Selective retinal therapy with a continuous line scanning laser

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ABSTRACT

This study evaluates the effects of exposure duration, beam diameter, and power on the safety, selectivity, and healing of retinal lesions created using a continuous line scanning laser. A 532 nm laser (PASCAL^{TM}) with retinal beam diameters of 40 and 66 μm was applied to 60 eyes of 30 Dutch-Belted rabbits. Retinal exposure duration varied from 15 to 60 μs. Lesions were acutely assessed by ophthalmoscopy and fluorescein angiography (FA). RPE flatmounts were evaluated with live-dead fluorescent assay (LD). Histological analysis was performed at 1 hour, 1 and 3 days, 1 and 2 weeks, and 1 and 2 months following laser treatment. Ophthalmoscopic visibility (OV) of the lesions corresponded to photoreceptor damage on histological analysis at 1 hour. In subvisible lesions, FA and LD yielded similar thresholds of RPE damage. The ratios of the threshold of rupture and of OV to FA visibility (measures of safety and selectivity) increased with decreasing duration and beam diameter. Above the threshold of OV, histology showed focal RPE damage and photoreceptor loss at one day without inner retinal effects. By one week, continuity of photoreceptor and RPE layers was restored. By 1 month, photoreceptors appeared normal while hypertrophy and hyperpigmentation of the RPE persisted. Retinal therapy with a fast scanning continuous laser achieves selective targeting of the RPE and, at higher power, of the photoreceptors. The damage zone in the photoreceptor layer is quickly filled-in, likely due to photoreceptor migration from adjacent zones. Continuous scanning laser can treat large retinal areas within standard eye fixation time.

Keywords: selective retinal therapy, retinal photocoagulation, microsecond pulse duration, scanning laser, retinal pigment epithelium, healing of laser lesions.

1. INTRODUCTION

Since its introduction nearly 40 years ago, laser photocoagulation remains the standard of care for many retinopathies.[1,2] By destroying retinal cells, panretinal laser photocoagulation (PRP) is postulated to reduce metabolic demand to match the poor perfusion of ischemic retina. Production of hypoxia-inducible angiogenic factors is thereby reduced and retinal neovascularization regresses.[3,4,5,6] Since photoreceptors are the most numerous and metabolically active cells in the retina (containing large numbers of mitochondria), the therapeutic effect of PRP in ischemic diseases such as proliferative diabetic retinopathy is likely achieved by the destruction of a fraction of the photoreceptors, without needing to damage the inner retina.

In conventional retinal photocoagulation, pulse durations are typically from 100 to 200 ms, laser spot diameters are from 100 to 500 μm, and powers range from 100 to 750 mW.[7,8,9] These parameters produce ophthalmoscopically visible gray-white lesions due to thermal denaturation (coagulation) of photoreceptors and the inner retina. Heat is produced by light absorption in pigmented cells, predominantly in the retinal pigment epithelium (RPE) and choroid, and subsequently diffuses into the inner retina.[10,11]

Conventional photocoagulation application, however, has significant side-effects, such as pain during treatment, permanent retinal scarring and decreased peripheral, color, and night vision.[12,13] Retinal scars can initiate infiltrative/inflammatory processes involving additional cell loss, can enlarge post-operatively,[14,15,16] and cause choroidal neovascularization,[17,18] subretinal fibrosis,[19,20,21] and additional visual field loss.[22,23,24,25,26]

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Recent evidence has shown that photocoagulation lesion size decreases over time in rodents[27] and rabbits.[28] In smaller and less intense laser lesions, migration of photoreceptors from the undamaged surrounding areas result in complete filling-in of the gap in the outer retina.[28] A similar phenomenon has been observed in snake eyes.[29]

A new method of retinal photocoagulation termed pattern scanning laser photocoagulation (PASCAL, OptiMedica Corp, Santa Clara, CA) allows for patterns of 4 to 56 burns to be applied in less than one second using a scanning laser with shorter pulse durations (10-30 ms).[30] Retinal lesions produced by this system are more confined to the RPE and photoreceptor layers.[31] In addition, due to reduced heat diffusion into the choroid, PASCAL treatment was found to be less painful than conventional laser.[32] Despite the decreased pulse duration in PASCAL (20 ms), its clinical efficacy has been shown to be equivalent to conventional photocoagulation (100 ms) in several small clinical studies.[22,33,34]

