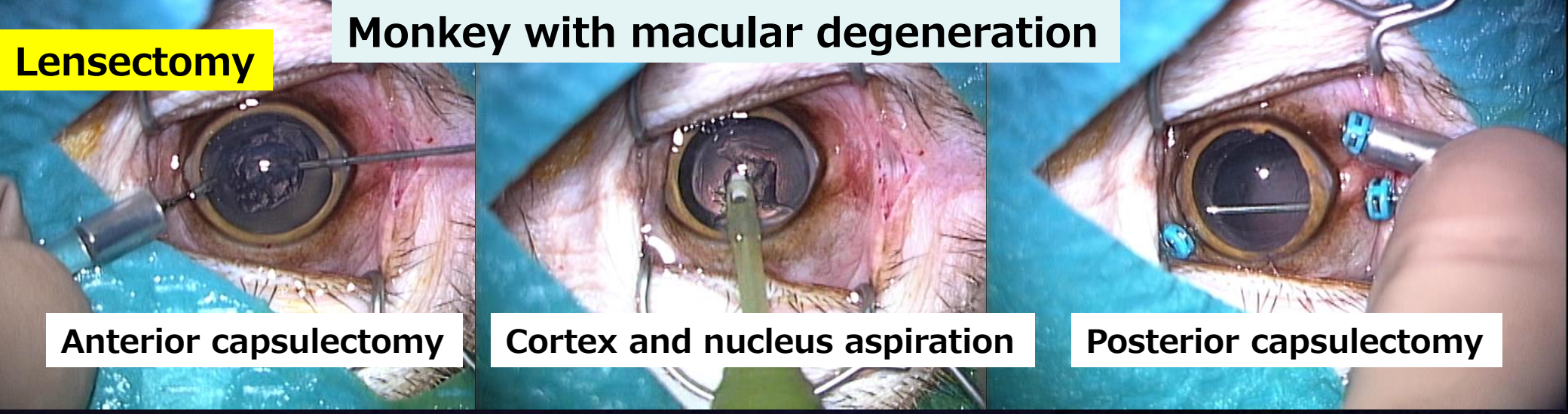



| 1 min | 10 min | 10 min | 10 min | 10 min |
|---|---|---|---|---|
| Nylon mesh anchor | **Plain film** with platinum weight ***No light*** | **Plain film** with platinum weight ***Light flashing*** | **Dye-coupled film** with platinum weight ***No light*** | **Dye-coupled film** with platinum weight ***Light flashing*** |

