様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

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研究課題名（和文）変性網膜内層機能の最適化とiPSC由来網膜移植時のシナプス形成の促進に関する研究

研究課題名（英文）Probing the effect of degenerated retina potentiation on the synaptogenesis after iPSC-derived retinal transplantation

研究代表者

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交付決定額（研究期間全体）：（直接経費）　　3,100,000円

研究成果の概要（和文）：正常な網膜神経回路は、過去数十年の間に概ね明らかにされてきたが、最近、病気の網膜モデルの研究と解明によって新たな疑問が探求されてきた。視細胞変性後残りの疾患網膜内層では、神経節細胞の多くがリズミカルな膜電位振動と自発的なスパイク活動を示すことが確認されている。しかし、この過活動が網膜回路の再構成に影響を与えるかどうかは不明である。そこで本研究では、幹細胞由来網膜移植後の網膜再構成に過活動を薬理学的に抑制する効果を調べることを目的としている。多電極電気生理記録により、移植された網膜の機能評価法を確立し、網膜内側亢進抑制を行った場合と行わなかった場合の移植マウスの光応答性を比較するために用いた。

研究成果の学術的意義や社会的意義
Although the present study is still preliminary with much room for improvement technically, the results indicate the potential of host retina manipulation to optimize retinal transplantation therapy, and lead to the idea for a more thorough investigation in the following KAKENHI study.

研究成果の概要（英文）：While fundamental properties of the normal retinal wiring are largely revealed in the past several decades, other counterintuitive but intriguing properties have recently been explored from diseased retinal models. The inner retinal hyperactivity has been commonly seen in deafferented retinas, in which many of the residual retinal ganglion cells are found exhibiting rhythmic membrane potential oscillation and spontaneous spiking activity. However, whether the inner retinal hyperactivity would affect the reconstruction of retinal circuitry remains unclear. The present study is therefore aimed to probe the effect of pharmacological suppression of inner retinal hyperactivity on retinal reconstruction after stem cell-derived retinal transplantation. By MEA recording, the systematic functional evaluation method of transplanted retinas has been established and used to compare the light responsiveness in transplanted mice treated with or without inner retinal hyperactivity blockade.

研究分野：retinal neurobiology

キーワード：transplantation　organoid　retinal degeneration　amacrine cell　electrophysiology　ganglion cell

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

As the most accessible part of the central nervous system, how the visual information is processed in the intricate neural circuits of mammalian retinas has been recurrently asked and studied as the overarching question in retinal neurobiology. Changes of ambient light can be precisely conveyed by the delicate retinal circuitry to the visual brain, which can be generalized to ON (depolarize when light gets brighter) and OFF (depolarize upon dimming) pathways. Different than direct connections from cone bipolar cells (CBs) to the retinal ganglion cells (RGCs), rod bipolar cells (RBCs) synapse onto AII amacrine cells (AII-ACs), which transmit the rod signals through gap junction and glycinergic transmission into ON and OFF cone pathways and finally output through RGCs.

While fundamental properties of the normal retinal wiring are largely revealed in the past several decades, other counterintuitive but intriguing properties have recently been explored in diseased retinal models. In retinal degenerated mice like *rd1*, a well-characterized animal model of retinitis pigmentosa, RGCs exhibit rhythmic spiking activity, which may disrupt signaling to the visual brain. This pathological hyperactivity is in fact also observed in bipolar and amacrine cell types, suggesting a functionally disorganized inner retinal circuitry. Recent studies suggest such hyperactivity partially originates from the intrinsic bursting property of AII-ACs and spreads through the AII-ON cone bipolar gap junction network, which is hidden under functional photoreceptor signaling in healthy retina wherein the outer retinal signaling is functional.

As an intrinsic property of inner retina, how this pathological hyperactivity is chained in the healthy retina remains unknown. RBCs presumably govern AII-ACs by glutamate transmission but are found inactivated in degenerated retinas and hence unleash the AII-AC hyperactivity. In addition, it is of great interest to clarify if the inner retinal hyperactivity would affect the reconstruction of retinal circuitry when provided with healthy photoreceptors derived from ES/iPS cells. It is therefore probed in the present study to test the effect of pharmacological suppression of inner retinal hyperactivity on retinal reconstruction after stem cell-derived retinal transplantation.

