Photoelectric Dye-Based Retinal Prosthesis (OuReP) As a Novel Type of Artificial Retina

Authors
Toshihiko Matsuo,[1),2)] ,
Tetsuya Uchida[3)]
Affiliations
[1)] Ophthalmology, Okayama University Hospital, Okayama City, Japan
[2)] Okayama University Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama City, Japan
[3)] Polymer Materials Science, Okayama University Graduate School of Natural Science and Technology, Okayama City, Japan
Correspondence to:
Toshihiko Matsuo, MD, PhD, Regenerative and Reconstructive Medicine (Ophthalmology), Okayama University Graduate School of Interdisciplinary Science and Engineering in Health Systems, Shikata-cho 2-5-1, Okayama City 700-8558, Japan.
E-mail:
matsuot@cc.okayama-u.ac.jp

Abstract
We have developed the world's first novel type of artificial retina, OUReP (Okayama University Retinal Prosthesis), in which a photoelectric dye that converts light energy into electric potential is covalently bonded to the surface of a polyethylene thin film as an insulator. The receptor that absorbs light and the output device that generates displacement current to stimulate nearby neurons are integrated in a sheet of thin film. It has become possible to measure the surface potential of the artificial retina OUReP using a Kelvin probe that measures the surface potential of semiconductors. When light is turned on and off to the artificial retina OUReP, the surface potential changes rapidly. As the light intensity is increased, the potential change on the surface of the artificial retina becomes larger. As for safety, the artificial retina OUReP was not toxic in all tests for biological evaluation of medical devices. As for efficacy, the artificial retina OUReP was implanted under the retina by vitreous surgery in monkey eyes which had chemically-induced macular degeneration with photoreceptor cell loss. Over the next 6 months, retinal detachment did not occur during the course, and the artificial retina was in contact with the retinal tissue. The amplitude of the visual evoked potential attenuated by macular degeneration recovered 1 month after implantation of the artificial retina, and the recovery of amplitude was maintained until 6 months after the implantation. By using multielectrode array-mounted dish recording system, it has been proved that action potential spikes are induced when the artificial retina is placed on degenerative retinal tissue of retinal dystrophic rats or

mice and exposed to light, which is used as an index of the effectiveness of the artificial retina. We have established manufacturing and quality control of the device in a clean room facility, proved the safety and efficacy, and are preparing for first-in-human investigator-initiated clinical trials.

Key words: artificial retina; retinal prosthesis; photoelectric dye; polyethylene film; monkey surgery; multielectrode array dish recording; vitrectomy; disposable injector; sustainable development goals; rabbit surgery, dog surgery; retinal dystrophic rat (RCS rat); retinal dystrophic mice (rd1 mice)

1. Introduction

We can roughly grasp objects and avoid obstacles to move around because we have a wide field of view which has, though, low resolution of visual acuity of about 0.1 in decimals, corresponding to 20/200. The high-resolution retinal region with visual acuity of 1.0 in decimals, corresponding to 20/20, is only confined to a very narrow area of the retinal center, called the fovea centralis of the macula. Indeed, when we have visual acuity of 0.1 (20/200), we can read characters by enlarging them on a tablet personal computer with a camera, for instance, iPad. These lines of evidence suggest that wider visual field with visual acuity at the level of 0.1 would be set as the functional goal for vision in general as the minimal requirement.

The beginning of vision is the photoreceptor cells in the retina in the eyeball, which convert light energy into cell membrane potentials and propagate the signals to the brain via relays of nerve cells (neurons). Diseases in which these photoreceptor cells die include retinitis pigmentosa in the category of congenital diseases and age-related macular degeneration in the category of acquired diseases. Although the photoreceptor cells are dead in these diseases, there are still surviving nerve cells (retinal ganglion cells) in the degenerated retinal tissue that formulate the optic nerve as their axons and connect to the brain. In the basic concept of artificial retina, an artificial substance that converts light into electrical signals stimulates the nerve cells that connect to the brain for vision.

2. Artificial retina with electrode array system on the market

For the first time in 2013, the Food and Drug Administration (FDA) in the United States approved an artificial retina called Argus II as a medical device for the manufacture and sale.[1] In the system, an electrode array that combines 60 electrodes are implanted in the eye, image information from an external camera with eyeglasses is processed, and electric currents are outputted to stimulate the retina. In Europe and the United States, it has since been sold at a price of about $150,000, and more than 200 patients who have lost their eyesight due to retinitis pigmentosa have undergone the implant surgery. By implanting the artificial retina, it became possible for patients to understand the rough movements, and it was confirmed that the therapeutic concept of the artificial retina is clinically applicable. In this Argus II system, when an aggregate (array) of 60 electrodes with each diameter of 1 mm is fixed to the surface of the retina and an electric current is conducted from each electrode, the nerve fiber layer running from the periphery on the surface of the retina is first stimulated. The retinal ganglion cell layer beyond the nerve fiber layer is also stimulated at the same time. In this way, it is surprising that the vision of hand movement can be restored even by vertical and horizontal diffusion of electric charge injection which is outputted from the 6 x 10 mm square electrode array, indicating that the processing mechanism of the brain related to vision has great adaptability.

In order to improve the visual quality of the artificial retina, it is first necessary to bring a large-area artificial retina into contact with the back of the retina (under the retina) in order to obtain a wide field of view. The artificial retina installed upon the surface of the retina on the vitreous side stimulates the nerve fiber layer running from the peripheral retina which is different from the retinal region with the point of stimulation as in the Argus II electrode array system. In contrast, the artificial retina installed under the retina is in direct contact with the retinal nerve cells and thus only nerve cells in the retinal region can be stimulated. Secondly, in order to increase the resolution, it is necessary to reduce the individual pixel area and increase the number of pixels. As long as electrodes and photodiodes are used as elements, it is considered difficult to achieve these two goals (artificial retina with a large number of pixels and a large area) at the same time.