Many diseases involving the macula, such as age-related macular degeneration, diabetic macular edema, geographic atrophy, and central serous chorioretinopathy (CSC), are thought to involve dysfunction of the RPE. This suggests that RPE-specific treatments might help in these conditions, while avoiding destruction of photoreceptors.
The first RPE-selective retinal laser treatment was achieved using 5 µs argon laser pulses at 514 nm and a repetition rate of 500 Hz in rabbit eyes.[35] It has been shown that microsecond pulses can produce intracellular microbubbles around melanosomes leading to selective death of RPE cells while the surrounding retinal temperature remains sublethal.[36] Selective RPE treatment without photoreceptor damage was termed Selective Retinal Therapy (SRT). Preliminary clinical trials conducted with an Nd:YLF laser using pulse durations of 1.7 µs, have demonstrated no visual loss after the treatment, as confirmed by microperimetry.[37] SD-OCT imaging in humans has demonstrated unaffected neural retina and RPE thinning at 1 hour and normal neural retina and RPE at 1 year after SRT.[38] At energies corresponding to selective damage of the RPE, SRT does not produce an immediate ophthalmoscopically visible retinal lesion.[39]

In 2000, the first clinical study reported the efficacy of SRT in 12 patients with diabetic maculopathy, 10 patients with soft drusen, and 4 with central serous chorioretinopathy (CSC).[40] SRT has been shown in other small clinical trials to be both safe and effective in treating CSC,[41] diabetic macular edema,[42] and persistent subretinal fluid after rhegmatogenous retinal detachment repair.[43] SRT is currently being investigated for its utility in treating drusen and branch retinal vein occlusion. Preliminary results from an international multicenter trial have been reported to be quite promising among 60 patients with diabetic maculopathy and 10 patients with CSC.[44] SRT, however, requires a dedicated clinical system which entails additional cost, and such systems have not yet gained widespread acceptance in clinical practice.[45,46,47]

Microsecond exposures can also be produced with a continuous scanning laser. With appropriately high scanning speed, selective RPE damage has been recently demonstrated.[48] That system, however, used a narrow beam of 18 µm, which is unlikely to become practical for clinical application due to the difficulty of very tight focusing with a slit lamp-based optical system.

This study evaluates the possibility of using PASCAL, a clinically available scanning laser system, for selective RPE treatment in a continuous line scanning mode. We assess the safety and selectivity of the treatment at various scanning velocities and beam sizes, and assess the thresholds of ophthalmoscopic and angiographic visibility, RPE cellular viability, and rupture of Bruch's membrane. We also histologically examine the dynamics and extent of healing of the retinal lesions from 1 hour to 4 months.

2. METHODS

2.1 Scanning laser system with microsecond dwell time

The PASCAL laser system (OptiMedica Inc, Santa Clara, CA) uses a 532 nm optical radiation coupled into a multimode step index optical fiber. The exit surface of the fiber is telecentrically imaged through the scanning system onto the retina providing a variety of spot sizes with top-hat intensity profiles. At the aerial image plane of the slit lamp microscope the laser spots measured 400, 200, 100, and 60 µm in diameter, with the laser intensity transition from 10 to 90% occurring over 6 µm. Variation of the beam intensity within the top-hat area did not exceed +/- 7%. The software controlling the PASCAL system was modified for rapid scanning of the laser to achieve microsecond dwell times, with a scanning speed up to 6.6 m/s, limited by the galvanic mirror actuators.

The graphical user interface (GUI) was used to control laser parameters, including the beam diameter, laser power, scanning velocity, aiming beam intensity, line length, number of lines (1-3) in the pattern, spacing between the lines, and pattern repetition rate. Once the treatment parameters were appropriately selected, a foot pedal was used to activate the laser.

Retinal exposure duration, or beam dwell time, is defined as the beam diameter divided by the scanning velocity, and corresponds to the maximum amount of time the RPE cells are exposed to the laser light. For example, for an aerial beam diameter of 100 μm and a velocity of 6.6 m/s, the exposure duration would be 15 μs.