２．研究の目的

This study aimed to potentiate the outer retinal reconstruction after iPSC-derived retinal transplantation by restraining the AII-AC oscillation using flupirtine, a potassium channel modulator that specifically leads AII-AC hyperpolarization and therefore ceases the inner retinal hyperactivity resulted from AII-AC oscillation. Along with the establishment of functional assay using multi-electrode array (MEA) recording, a systematic quantitative evaluation of transplanted retinas was conducted to compare the light responsiveness in transplanted mice treated with or without long-term flupirtine treatment.

３．研究の方法

Animals

All animals were treated in accordance with the Association for Research in Vision and Ophthalmology statement for the use of Animals in Ophthalmic and Vision Research. Animal experiments were conducted with the approval of the Animal Research Committee at RIKEN Center for Developmental Biology (now Center for Biosystems Dynamics Research). C57BL/6J-Pde6brd1-2/rd1-2J/J (JAX stock #004766) mice were crossed with B6;FVB-Tg(Pcp2-EGFP)2Yuza/J (JAX stock #004690) (Tomomura et al., 2001) to generate the end-stage retinal degeneration mouse model with GFP-expressing ON bipolar cells (hereinafter referred as rd1-2J;L7-GFP). Mice were housed under the standard 12-hr light/dark cycle with free access to water and food.

Retinal organoid preparation and transplantation

Procedures for maintenance, differentiation and preparation of mouse ESC-derived retinal organoids (ESC-retinas) for transplantation were previously described (Assawachananont et al., 2014; Iraha et al., 2018). Briefly, the retinal organoids were differentiated from Thy1-GCaMP6f;Ribeye-reporter ES cells and the optic vesicle structures (at differentiation day 13) were cut to small pieces (around 0.5 mm × 2 mm) on the day of transplantation. Mice were anesthetized with isoflurane using an inhalation anesthetic system (Narcobit-E type II, Natsume Seisakusho, Tokyo, Japan). Anesthesia was maintained 2.0-5.0% isoflurane at an O2 flow rate of 1.5 L/min using a modified nosecone for mice. Pupils were dilated with Mydrin-P® (0.5% phenylephrine + 0.5% tropicamide; Santen Pharm Co., Osaka, Japan). The prepared retinal sheets were inserted into the subretinal space of 10- to 15-week-old rd1-2J;L7-GFP mice, along with 1 mM valproic

acid using a glass micropipette with a tip diameter of approximately 500 μm. Indomethacin (10 mg/L) was added to the drinking water of all transplanted mice starting on the day of transplantation, including the mice treated with flupiritne (described in the next section).

Flupirtine treatment

Transplanted mice were divided into 4 groups and treated with 0 mM, 0.5 mM, 1mM, and 2mM flupirtine added in drinking water, respectively. The 100 mM stocking solution of flupirtine maleate (Tokyo Chemical Industry, Japan) was dissolved in DMSO and stored at -30℃. Treatments with flupirtine were started around 1.5 weeks after transplantation, when the graft photoreceptors were about to form synapses but not yet respond to light as observed preliminarily. Flupirtine treatments were continued until the day of recording described as below. Blood of animals in all groups were freshly collected right after the enucleation from the hole of removed eyeball, centrifuged at 1200 G for 15 minutes at 4 ℃to isolate plasma. The plasma concentration of flupirtine was measured using high performance liquid chromatography.