3. Photoelectric dye molecules as a key element of the device

To think of the artificial retina simply, it can be said that elements that convert light into electrical signals are arranged in a plane to stimulate nerve

cells in the adjacent retina. As an element of the artificial retina that is neither an electrode nor a photodiode, we have arrived at photoelectric dye molecules that convert light energy into electric potential in the repertoire manufactured by Hayashibara Co., Ltd. (Nagase & Co. Ltd) in Japan. The photoelectric dyes have been originally produced for dye-sensitized solar cells. We selected a photoelectric dye that has stable molecular structure and has absorption wavelength in the visible light (Fig. 1), verified that the photoelectric dye stimulates nerve cells under light exposure,[2] and applied for a patent in 2002. A US patent was granted in 2006,[3] a Japanese patent was granted in 2012, and both patents were transferred to Okayama University in 2014. In 2018, a US patent on the manufacturing was also granted.[4]

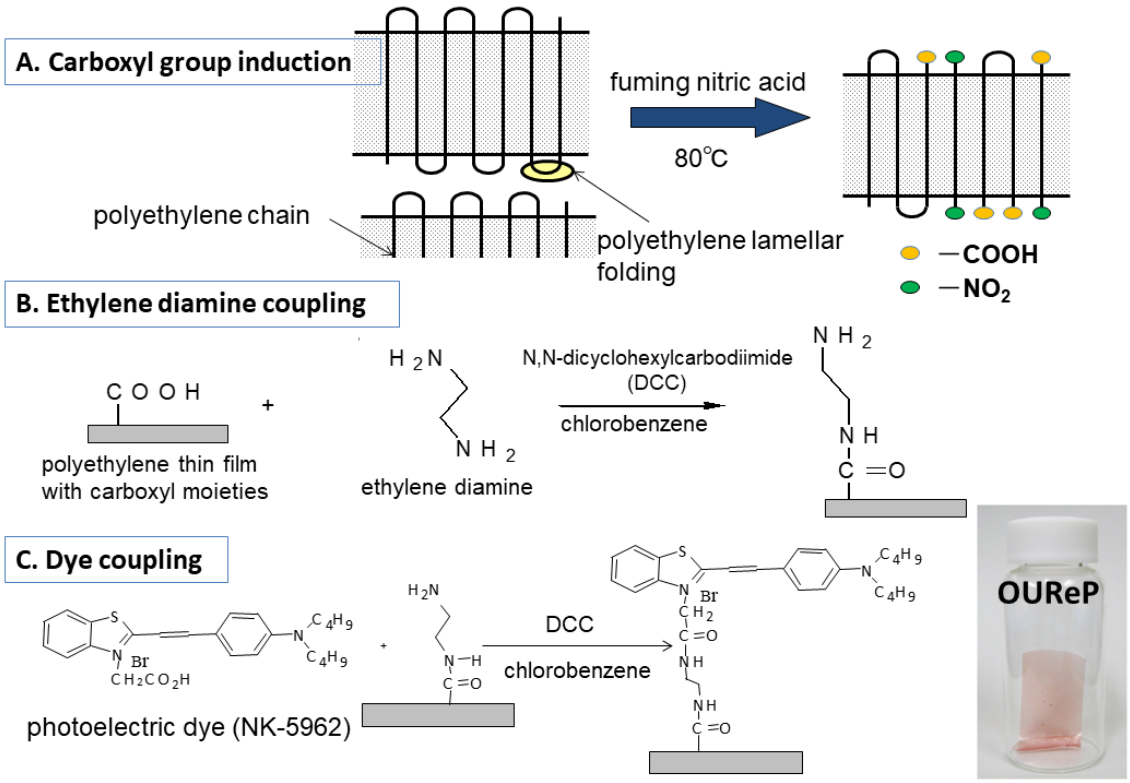

Fig. 1. Chemical process to produce photoelectric dye-coupled polyethylene thin film as artificial retina OUReP. Carboxyl group (COOH) is induced on polyethylene thin film surface by fuming nitric acid treatment (**A**), ethylene diamine is coupled to carboxyl group on the film surface (**B**), and then photoelectric dye is bonded (**C**).

4. Polyethylene thin film as a basal component of the device

We encountered a polyethylene thin film as a soft and stable film that binds photoelectric dye molecules. Polyethylene is also implanted in the living body as a component of an artificial joint, and it is considered that there is no problem in *in-vivo* stability and biocompatibility. The surface of the polyethylene thin film was treated by fuming nitric acid to introduce a carboxyl (COOH) group, and the candidate photoelectric dye (NK-5962) was covalently bonded via the reactive group (Fig. 1) to establish the prototype of the artificial retina, OUReP (Okayama University Retinal Prosthesis).[5-7] Using this prototype, we investigated the response in cultured neurons and in the isolated retinal tissues,[6,7] and demonstrated visual recovery by implanting it under the retina of the eyes in hereditary retinal dystrophic rats (RCS rats).[8-11] In RCS rat studies, plain polyethylene films with no photoelectric dye-coupling were implanted under the retina in the eyeball as controls. Compared with control RCS rats, RCS rats with OUReP implantation under the retina in the eyeball showed better vision in behavior tests, and better electrophysiological response in the retina and in the brain, as revealed by electroretinography and visual evoked potential, respectively.[8-11]

In parallel, the properties of the polyethylene thin film surface were changed so as not to cause glial foreign body reaction,[12] and further improvements were made to bond photoelectric dye molecules to the polyethylene thin film surface at high density. The feature of this artificial retina is that the photoelectric dye is bonded to both sides of the polyethylene thin film which is an insulator, and the receptor that absorbs light and the output device that generates electric potential are integrated in a sheet of thin film. Therefore, other parts such as an external electric battery are not required.