Experimental procedure

# Monkey with macular degeneration

## Lensectomy



Anterior capsulectomy

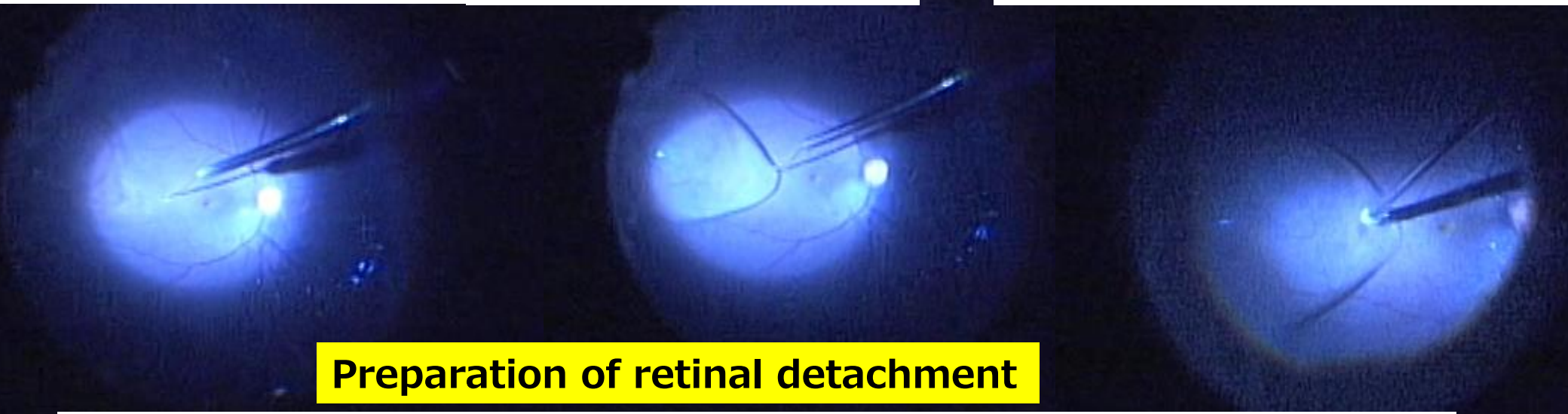
Cortex and nucleus aspiration

Posterior capsulectomy

38G needle retinal tipping

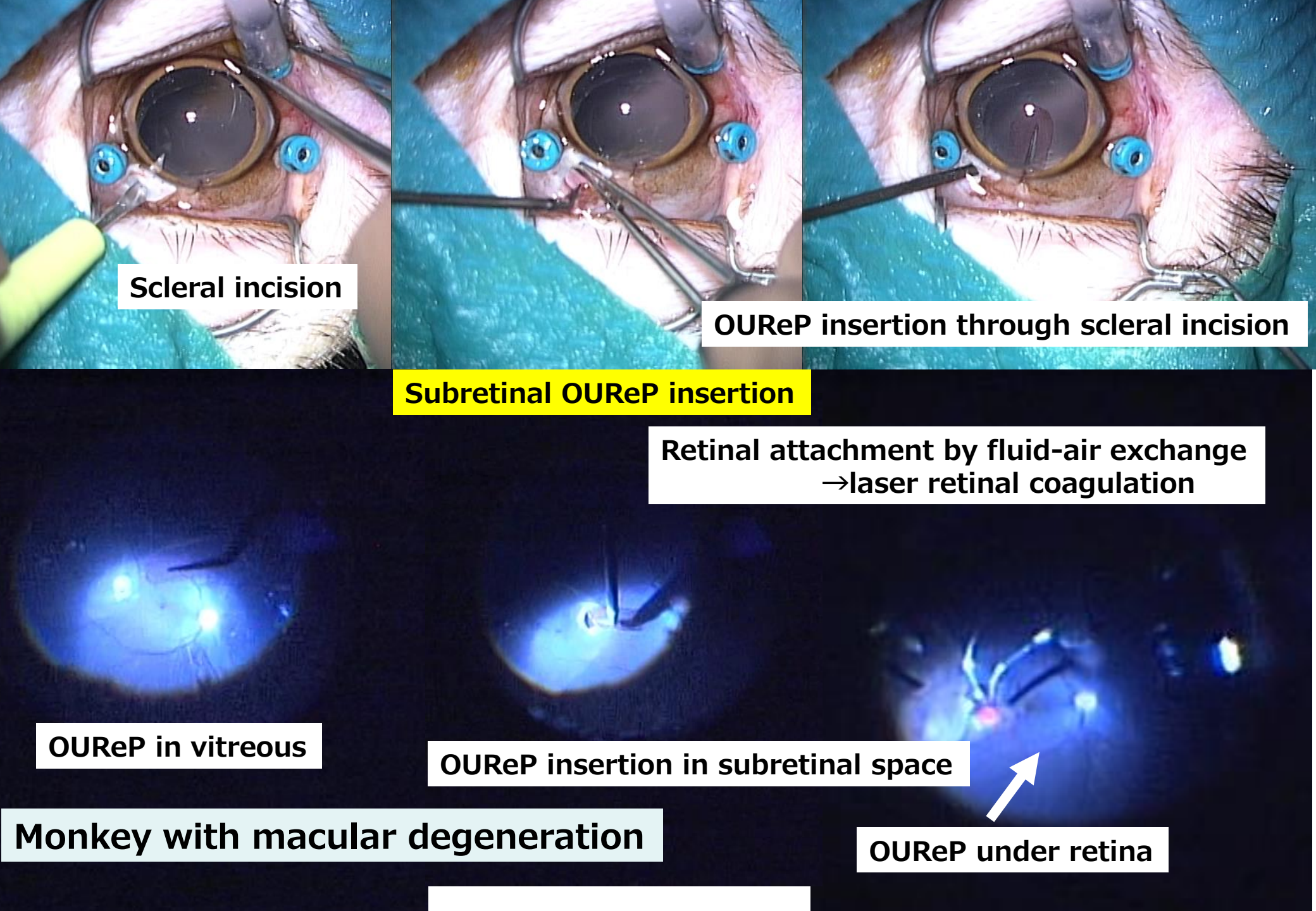
Subretinal fluid injection

Retinal tear made by 25G diather



## Preparation of retinal detachment

Matsuo T, Uchida T, Sakurai J, Yamashita K, Matsuo C, Araki T, Yamashita Y, Kamikawa K.
Visual evoke potential recovery by subretinal implantation of photoelectric dye-coupled thin film retinal prosthesis (OUReP™) in monkey eyes with macular degeneration. ***Artificial Organs*** 2018;42:E186-E203.


Scleral incision
OUReP insertion through scleral incision
Subretinal OUReP insertion
Retinal attachment by fluid-air exchange
→laser retinal coagulation
OUReP in vitreous
OUReP insertion in subretinal space
Monkey with macular degeneration
OUReP under retina