Multielectrode array recording and analysis

Mice transplanted with mouse ESC-retinas were used for multielectrode array (MEA) recording at around 8-9 weeks post-transplantation, except for one group of mice described later in the Results and Discussion. Animals were dark-adapted for 1-3 days prior to MEA recording using the USB-MEA60-Up-System (MultiChannel Systems, Germany) with the standard 8x8 probe (60MEA200/30iR-Ti-gr) as previously described (Iraha et al., 2018; Tu et al., 2018). The animals were deeply anesthetized with sevoflurane inhalation and sacrificed immediately by decerebration. Eyeballs were taken out by gently cutting off the optic nerves to avoid ganglion cell damages. Cornea and lens were removed first, and the remaining eyecups were then kept in constantly oxygenated (95% O2 and 5% CO2) Ames' medium (A1420, Sigma-Aldrich) at room temperature until use. Retinas were freshly isolated with vitreous body carefully removed for having good contact with MEA probe. The grafted areas were identified by their characteristic whitish, spotted looking, and mounted on the electrodes with the ganglion cell side down in assistance of a 0.5-g-weighted anchor with mesh. The mounted retinas were constantly perfused at 3-3.5 mL/min with warmed (34 ± 0.5° C) Ames' medium with 10 μM opsinamide (AA92593, Sigma-Aldrich) to suppress the melanopsin-driven ipRGC light responses during recording. Retinas were allowed to recover in the MEA chamber for at least 20 min before recording while the intrinsic hyperactive RGC firing was monitored as one of the degenerated retina features. During recording, L-AP4 (10 μM; 016-22083, Wako) was added to block the type 6 metabotropic glutamate receptor (mGluR6)-mediated transmission between photoreceptors and ON bipolar cells. The aforementioned procedures were conducted under dim red light with a peak wavelength at 690 nm. After recording, the IR and fluorescence images of the samples were taken. Retinas were then detached from the electrodes and fixed for 15 min with 4% PFA at room temperature for immunohistochemistry.

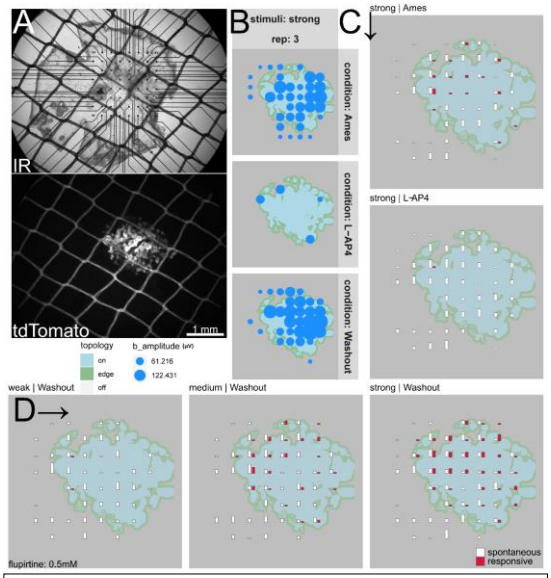

Figure 1. An example showing the graft topology and response heatmap. A, the retina with graft mounted on the MEA probe. The optic nerve disc and surgery damages can be seen in the IR-DIC photo, and graft rosettes could be identified by their RIBEYE-tdTomato expression after recording. **B**, graft topology manually determined according to tdTomato fluorescence and mapped in correspondence with the electrodes. Graft-covered areas were labeled in light-blue ("on" the graft), uncovered areas in light-gray ("off" the graft), and pixels surrounding rosettes were defined as "edge" of the graft (green). The amplitude of mERG b-wave detected at each electrode was depicted as blue spots. **C and D**, histograms of spontaneous-firing (white) and light-responsive (red) RGC numbers defined by the temporal spiking patterns in correspondence to light stimulation. **C** shows the RGC response changes in the absence and presence of L-AP4, and **D** shows the increase of responsive RGC numbers along with the light intensity changes.

The 10-ms and 1-s long full-field light stimuli were generated using a white LED source with irradiance ranging from 10-13 log photons/cm2/s at the focal plane of electrodes, covering the scotopic/mesopic to mesopic/photopic range. Three repeats for each light intensity were recorded as a set before, during and after the application of L-AP4 to confirm the origin of light responses. Using different band pass filters, field potentials (microERG or mERG; 1-50 Hz Butterworth) and RGC action potentials (spikes; 200-2800 Hz Butterworth) were extracted for analysis. Candidate mERG a-waves were defined as local minima within 55 ms after the onset of 10-ms light pulse and b-waves as local maxima within 120 ms. Among these, the largest peaks within the time windows were then assigned as tentative a- and b-waves. The RGC spikes were sorted using Spike 2 Version 7.2 (Cambridge Electronic Design) to separate individual cells on the same

electrodes based on spike amplitude and shape. By the tdTomato expression of the graft photoreceptors, the approximate graft location related to the MEA electrodes was manually mapped at a resolution of 552 x 552 pixels, and each pixel was defined as “on” or “off” the graft, or at the “edge” of the graft. The development and details of the currently used analysis is described in the first section of Results and Discussion.