5. Kelvin probe to measure surface electric potential changes

At the initiative by Kenichi Takarabe, in Faculty of Science, Okayama University of Science, a semiconductor expert who presides over "Semiconductor Net Okayama," it has become possible to measure the surface potential of the artificial retina OUReP using a Kelvin probe that measures the surface potential of semiconductors (Fig. 2).[13] When light is turned on and off to the artificial retina OUReP, the surface potential changes rapidly. As the light intensity is increased, the potential change on the surface of the artificial retina becomes larger (Fig. 2). At the brightness of the room light of 100 to 200 lux, the potential of the artificial

retina surface is induced to change by 100 to 200 mV.[14]

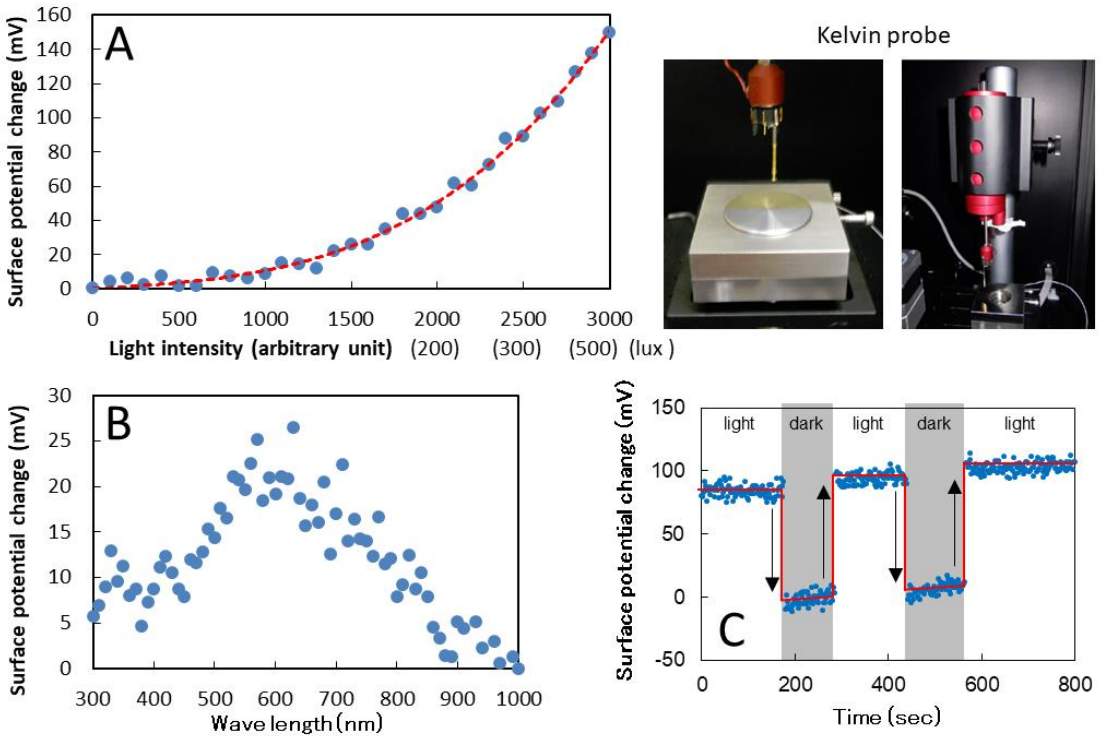

Fig. 2. Kelvin probe measurement of surface electric potential changes on artificial retina OUReP. Surface electric potential changes become larger in response to increase of light intensity (**A**), are induced by visible light wavelength (**B**), and without time lag (**C**).

6. Basic principle of photoelectric dye-based retinal prosthesis

Electrically stimulating devices have been widely used in human body for many years: for instance, a heart pacemaker to stimulate cardiomyocytes,[15] and neurostimulators for vagus nerve stimulation in epilepsy and deep brain stimulation in Parkinson disease.[16,17] All devices output conduction current of electron charges which flows out from direct current (DC) electric battery attached to devices. Displacement current is another type of electric current. The displacement current is generated in electric battery which consists of capacitor and electric generator with temporal dependence of electric flux. The displacement current which is generated in this type of electric battery induces, outside the battery, the electric current into the electric conductive medium attached to this battery. This electric current, outside the battery, is also called as the displacement current. For instance, the pyroelectric

sensor, which detects infrared light, operates with the displacement current mode and is commercially distributed.[18,19] Capacitive current has basically the same definition as the displacement current, and has been applied to devices for neural-prosthetic interface such as BION^{TM} (BIOnic Neuron) system.[20]

Until now, no device to output displacement current or capacitive current is at clinical use in human body. We have designed photoelectric dye-coupled thin film (OUReP) to output electric potential probably as displacement current in response to light.[13,14] A similar attempt to use the photoelectric dye to stimulate neuronal cells was done by the other group of researchers.[21]

7. Biological safety tests for a medical device

In the process when we investigated that this photoelectric dye (NK-5962) was not toxic, we also found that it had the effect of suppressing nerve cell death, namely preventing neuronal apoptosis.[22,23] In March 2012, the Ministry of Health, Labor and Welfare's Pharmaceutical and Food Safety Bureau in Japan published “the guidelines for biological safety evaluation necessary for application for manufacturing and marketing approval of medical devices", leading to common recognition regarding the safety evaluation of medical devices in Japan. It is based on ISO 10993 “Biological evaluation of medical devices”. The artificial retina OUReP was not toxic in cytotoxicity test, skin sensitization test, genetic toxicity tests (bacterial reverse mutation test, human chromosomal aberration test), implantation test, eye irritation test, acute and repeated-dose systemic toxicity tests. In addition, the photoelectric dye itself, which is a key element of the artificial retina, was not toxic in all of these tests.

8. Clean room facility for manufacture and quality control

In December 2014, Minori Industry Co., Ltd., a small and medium-sized manufacturing company in a different specialty of industry in Okayama Prefecture, Japan, signed a joint research agreement with Okayama University regarding basic manufacturing technology for the artificial retina. In January 2015, we rent an office space at the Okayama University Incubator operated by the Organization for Small & Medium Enterprises and Regional Innovation, an affiliated organization of the Ministry of Economy, Trade and Industry in Japan, and in May, built a clean room manufacturing facility (Fig. 3). In March 2016, Minori Industry Co., Ltd. registered the medical device

manufacturing industry in Okayama Prefecture at this manufacturing site. Tetsuya Uchida as a collaborating scientist, will be in charge of the clinical trial device manufactured under the quality management system (QMS), and the device will be provided for a first-in-human investigator-initiated clinical trial conducted at Okayama University Hospital.