Pre-degeneration

**Cobalt chloride injection**

Post-degeneration

**OUReP implantation**

No. 2 monkey in 6 months

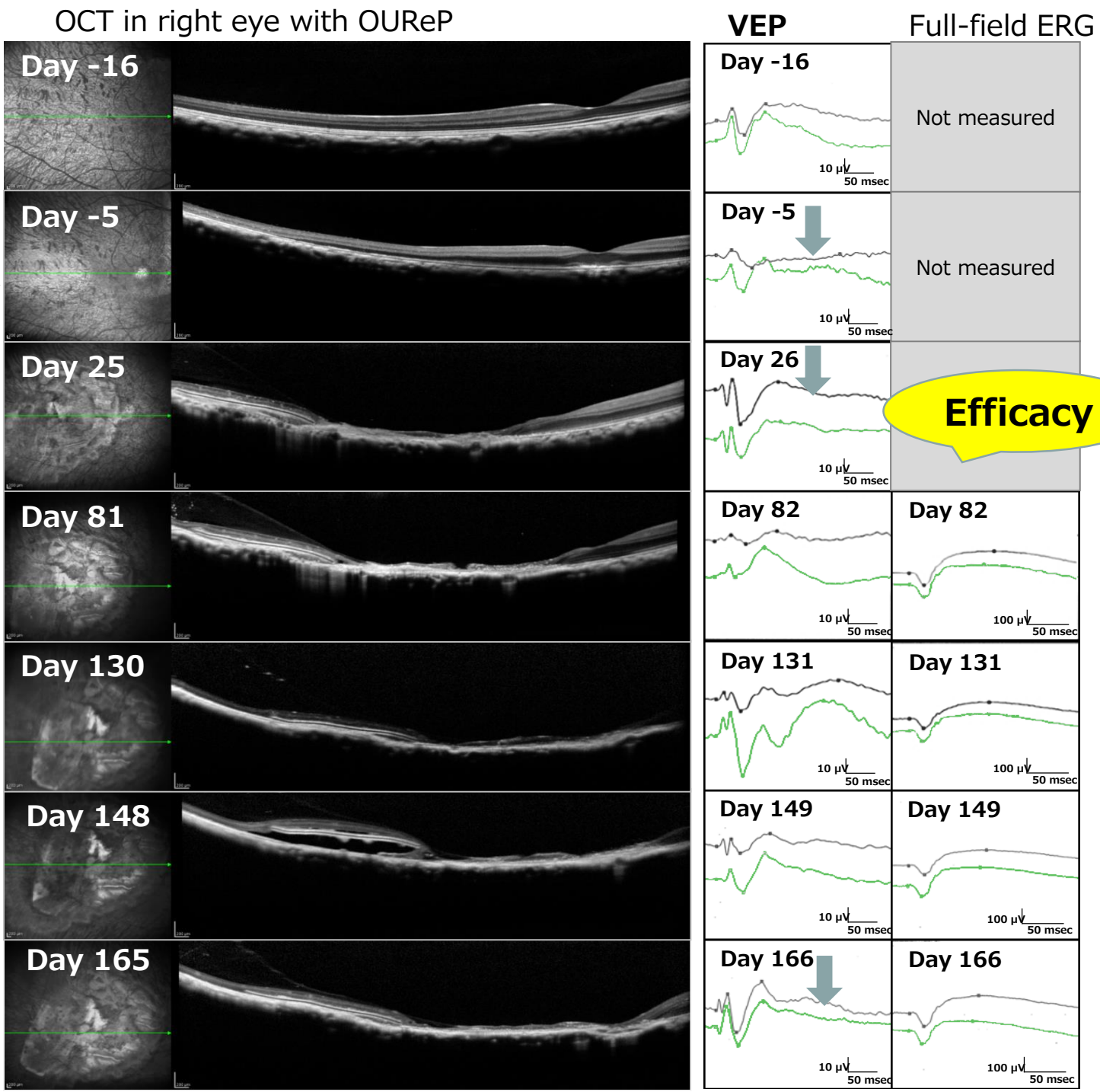
OCT

→ OCT imaging

VEP

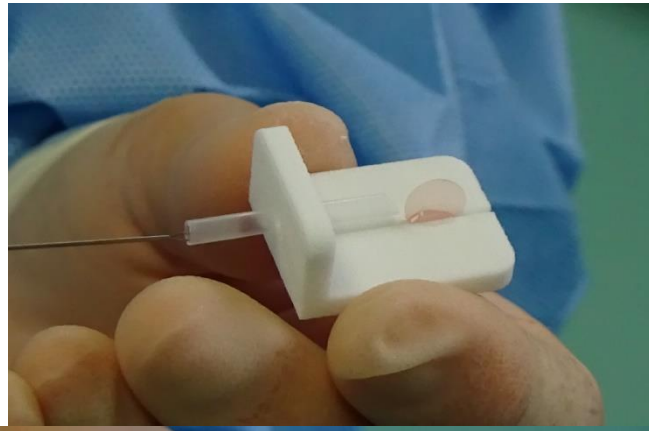
Right eye with OUReP

Left eye as control

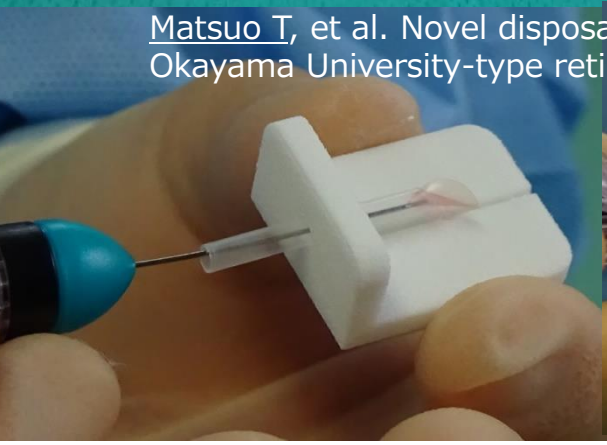