Immunohistochemistry and imaging

The retinas after MEA recording were immunostained for mGluR6 (a generous gift from Drs. Jinny Chen and Ching-Kang Chen) at 4 ° C for 7-10 days, followed by 2-day incubation of the secondary antibody. Samples were mounted using VECTASHIELD Antifade Mounting Medium (H-1000, Vector) and kept at 4 ° C for long-term preservation. Z-stack imaging was taken across the full sample depth and tiled automatically to cover the grafted and neighboring areas with a Leica-TCS SP8. Imaris software (Bitplane) was used to view and process the 3D images.

４．研究成果

MEA recording and analysis of transplanted retinas

In order to objectively assess the functional recovery of transplanted retinas, MEA recording has been utilized to detect the light responsiveness of acute retinal preparation. The general recording protocol is described in the Materials and Methods section, similar to many other studies using MEA recording. Different from any other retinal models, either normal or degenerating, however, the data acquired from transplanted retinas is unique and requires novel ways to analyze for several reasons. First of all, the grafts only partially cover the degenerated host retinas and result in locally reconstructed signaling intermingled with pathological spontaneous activities. Such situation makes the graft topology extremely critical and requires correct mapping of the graft location on the MEA probe with multiple electrodes. Secondly, as reported previously, both action potentials of RGCs in direct contact with electrodes and field potentials, also known as mERG, originated from distal photoreceptor/bipolar cell populations can be detected by MEA recording. As the inserted retinal sheets contain not only photoreceptors but also other inner retinal neuron types, the mERG b-waves (bipolar cell depolarization) may originate from photoreceptor-bipolar cell transmission inside the graft (intra-graft) and/or between the graft-host. Therefore, it is important to consider the detected mERG b-waves and RGC spikes at the same electrodes together, in order to distinguish the effective (graft-host connection) and the ineffective (intra-graft) signal transmissions, as the former potentially leads to host RGC light responses while the latter not. Thirdly, the interaction between RGCs’ light responsiveness and spontaneous firing has been focused, as it is hypothesized that the pathological inner retinal hyperactivity would be suppressed by the reconstruction of retinal circuity after transplantation. As indicated preliminarily, the spontaneous firing frequency of RGCs that located within the grafted areas and showed light responses became lower compared to those without graft-dependent light responsiveness. Finally, the combination of retinal sheet preparation, transplantation process, graft-host interaction, and pharmacological treatments, etc., results in huge variation. It is therefore critical to take into account of all these properties and even the interactions between different parameters when quantifying and comparing the MEA recording results. Bayesian parameter estimation and various statistical distribution hypotheses have been utilized to correctly describe and quantify the results and differences of samples. In collaboration with one of the lab members, Dr. Takesi Matsuyama, the MEA recording and analysis protocol has been developed and contributed as a book chapter under invitation to the Methods in Molecular Biology series. An example of how the data was visualized is shown in Figure 1. Note that the light responding RGCs were only seen in the grafted area (Figures 1C and 1D), while the spontaneous firing cells were unrelatedly distributed.

Effect of flupirtine on retinal reconstruction after transplantation

The effect of flupirtine treatment in drinking water was evaluated by MEA recording following the aforementioned protocol. Except for the control (0 mM flupirtine) group, mice were treated with flupirtine at 3 different concentrations continuously from 10 days after transplantation. The preliminary results show that the probability of detectable mERG b-wave was decreased along with the increase of flupirtine concentration (Figure 2, right panel). On the other hand, the light responsive RGC ratios to the same 10-ms flash stimulation were increased when treated with 0.5 mM flupirtine but dropped in groups with higher doses of flupirtine that inevitably followed by higher dose of DMSO as the solvent for flupirtine maleate (Figure 3). This indicates flupirtine may contribute to less intra-graft connection (b-wave) and promote more host-graft connection (spikes) in lower concentration (0.5 mM), however, higher concentration groups performed worse than no-treatment group, which may resulte from the high concentration of DMSO as solvent of flupirtine maleate. Local controlled release of flupirtine may be required to confirm the results.

Also, the plasma concentration may be varied among animals and is also required to be included in the statistical analysis.