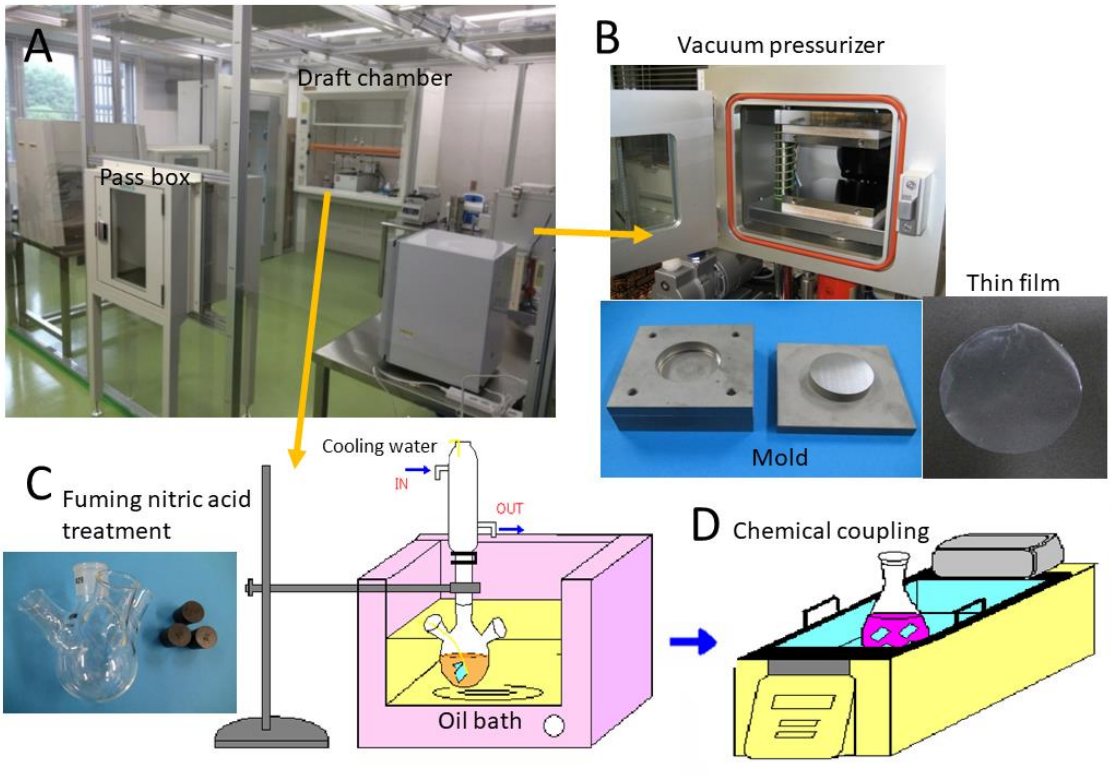

Fig. 3. Clean room facility for manufacturing of artificial retina OUReP. Ceiling and walls of clean room are made by transparent acrylic boards (**A**). Polyethylene thin film is produced by mold in vacuum pressurizer (**B**), treated with fuming nitric acid to induce surface carboxyl group (**C**), and chemically coupled with ethylene diamine and then with photoelectric dye (**D**).

9. Preclinical animal tests for safety and efficacy

In dogs and rabbits, the artificial retina OUReP was implanted under the retina in the eyeball in the same manner as in human vitreous surgery, and the safety of the surgery was evaluated.[24,25] In monkeys, cobalt chloride solution was injected under the retina of the right eye to create chemically induced macular degeneration with photoreceptor cell loss, and the artificial retina OUReP was implanted under the retina by vitreous surgery.[26] Over the next 6 months, the condition of the retina was observed with optical coherence tomography (OCT),

and in addition, the visual evoked potential (VEP), which is the electrical activity of the occipital lobe induced by light flashing in front of the eye, was recorded. As a safety index, retinal detachment did not occur during the course, and the artificial retina was in contact with the retinal tissue. As an index of efficacy, the amplitude of the visual evoked potential attenuated by macular degeneration recovered 1 month after implantation of the artificial retina, and the recovery of amplitude was maintained until 6 months after the implantation (Fig. 4).[26]