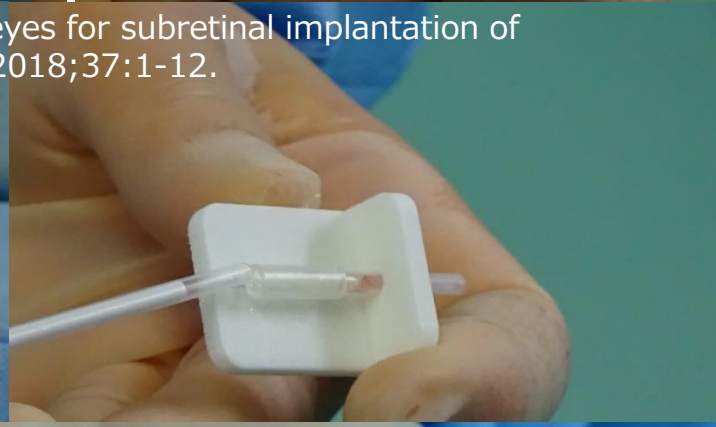

# OUReP Injector Kit

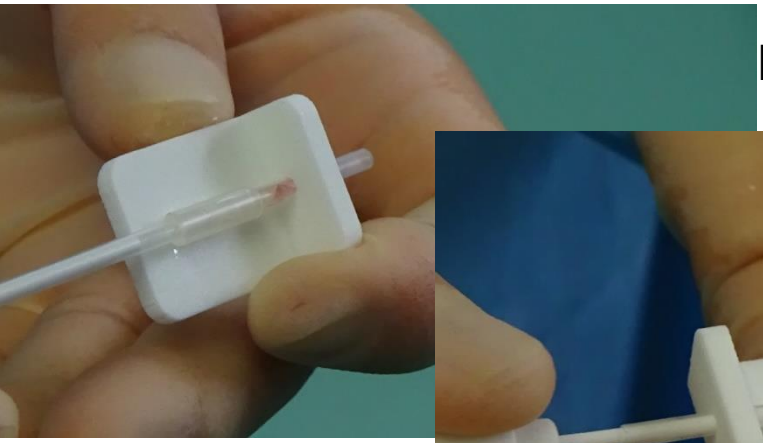
**For safe surgery**



Matsuo T, et al. Novel disposable injector (OUReP Injector) tested in rabbits' eyes for subretinal implantation of Okayama University-type retinal prosthesis (OUReP). ***Animal Eye Research*** 2018;37:1-12.