2.2 Retinal laser application

Thirty Dutch Belted rabbits (weight 1.5 – 2.5 kg) were used in accordance with the Association for Research in Vision and Ophthalmology Statement Regarding the Use of Animals in Ophthalmic and Vision Research, after approval from the Stanford University Animal Institutional Review Board. The rabbits were anesthetized using ketamine hydrochloride (35 mg/kg, IM), xylazine (5 mg/kg, IM), and glycopyrrolate (0.01 mg/kg, IM) administered 15 minutes before the procedure. Pupillary dilation was achieved by 1 drop each of 1% tropicamide and 2.5% phenylephrine hydrochloride. One drop of topical tetracaine 0.5% was instilled in each eye prior to treatment.

A Mainster standard retinal laser contact lens (model no. OMRA-S; Ocular Instruments, Bellevue, WA) was used to focus the laser on the rabbit fundus. Taking into account the combined magnifications of the contact lens and rabbit eye (x0.66)[49] the aerial image of 100 and 60 μm corresponded to retinal spot size of 66 and 40 μm, respectively. Using the line scanning software, line patterns were applied in either single or triple lines separated by two line diameters. Conventional, intense marker spot lesions were placed adjacent to the lines to facilitate later histological localization of the barely visible and invisible line lesions.

2.3 Retinal histology

Rabbits were sacrificed at 1 hour, 1 and 3 days, 1 and 2 weeks, and 1 and 2 months post-treatment with a lethal dose of pentobarbital and phenytoin (Beuthanasia, 150 mg/kg, IV) injected into the marginal ear vein or, in cases in which IV injection was unable to be achieved, intracardiac. Eyes were enucleated and fixed in 1.25% glutaraldehyde / 1% paraformaldehyde in cacodylate buffer at pH 7.2 overnight at room temperature. The eyes were then post-fixed in osmium tetroxide, dehydrated with a graded series of ethanol, processed with propylene oxide, embedded in an epoxy resin, and sectioned into 1 μm-thick sections. Samples were stained with toluidine blue and examined by light microscopy.[50]

Serial sections of the retina were examined, and 12 lines from 2 different animals (4 eyes) were analyzed for each of the 6 time points and scanning laser parameter settings. Lesion width was measured as the furthest extent of damage visible along the RPE-photoreceptor junction. The mean and standard deviation of these 12 numbers were calculated using Microsoft Excel.

2.4 Measurement of Visibility and Rupture Thresholds

The clinical appearance of the laser lesions were graded by a single masked observer 30 seconds after the treatment. This observer measured the threshold of ophthalmoscopic visibility and rupture. A rupture of Bruch's membrane was assumed to occur if small bubbles with or without hemorrhage appeared at the lesion site. The visibility limit was described as any faint lightening of the fundus pigmentation that corresponded with the area of laser application. ED_{50} measurements were made with a probit analysis using StatPlus (AnalystSoft, Vancouver, Canada) to calculate the thresholds in four to eight eyes for each threshold measurement.

2.5 Fluorescein angiography

Fluorescein angiography (FA) was performed immediately after placement of laser. 0.3 mL of fluorescein 10% (Fluorescite; Alcon Laboratories, Switzerland) was slowly injected over 10 seconds into the marginal ear vein as described previously.[51] Fundus photographs were taken with a Topcon TRC 50x fundus camera (Topcon, Japan) using a

Kodak Megaplus Camera, Model 1.4, operated by the Winstation imaging software (Ophthalmic Imaging Systems, Inc, Sacramento, CA). Photographs were taken starting a few seconds after the injection, and thereafter every 20 seconds for 5 minutes.

2.6 LIVE/DEAD fluorescent assay

The LIVE/DEAD Reduced Biohazard Viability/Cytotoxicity Kit #1 (Molecular Probes, Invitrogen, Carlsbad, California) was used to assess RPE cell viability. This kit uses a SYTO green fluorescent nucleic acid stain to label all cells and a DEAD Red (ethidium homodimer-2) nucleic acid stain to label only cells with compromised cell membranes. Immediately after sacrificing the animal, the eyes were enucleated and the anterior portion (lens, cornea, anterior chamber) of the eye dissected away. The vitreous was then removed, and the irradiated portion of the retina, RPE, choroid, and sclera was sectioned. The retina was then gently peeled away from the RPE, and the fluorescent stain was placed directly on the RPE. These sections were incubated in a humid chamber for 20 minutes at room temperature, whereupon they were imaged on an inverted fluorescent microscope.