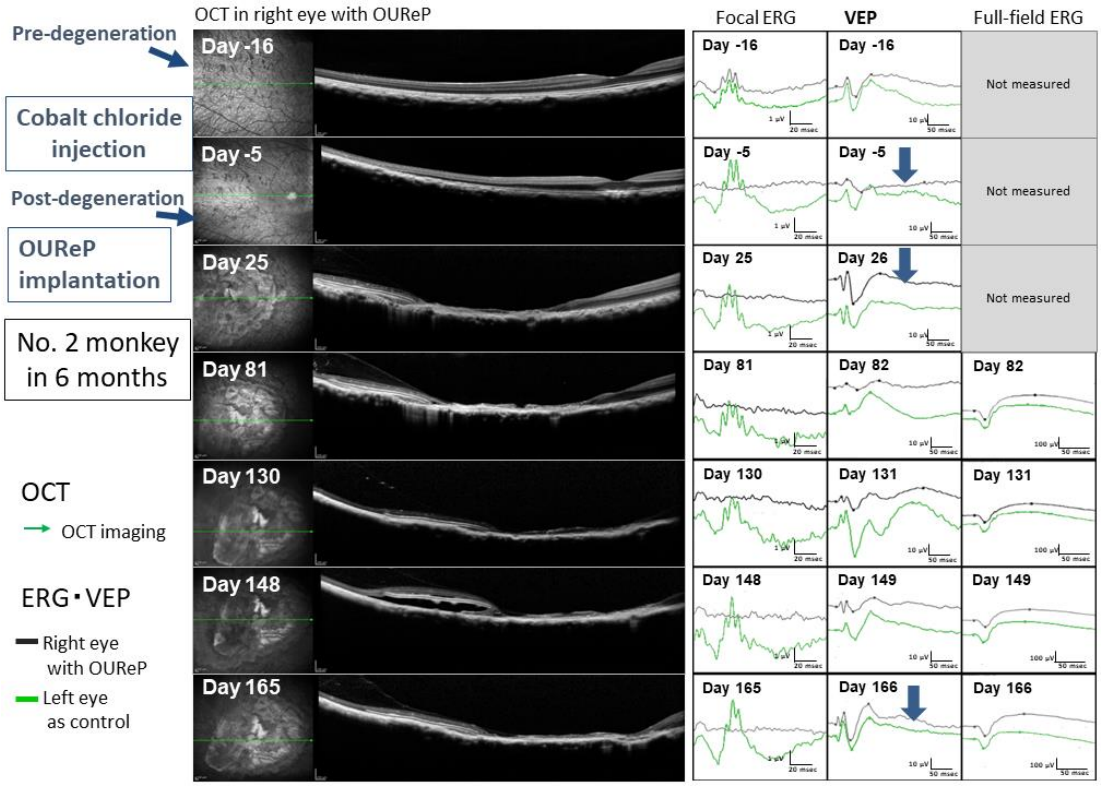

Fig. 4. Artificial retina OUReP implantation in monkey eye with chemically (cobalt chloride) induced macular degeneration. Note retinal attachment by optical coherence tomography (OCT) and visual evoked potential (VEP) amplitude recovery for 6 months. Modified from reference 26.

In the dog,[24] rabbit,[25] and monkey tests,[26] the artificial retina OUReP was inserted by grasping the artificial retina with tweezers (vitreous forceps) and carrying it under the retina, but it was difficult to perform each step as a surgical procedure. Therefore, we developed the OUReP Injector, a disposable injector that rolls the artificial retina and pushes it under the retina (Fig. 5, Fig. 6).[27,28] The latest injector is made of polypropylene with a curved tip tube with an inner diameter of 1.4 mm and a wall thickness of 0.1 mm, and is

manufactured by Minori Industry Co., Ltd. using a straw manufactured by Shibase Co., Ltd., in Okayama, Japan (Fig. 5, Fig. 6).[28]

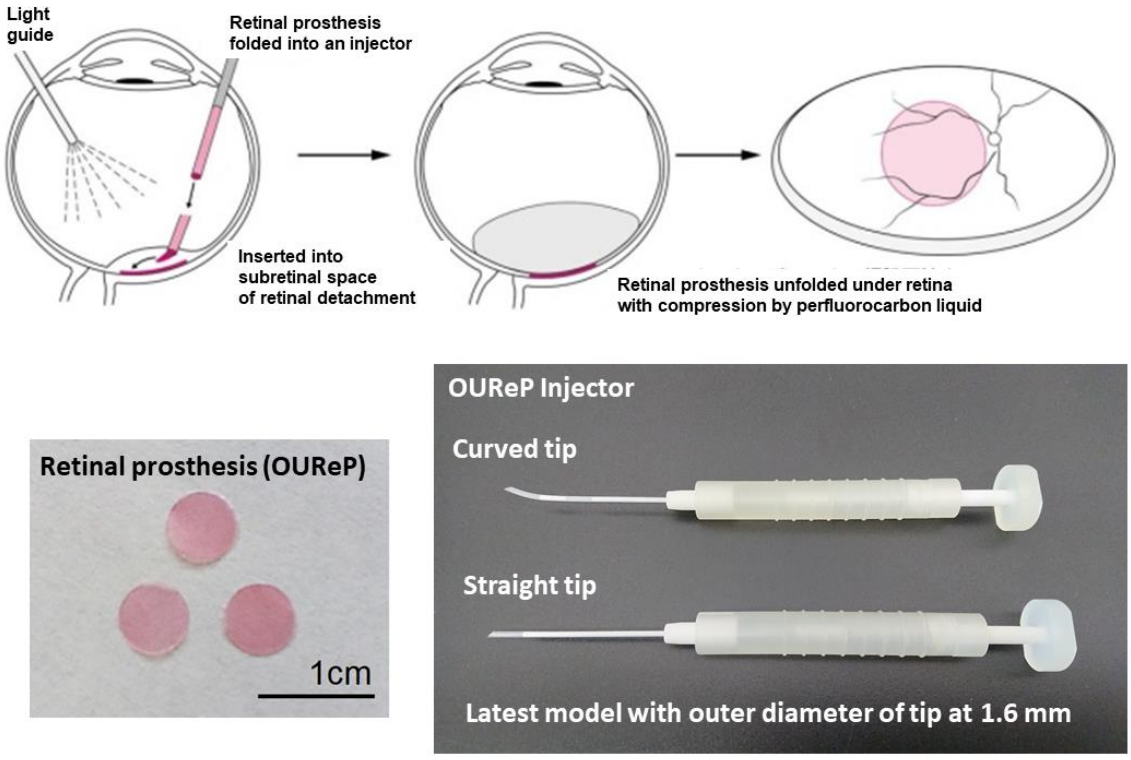

Fig. 5. Disposable OUReP Injector. Schematic drawing of surgical procedures (**top**) and latest models of OUReP Injector (**bottom**).