On the other hand, when comparing the probability of ON-type, OFF-type and non-responsive RGC populations among all 4 groups, no obvious difference was found, indicating the flupirtine treatment does not affect the composition of reconstructed retinal circuits, i.e. favoring ON or OFF pathways. Similar trend was also found when comparing the spontaneous firing rates of RGCs (data not shown).

Comparison with different transplantation preparations

The examination and analysis of flupirtine-treated mice after transplantation was conducted in parallel with many other transplantation preparation and combination, including mouse-mouse transplantation with genetic modified retinal organoids (wildtype vs. knockout lines), human-rodent transplantation using immune-deficient animal models (xenotransplantation), human-rodent transplantation with genetically modified human retinal organoids, and even the developing/degenerating mouse retinas without transplantation. Part of the results has been recently reported in peer-reviewed journals (Akiba et al., 2019; Iraha et al., 2018; Mandai et al., 2017; Tu et al., 2018), and some others are now being prepared for publication. Although the data for the others were not reported here, details may be found in recent publication from this lab. In general, the ratios of responsiveness RGCs in total detected RGC numbers are similar among different mouse-mouse preparations, showing the MEA recording protocol, even using systems with different electrode sizes provided by different manufacturers, is robust and stable. Similar topology- and condition-dependent distributions are observed in all mouse-mouse preparation, indicating the detection of light responses relies on the graft photoreceptor transmission, via either graft or host bipolar cells. An opposite trend of mERG b-wave probability and host RGC responsiveness, however, has been observed in the other mouse-mouse preparation using grafts with different levels of inner retinal neuron numbers but not in the present study. On the other hand, fast (conventional) mERG b-waves were stably detected in mouse-mouse preparation while only slow (unconventional) b-waves were sometimes observed in the human-rat/mouse preparation, suggesting differences in composition and size of graft cells, graft-host synaptic formation, and graft photoreceptor light sensitivity potentially due to species differences.

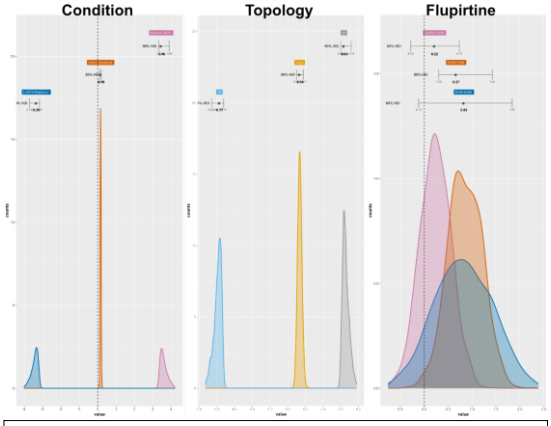

Figure 2. Comparison of mERG b-wave probabilities.
Left, comparison of mERG b-wave probability in recording before, during and after L-AP4 application, showing the mERG b-waves diminished in the presence of L-AP4. **Middle**, the distribution of mERG b-wave probabilities in channels covered by (on), near (edge), or distal from (off) the grafts, showing the graft origin of detected mERG b-waves. **Right**, the comparison of mERG b-wave probability among mouse groups treated with or without flupirtine after transplantation, showing a decrease of b-wave detection along with the increase of flupirtine concentration added in drinking water.

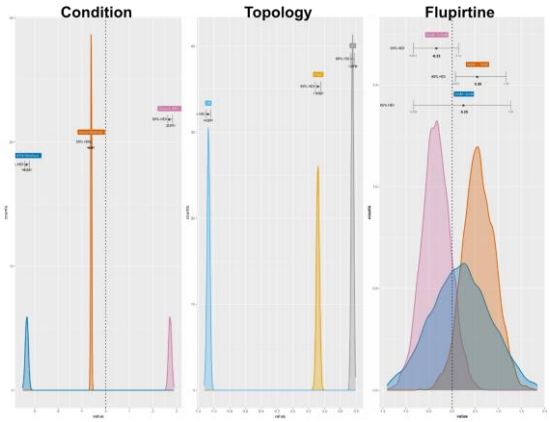

Figure 3. Comparison of RGC responsiveness to 10-ms flash stimuli.
Left, comparison of responsive RGC densities before, during and after L-AP4 application. The sensitivity to L-AP4 indicates RGC light responsiveness is photoreceptor-bipolar cell transmission-mediated, which is similar to mERG b-wave but with a clear increase after L-AP4 washout. **Middle**, the distribution of RGC responsiveness in channels covered by (on), near (edge), or distal from (off) the grafts, showing the graft origin of host RGC light responses. **Right**, the comparison of RGC responsiveness among mouse groups treated with or without flupirtine after transplantation. Different from mERG b-wave, the RGC responsiveness slightly increased when treated with low concentration of flupirtine (0.5 mM).