3. RESULTS

3.1 Thresholds determination

The thresholds for rupture of Bruch's membrane, ophthalmoscopic and FA visibility, as well as LIVE/DEAD (LD) assay were determined for beam sizes of 40 and 66 μm and dwell times of 15 and 60 μs. Figure 1 demonstrates the appearance of the line patterns using these techniques. Patterns included 10 groups of 3 lines in each, arranged in two rows, with conventional spot marker lesions in between. Laser power increases between these 10 groups from left to right and from top to bottom. In an example shown in Figure 1A, the bottom 4 lesions from the right (numbers 7 – 10) are visible ophthalmoscopically. With FA, the bottom 5 and the top 2 lesions on the right (numbers 4 – 10) are visible (Figure 1B).

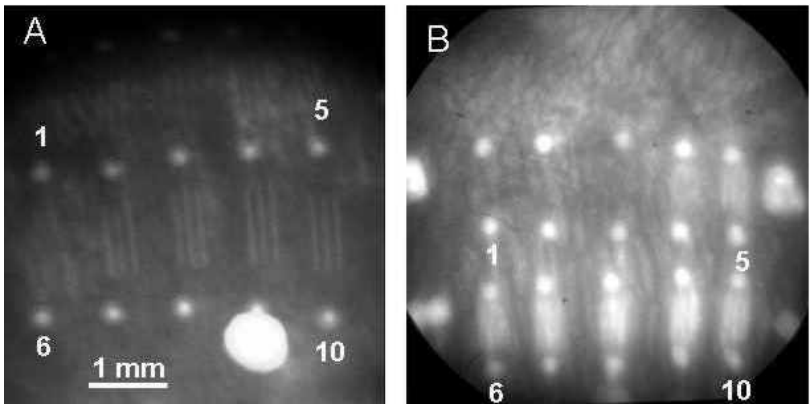

Figure 1. Determination of ophthalmoscopic visibility, angiographic visibility, and live-dead staining thresholds of the retinal lesions. Sets of three lines are placed in a grid of increasing power (from top left to bottom right) with visible marker burns to facilitate localization. Sets of lines are referred to from 1 in the top left to 10 in the bottom right. **A.** Fundus photograph showing marker burns and patterns of 3 lines applied at increasing laser power. Ophthalmoscopic visibility threshold power is at the lesion #7. **B.** FA photograph showing marker spot lesions and 2 rows of line patterns of increasing laser power. The first three sets of lesions in the top row (1-3) are angiographically invisible; lesion #4 indicates angiographic threshold.

Measured thresholds of these visibility criteria and rupture are summarized in Table 1. The threshold of RPE damage is defined as ED_{50} level of the FA visibility. The ED_{50} for LD visibility corresponded exactly with that of FA ED_{50} (data not shown). The ED_{50} level of OV corresponds to the threshold of the photoreceptor damage.

Table 1. Threshold of angiographic and ophthalmoscopic visibility and rupture: Mean and standard deviations of the ED_{50} values for angiographic visibility, ophthalmoscopic visibility,and rupture for beam sizes of 40 and 66 μm and dwell times of 15 and 60 μs.

Beam size (μm)	Dwell time (μs)	ED50 FA (mW)	ED50 ophthal (mW)	ED50 rupture (mW)	Ophthal / FA	Rupture / Ophthal	Rupture / FA
40	15	375 ± 146	1043 ± 227	2263 ± 206	3.10 ± 1.38	2.09 ± 0.13	7.16 ± 2.69
40	60	131 ± 43	216 ± 37	988 ± 48	1.81 ± 0.81	4.53 ± 0.23	7.05 ± 0.96
66	15	500 ± 122	1253 ± 205	2600 ± 200	2.58 ± 0.53	2.32 ± 0.22	5.08 ± 0.45
66	60	280 ± 67	458 ± 121	1260 ± 65	1.65 ± 0.37	2.76 ± 0.15	4.46 ± 0.25

As expected, the ED_{50} for all thresholds increases with decreasing pulse duration. Since retinal rupture is an undesirable outcome, its threshold represents an upper limit of the safe dynamic range of the retinal treatment. The ratio of the threshold power for rupture to that of FA visibility defines the safe therapeutic window of this treatment. Smaller beam size (40 μm vs 66 μm) resulted in a higher safety ratio: 7.16 vs 5.08 for 15 μs dwell time and 7.05 vs 4.46 for 60 μs dwell time ($p < 0.01$). Shorter dwell times resulted in only a slight, statistically non-significant increase in the safe dynamic range: 7.05 vs. 7.16 for a beam size of 40 μm and 4.46 vs. 5.08 for a beam size of 66 μm for dwell times of 60 μs and 15 μs, respectively.