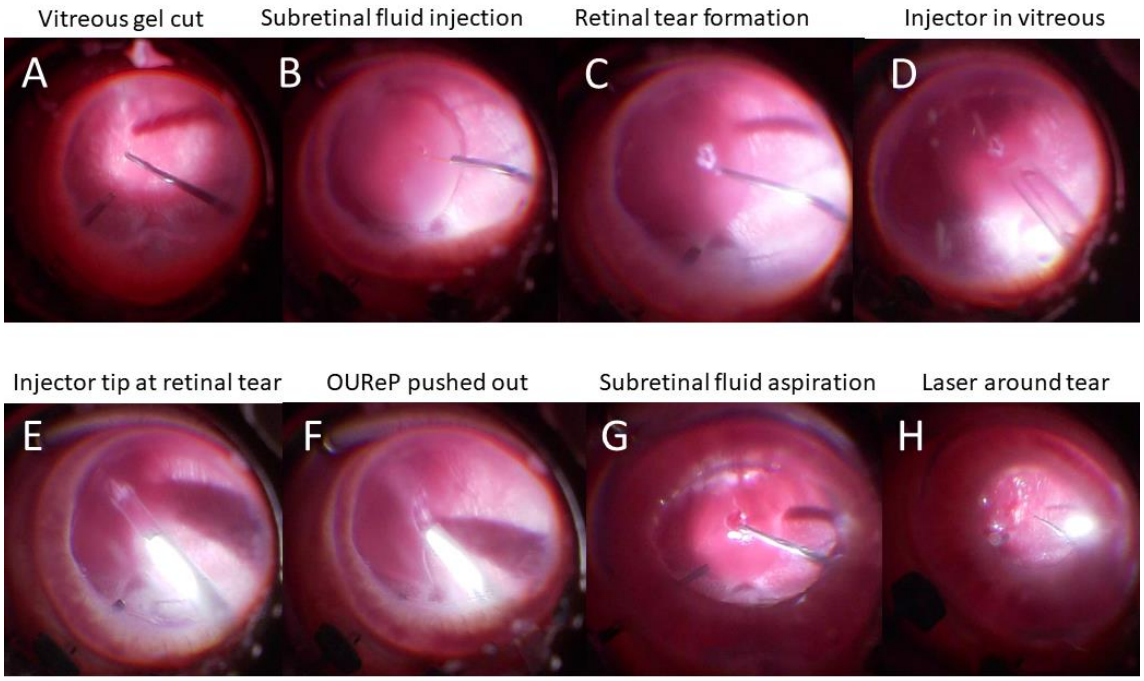

Fig. 6. Vitreous surgery images to implant artificial retina OUReP by OUReP Injector in a rabbit eye. After vitreous gel is cut (**A**), retinal detachment is induced by subretinal injection of fluid with 38-gauge tip (**B**), and a retinal tear is made by coagulation with diathermy (**C**). OUReP Injector is inserted into vitreous through scleral incision (**D**), and advanced to the retinal tear (**E**). OUReP is pushed out into the subretinal space (**F**). Fluid in vitreous is changed to air, subretinal fluid is aspirated (**G**), and laser is applied around the tear (**H**). Modified from reference 28.

10. Action potential spike induced in dystrophic retinal tissues by OUReP

Strains that develop hereditary retinal degeneration (dystrophy) are maintained and marketed in rats[14] and mice.[29] In the experimental procedure when normal retinal tissue of rats and mice is removed from the eyeball and placed on a petri dish (multi-electrode petri dish) in which electrodes are embedded and exposed to light, a light-evoked action potential spike, which is the activity of nerve cells in the retinal tissue, is recorded. In contrast, light-evoked action potential spikes do not occur when degenerative retinal tissue is removed from the eyeball of retinal dystrophic rats or mice, placed in a multi-electrode petri dish and exposed to light. It has been proved that action potential spikes are induced when the artificial retina OUReP is placed on degenerative retinal tissue and exposed

to light, which is used as an index of the effectiveness of the artificial retina (Fig. 7).[14,29]

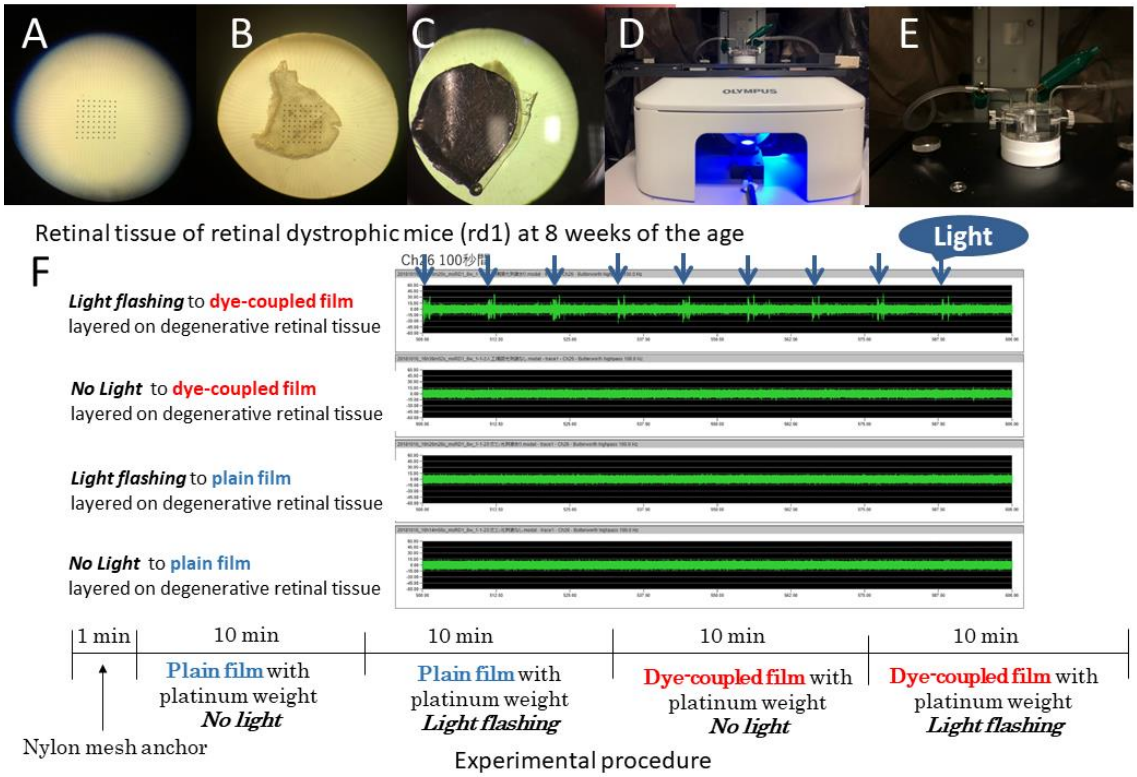

Fig. 7. Action potential spike recording in degenerative retinal tissue of mice by multielectrode array dish. Dish bottom has 64 electrodes (**A**). Degenerative retinal tissue isolated from eyes of rd1 mice at the age of 8 weeks is placed on multielectrode array (**B**), and artificial retina OUReP with platinum weight at top is layered upon the retinal tissue (**C**). Multielectrode array dish (**E**) is placed on the stage of dissecting microscope with light source at bottom (**D**). Plain film with no dye coupling as control is first layered on the retinal tissue and then dye-coupled film as artificial retina OUReP is layered (**F**). Modified from reference 29.