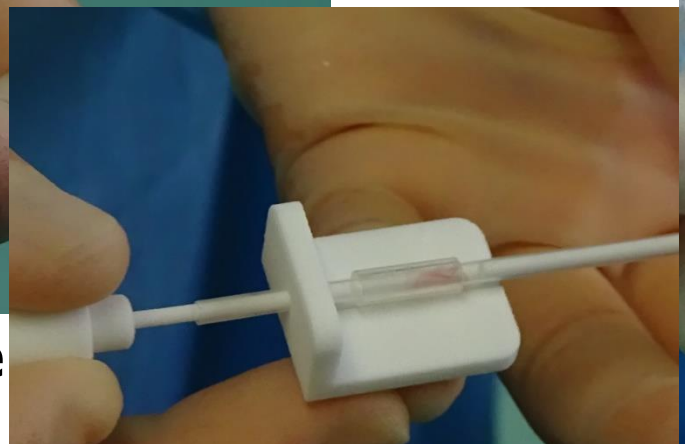






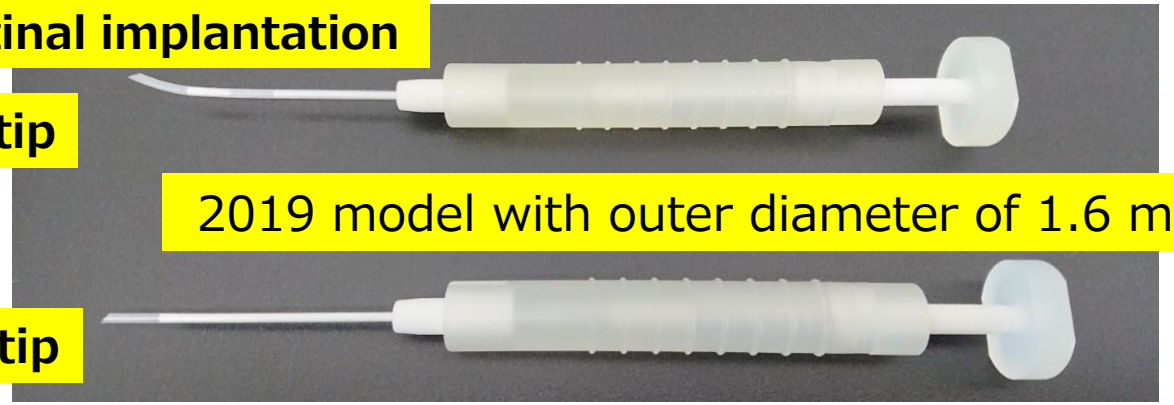
**Front loading**

**2.3 mm in size**

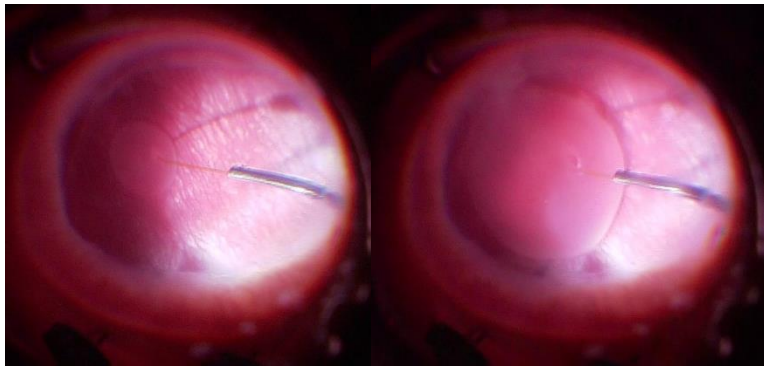


# Safe surgery for OUReP subretinal implantation

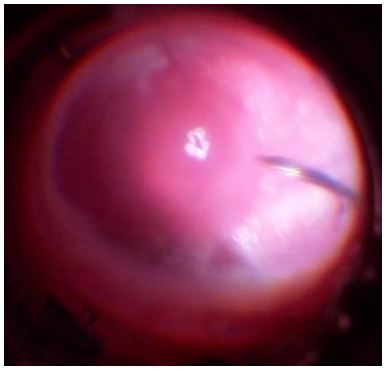
disposable
OUReP Injector




Bleb retinal detachment by 38G-tip infusion

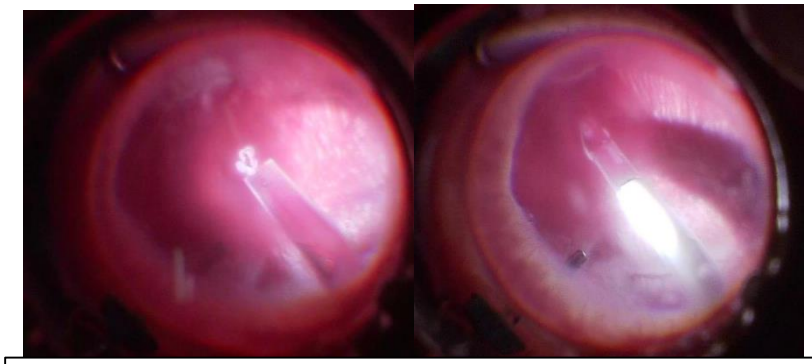


Retinal tear made by coagulation

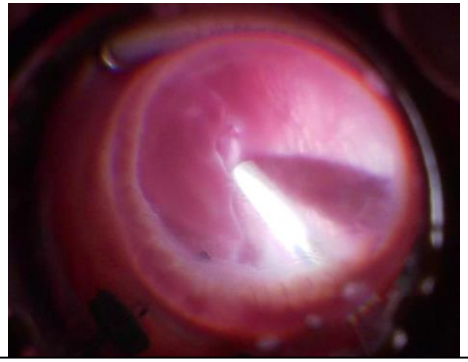


Injector tip inserted into vitreous

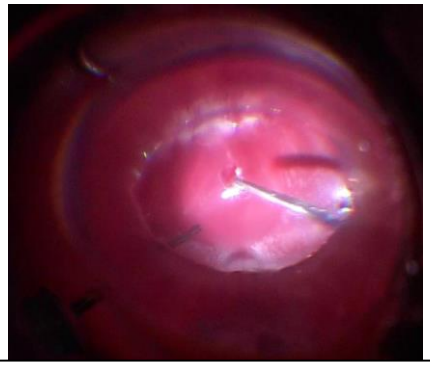
Injector tip inserted through retinal tear



OUReP film pushed out



Subretinal fluild aspirated



Matsuo T, Matsuo C, Uchida T, Yamashita K, Tanaka T, Kawakami Y, Hitomi T, Taga K, Sanada T, and Yamashita Y.
Curved-tip disposable injector (OUReP Injector) to insert photoelectric dye-coupled polyethylene film (OUReP) as retinal prosthesis into subretinal space of rabbit eyes. Journal of Surgical Techniques and Procedures 2020;4:1040.

# OUReP™ manufacturing and doctor-initiated clinical trial