The treatment selectivity (i.e. RPE damage with sparing of photoreceptors) can be estimated as the ratio of the thresholds of OV to FA. In contrast to the safe therapeutic window, the dwell time markedly impacts lesion selectivity. Reducing the beam size from 66 μm to 40 μm resulted in minimal increase in the OV to FA ratio from 2.58 to 3.10 for 15 μs dwell time and from 1.65 to 1.81 for 60 μs dwell time. However, reducing dwell time from 60 to 15 μs resulted in a significant increase in the treatment selectivity, from 1.81 to 3.10 for 40 μm lesion size and from 1.65 to 2.58 for 66 μm lesion size ($p < 0.01$).

Increasing the number of repetitions of the scan to 10 or 100 did not improve the safety window or the treatment selectivity (data not shown).

3.2 Healing of retinal line lesions

Healing of retinal lesions produced by line scanning laser with microsecond exposures was followed over 2 months for both combinations of dwell times and beam sizes at three laser intensities. Representative lesions are shown in Figures 2 - 5.

In ophthalmoscopically invisible lesions at 1 day, RPE cells appear collapsed, and outer segments appear hyperpigmented and increased in density (Figures 2 and 3). There is no evidence of photoreceptor or nuclear loss. At 3 days both above the original lesion and also in the adjacent initially unaffected areas, the outer segments appear in an oblique orientation, edema exist between outer segments and RPE, and the outer segment thickness shows marked variability. At 3 days, there is no evidence of photoreceptor death and nuclear loss for ophthalmoscopically invisible lesions (Figure 2), whereas this is noted for visible lesions (Figure 4). The average width of these ophthalmoscopically invisible lesions at 3 days was 118 μm (SD 9.5 μm), which is twice the width of the laser beam. Photoreceptors regain their normal morphology by 1 week (Figure 2).

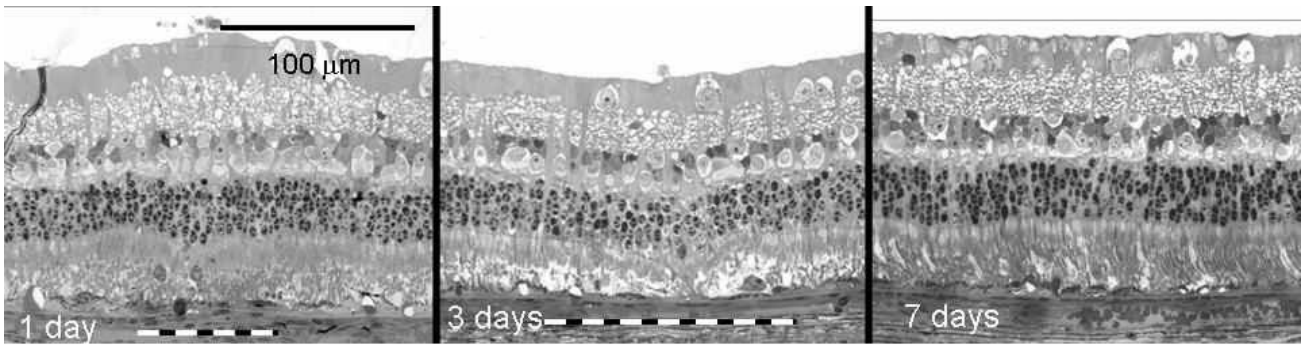

Figure 2. RPE-selective treatment in clinically invisible lesion at 1 day, 3 days, and 7 days after treatment. Beam diameter 66 μm, dwell time 15 μs, power 1100 mW. All fundus photographs were taken with a 20x microscope objective. One day demonstrates RPE cell collapse and outer segment hyperpigmentation and increased density. At three days, damage to the outer segments expands to a width twice that of the laser beam and initial lesion size with edema between the outer segments and RPE. By 1 week, the RPE defect and the damage to the outer segments has largely resolved.