11. Investigator-initiated clinical trial in consultation with PMDA

A consultation system to support from the beginning the development of pharmaceuticals and medical devices for venture companies and universities has started in 2011 as Pharmaceutical Affairs Strategic Consultation (renamed to Regulatory Science (RS) Strategic Consultation from 2017) at the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. On January 11, 2013, we attended a PMDA interview for the first time and learned that an investigator-initiated clinical trial can be conducted for academia-produced devices that are not manufactured by companies. We have been consulting

with PMDA at the aim of conducting clinical trials led by investigators. In the plan of a first-in-human investigator-initiated clinical trial, six patients with retinitis pigmentosa will be treated with implant surgery (Fig. 5, Fig. 6). The visual acuity of the eye with implant surgery will be at the level of light perception, and the visual acuity of the other eye was at the level of hand movement or light perception. The inclusion criteria are that there remains retinal layer structure to connect to the brain as revealed by optical coherence tomography (Table 1).[30,31]

Table 1. Inclusion and exclusion criteria in the first-in-human clinical trial for OUReP

Inclusion criteria
1. Have the diagnosis of retinitis pigmentosa
2. Have best-corrected visual acuity of light perception in the operated-on eye
3. Have best-corrected visual acuity of hand movement or light perception in the fellow eye
4. Have two retinal layers (nerve fiber layer and inner plexiform layer) preserved in the operated-on eye demonstrated by optical coherence tomography (OCT)
5. At the age of 70 years or older
6. Provide written consent to join the trial
7. Will attend at follow-up examinations
Exclusion criteria
1. Have other eye diseases of glaucoma, optic nerve atrophy, or corneal opacity
2. Have the history of retinal detachment in the operated-on eye.
3. Have dense cataract which prevents fundus visualization
4. Have undergone cataract surgery within 2 weeks
5. Have drug allergy
6. Have systemically poor condition with cancer, chemotherapy, or immunosuppresants
7. Have severe hepatic, renal, cardiac, pulmonary, hematological, metabolic, or mental illness
8. Currently join other trials

12. Conclusions

The artificial retina OUReP is the world's first novel medical device composed of organic molecules as a key element. Since there are no precedents, we are formulating our own manufacturing and quality standards to prepare for ethical and scientific clinical trials. In Japan, the Pharmaceutical Affairs Act was amended in 2013, and

the name of the law was changed to "The Act on Securing Quality, Effectiveness, and Safety of Pharmaceuticals, Medical Devices, etc." and came into effect in 2014. Toward a clinical trial in which the artificial retina OUReP (class 3 medical device) is implanted using a disposable injector OUReP Injector (class 2 medical device), we are advancing manufacturing process control and quality control to create a clinical trial device outline and are implementing a clinical trial plan. We have a schedule to submit a notification of the plan to PMDA. The patients' wish and safety are the first priority, and we are working in collaboration with the patients' association. With the support of many people, we have finally reached the entrance to the clinical trial.

We are planning to supply at a cheap price the artificial retina OUReP to the blind people all over the world. "No one left behind in the world", as stated in the Sustainable Development Goals (SDGs) in the United Nations, is a key concept in this project. Retinal prosthesis with multielectrode array system has been sold at an expensive price in the United State and Europe, and this cost is not affordable in most people in the world including Japan. Japan has maintained national health insurance system since 1961 to provide medical services at low cost to all people. Recently, however, expensive new drugs and medical devices which have been included in the health insurance system put a heavy burden on the finance of the system. A new device at low cost will be provided by "industrial innovation" (SDG 9), and thus, "people's good health and well-being" (SDG 3) will be maintained at equal opportunity all over the world, leading to "reduced inequalities in the world" (SDG 10). "As partnerships for the goals" (SDG 17), we are working as a multidisciplinary team which consists of experts in universities and companies.

Funding

This study was supported in part by a grant for the Practical Research Program for Rare/Intractable Diseases (18950217, 2018) from the Japan Agency for Medical Research and Development (AMED).

Conflict of interest

The authors declare that they have no competing financial interests in this study.

References

1. Humayun MS, de Juan E Jr, Dagnelie G. The bionic eye: a quarter century of retinal prosthesis research and development. Ophthalmology 2016;123(10S):S89-S97.
2. Matsuo T. A simple method for screening photoelectric dyes towards their use for retinal prostheses. Acta Med Okayama 2003;57:257-260.
3. Okayama University (Assignee). Matsuo T, Dan-oh Y, Suga S (Inventors). Agent for inducing receptor potential. United States Patent. Patent No.: US 7,101,533 B2. Date of Patent: September 5, 2006.
4. Okayama University (Assignee), Uchida T, Matsuo T (Inventors). Method for producing artificial retina. United States Patent. Patent No. : US10,039,861 B2. Date of Patent : August 7, 2018.
5. Uchida T, Ishimaru S, Shimamura K, Uji A, Matsuo T, Ohtsuki H. Immobilization of photoelectric dye on the polyethylene film surface. Memoirs of the Faculty of Engineering Okayama University 2005;39:16-20.
6. Uji A, Matsuo T, Ishimaru S, Kajiura A, Shimamura K, Ohtsuki H, Dan-oh Y, Suga S. Photoelectric dye-coupled polyethylene film as a prototype of retinal prostheses. Artif Organs 2005;29:53-57.
7. Uji A, Matsuo T, Uchida T, Shimamura K, Ohtsuki H. Intracellular calcium response and adhesiveness of chick embryonic retinal neurons to photoelectric dye-coupled polyethylene films as prototypes of retinal prostheses. Artif Organs 2006;30:695-703.
8. Alamusi, Matsuo T, Hosoya O, Tsutsui MK, Uchida T. Behavior tests and immunohistochemical retinal response analyses in RCS rats with subretinal implantation of Okayama University-type retinal prosthesis. J Artif Organs 2013;16:343-351.
9. Alamusi, Matsuo T, Hosoya O, Tsutsui MK, Uchida T. Vision maintenance and retinal apoptosis reduction in RCS rats with Okayama University-type retinal prosthesis (OUReP^{TM}) implantation. J Artif Organs 2015;18:264-271.
10. Alamusi, Matsuo T, Hosoya O, Uchida T. Visual evoked potential in RCS rats with Okayama University-type retinal prosthesis (OUReP^{TM}) implantation. J Artif Organs 2017;20:158-165.
11. Matsuo T, Uchida T, Yamashita K, Takei S, Ido D, Fujiwara A, Iino M, Oguchi M. Vision evaluation by functional observational battery, operant behavior test, and light/dark box test in retinal dystrophic RCS rats versus normal rats. Heliyon 2019;5:e01936.
12. Tamaki T, Matsuo T, Hosoya O, Tsutsui KM, Uchida T, Okamoto K,