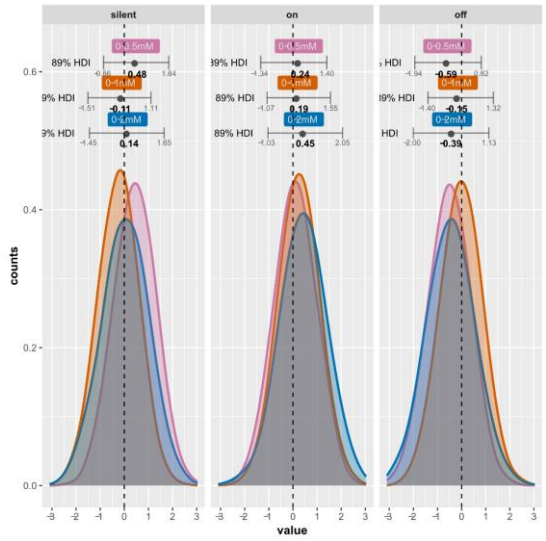

Figure 4. Comparison of RGC responsiveness to 1-s flash stimuli.
The RGC response types were divided into non-responsive as "silent", responsive to light onset as "on" and to light offset as "off" types. No clear difference was found in all 4 groups of mice treated with or without flupirtine.

５．主な発表論文等

〔雑誌論文〕　計6件（うち査読付論文　4件／うち国際共著　4件／うちオープンアクセス　5件）

１．著者名 Hung-Ya Tu, Take Matsuyama	４．巻 2092
２．論文標題 Multielectrode Array Recording of Mouse Retinas Transplanted with Stem Cell-Derived Retinal Sheets	５．発行年 2020年
３．雑誌名 Retinal Development. Methods in Molecular Biology	６．最初と最後の頁 207-220
掲載論文のDOI（デジタルオブジェクト識別子） 10.1007/978-1-0716-0175-4_15	査読の有無 無
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Tu Hung-Ya、Watanabe Takehito、Shirai Hiroshi、Yamasaki Suguru、Kinoshita Masaharu、Matsushita Keizo、Hashiguchi Tomoyo、Onoe Hirotaka、Matsuyama Take、Kuwahara Atsushi、Kishino Akiyoshi、Kimura Toru、Eiraku Mototsugu、Suzuma Kiyoshi、Kitaoka Takashi、Takahashi Masayo、Mandai Michiko	４．巻 39
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３．雑誌名 Investigative Ophthalmology & Visual Science	６．最初と最後の頁 1987
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１．著者名 Iraha Satoshi、Tu Hung-Ya、Yamasaki Suguru、Kagawa Takahiro、Goto Motohito、Takahashi Riichi、Watanabe Takehito、Sugita Sunao、Yonemura Shigenobu、Sunagawa Genshiro A.、Matsuyama Take、Fujii Momo、Kuwahara Atsushi、Kishino Akiyoshi、Koide Naoshi、Eiraku Mototsugu、Tanihara Hidenobu、Takahashi Masayo、Mandai Michiko	４．巻 10
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１．著者名 Kobayashi Wataru、Onishi Akishi、Tu Hung-Ya、Takihara Yuji、Matsumura Michiru、Tsujimoto Kazuko、Inatani Masaru、Nakazawa Toru、Takahashi Masayo	４．巻 59
２．論文標題 Culture Systems of Dissociated Mouse and Human Pluripotent Stem Cell-Derived Retinal Ganglion Cells Purified by Two-Step Immunopanning	５．発行年 2018年
３．雑誌名 Investigative Opthalmology & Visual Science	６．最初と最後の頁 776～776
掲載論文のDOI（デジタルオブジェクト識別子） 10.1167/iovs.17-22406	査読の有無 有
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４．発表年 2018年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考