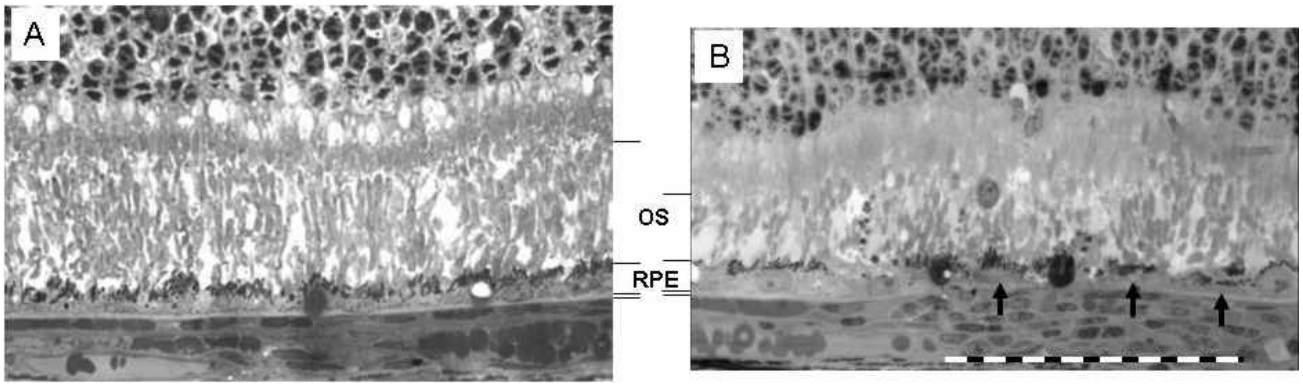

Figure 3. Clinically invisible lesion at higher magnification (40x). **A.** Untreated retina demonstrating normal RPE-photoreceptor architecture. **B.** Retina at 1 day after laser treatment (clinically invisible, beam diameter 66 μm, 15 μs, 1100 mW). RPE cells collapse (black arrows) at the site of laser application (white and black dotted line), and outer segments above them appear hyperpigmented with increased density.

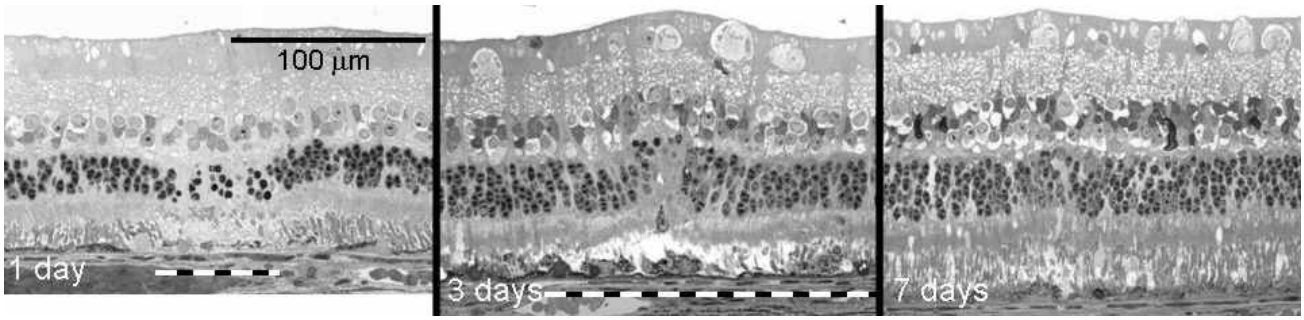

Figure 4. Resolution of photoreceptor damage in the visible lesions. Dwell time 60 μs, laser power 1000 mW, a single 66 μm line. Black, dotted bar indicates the extent of abnormal zone at the RPE-photoreceptor junction. Cellular loss is evident at 1 day in the outer nuclear layer (ONL). The extent of nuclear drop-out decreases at 3 days within the lesion, although the photoreceptor-RPE junction shows a widening of the area of disturbed anatomy demonstrated loss of the vertical orientation of outer segments, edema between the inner and outer segments, and marked variability of the inner and outer segment thickness. At 7 days, a complete restoration of normal anatomy returns to both the outer nuclear layer and outer segments.