Uji A, Ohtsuki H. Glial reaction to photoelectric dye-based retinal prostheses implanted in the subretinal space of rats. J Artif Organs 2008;11:38-44.
13. Matsuo T, Uchida T, Takarabe K. Safety, efficacy, and quality control of a photoelectric dye-based retinal prosthesis (Okayama University-type retinal prosthesis) as a medical device. J Artif Organs 2009;12:213-225.
14. Matsuo T, Sakurai M, Terada K, Uchida T, Yamashita K, Tanaka T, Takarabe K. Photoelectric dye-coupled polyethylene film: photoresponsive properties evaluated by Kelvin probe and *in vitro* biological response detected in dystrophic retinal tissue of rats. Adv Biomed Eng 2019;8:137-144.
15. Guinand A, Noble S, Frei A, Renard J, Tramer MR, Burri H. Extra-cardiac stimulators: what do cardiologists need to know? Europace 2016;18:1299-1307.
16. Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. JAMA Neurol 2013;70:163-171.
17. Edwards CA, Kouzani A, Lee KH, Ross EK. Neurostimulation devices for the treatment of neurologic disorders. Mayo Clin Proc 2017;92:1427-1444.
18. Muralt P. Micromachined infrared detectors based on pyroelectric thin films. Rep Prog Phys 2001;64:1339-1388.
19. Wang ZL. On Maxwell's displacement current for energy and sensors: the origin of nanogenerators. Mater Today 2017;20:74-82.
20. Loeb GE, Peck RA, Moore WH, Hood K. BION^{TM} system for distributed neural prosthetic interfaces. Med Eng Phys 2001;23:9-18.
21. Huang F, Bladon J, Lagoy RC, Shorrock PN Jr, Hronik-Tupaj M, Zoto CA, Connors RE, Grant McGimpsey W, Molnar P, Lambert S, Rittenhouse AR, Lambert CR. A photosensitive surface capable of inducing electrophysiological changes in NG108-15 neurons. Acta Biomater 2015;12:42-50.
22. Okamoto K, Matsuo T, Tamaki T, Uji A, Ohtsuki H. Short-term biological safety of a photoelectric dye used as a component of retinal prostheses. J Artif Organs 2008;11:45-51.
23. Liu S, Matsuo T, Hosoya O, Uchida T. Photoelectric dye used for Okayama University-type retinal prosthesis reduces the apoptosis of photoreceptor cells. J Ocul Pharmacol Ther 2017;33:149-160.
24. Matsuo T, Uchida T, Nitta M, Yamashita K, Takei S, Ido D, Tanaka M, Oguchi M, Furukawa T. Subretinal implantation of Okayama University-type retinal prosthesis (OUReP^{TM}) in

canine eyes by vitrectomy. J Vet Med Sci 2017;79:1939-1946.
25. Matsuo T, Uchida T, Yamashita K, Takei S, Ido D, Tanaka M, Oguchi M, Furukawa T. Visual evoked potential in rabbits' eyes with subretinal implantation by vitrectomy of Okayama University-type retinal prosthesis (OUReP^{TM}). J Vet Med Sci 2018;80:247-259.
26. Matsuo T, Uchida T, Sakurai J, Yamashita K, Matsuo C, Araki T, Yamashita Y, Kamikawa K. Visual evoked potential recovery by subretinal implantation of photoelectric dye-coupled thin film retinal prosthesis (OUReP^{TM}) in monkey eyes with macular degeneration. Artif Organs 2018;42:E186-E203.
27. Matsuo T, Uchida T, Yamashita K, Matsuo C, Kawakami Y, Hitomi T, Taga K, Sanada T, Yamashita Y, Kuramoto K. Novel disposable injector (OUReP Injector) tested in rabbits' eyes for subretinal implantation of Okayama University-type retinal prosthesis (OUReP). Anim Eye Res 2018;37:1-12.
28. Matsuo T, Matsuo C, Uchida T, Yamashita K, Tanaka T, Kawakami Y, Hitomi T, Taga K, Sanada T, 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. J Surg Tech Proc 2020;4:1040.
29. Matsuo T, Terada K, Sakurai M, Liu S, Yamashita K, Uchida T. Step-by-step procedure to test photoelectric dye-coupled polyethylene film as retinal prosthesis to induce light-evoked spikes in isolated retinal dystrophic tissue of rd1 mice. Clin Surg 2020;5:2903.
30. Matsuo T, Morimoto N. Visual acuity and perimacular retinal layers detected by optical coherence tomography in patients with retinitis pigmentosa. Br J Ophthalmol 2007;91:888-890.
31. Tamaki M, Matsuo T. Optical coherence tomographic parameters as objective signs for visual acuity in patients with retinitis pigmentosa, future candidates for retinal prostheses. J Artif Organs 2011;14:140-150. Erratum 2011;14:385.