Visible lesions were associated with photoreceptor death within one day of treatment (Figures 4 and 5). These lesions exhibited cellular loss at 1 day, with pyknosis and reduced numbers of nuclei in the outer nuclear layer (ONL), hypopigmentation of the inner and outer segments, hyperpigmented round foci at the inner segment/outer segment junction, oblique orientation of the outer segments, and some edema between the RPE and photoreceptors. The inner retina was well-preserved at all time periods. In the single line lesion (Figure 4) damage in the ONL decreases at 3 days

and resolves by 7 days. However, the abnormality at the photoreceptor-RPE junction widens significantly at 3 days compared to the initial lesion width, and then resolves by 7 days.

Placement of three adjacent line lesions separated by 2 beam diameters altered the healing dynamics remarkably (Figure 5). At 1 day, these lesions exhibited findings typical of single line lesions described above; i.e., pyknosis and reduced numbers of nuclei in the ONL, minor displacement of the ONL into the PR inner segments, slight edema and retinal thickening at the site of the laser patterns. At 3 days, however, a dramatic change is noted in the surrounding photoreceptor regions: the vertical orientation of the outer segments is replaced with a haphazard arrangement, edema exists between inner and outer segments, and inner and outer segment thickness shows marked variability. At the laser sites, the lesions show minimal pyknosis and greatly reduced numbers of nuclei in the ONL, increased displacement of the ONL into the PR inner segments, edema, and retinal thickening. By 2 weeks, continuity of the ONL and photoreceptor anatomy is restored. Small patches of RPE hypertrophy persist at 2 months (Figure 5, arrows), but relatively normal anatomy of the outer segments is restored. In addition, density of the inner and outer segments layers and ONL appears decreased both within the region of laser exposure and in the surrounding 120 μm.

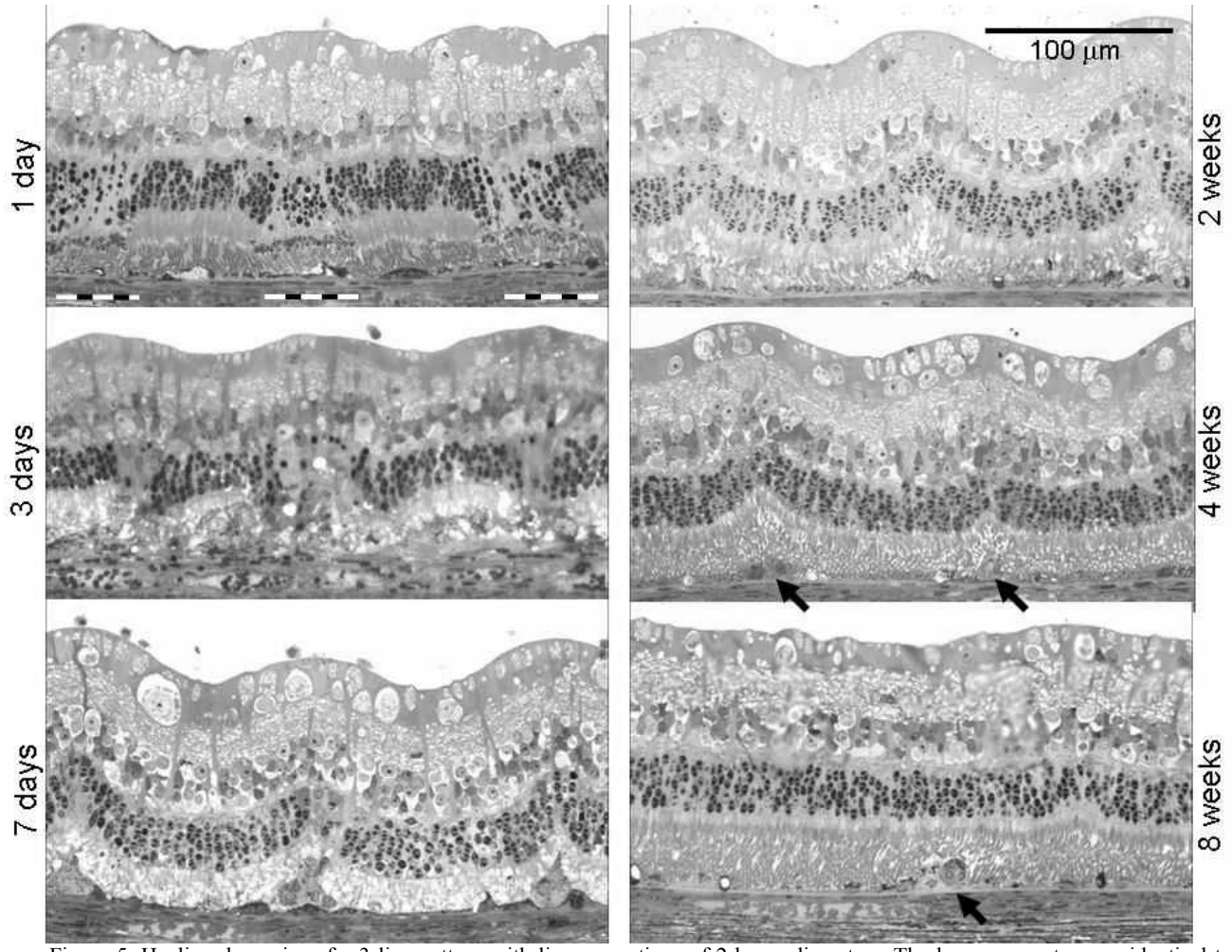

Figure 5. Healing dynamics of a 3-line pattern with line separations of 2 beam diameters. The laser parameters are identical to Figure 4. At one day there is pyknosis and nuclear drop out in the ONL. At 3 days, a dramatic change in normal anatomy is noted in the surrounding photoreceptor regions. By 2 weeks, nuclear continuity and photoreceptor anatomy are largely restored. The retina flattens by 2 months, while some RPE hypertrophy persists (black arrow).

4. DISCUSSION

RPE dysfunction occurs in several macular diseases, including age-related macular degeneration, diabetic macular edema, geographic atrophy, and CSC. This suggests a need for RPE-specific therapies, which SRT can achieve with microsecond pulses or the rapid scanning of a continuous laser.[52,53]

We find that 15 and 60 microsecond retinal exposures produced by line scanning mode of the PASCAL™ laser selectively damages the RPE at lower power and also photoreceptors at higher power. Decreasing dwell time (increasing scanning speed) results in improved selectivity of the RPE damage. We find that a single line scanning approach (i.e. no repetitive scanning) provides a sufficiently large safety window of 4.5 – 7.2. For comparison, safe therapeutic window of conventional photocoagulation with 100 ms pulses is approximately 4.[31]

The dynamic range increased for decreasing exposure duration and also for decreasing lesion width. For our beam sizes (40 and 66 μm) and pulse durations (15 and 60 μs), reducing the beam diameter was the most efficient means to increase the therapeutic window. In contrast, selectivity of RPE treatment, as determined by the ratio of OV to FA, was improved more by decreasing the dwell time.

Even if the threshold of ophthalmic visibility is exceeded, only relatively mild photoreceptor damage appears, and it resolves without retinal scarring within 1 week. While lesions resulting from the dense patterns of three lines healed slower – perhaps due to more limited capacity of adjacent photoreceptors to migrate into lesions – by 2 months photoreceptor continuity was restored in all cases, without scarring. These findings suggest that if the threshold of photoreceptor damage were inadvertently exceeded (e.g., due to pigmentation variation), permanent scars or scotomas would not ensue. This added safety is an attractive feature of microsecond laser for clinical use in the macula.

At 3 days after visible burn formation, mild abnormalities appear in the photoreceptor outer segments beyond the zone of RPE damage (Figure 4). This secondary effect of detaching and shortening of the outer segments from the underlying RPE may be due to proliferation and migration of surrounding RPE cells to restore continuity to the damaged area, which has been demonstrated to occur within one week.[28] Redistribution of the photoreceptors by lateral migration from the unaffected areas into the damage zone restores continuity of the photoreceptor layer, with ONL cell density slightly reduced adjacent to the lesions, as we observed. This rearrangement and depletion of photoreceptors is even more evident in dense patterns of multiple lines, as shown in Figure 5.

In contrast to a previous study by Framme *et al*,[44] we do not find that multiple scans improve the safety or selectivity of the treatment. This difference could be due to the greater role of thermal diffusion and heat accumulation in our approach since it involves larger beam size (40 and 66 μm vs 18 μm) and longer exposures (15 and 60 μs vs. 7.5 μs).

Selective treatment of RPE using a line scanning laser is a promising new modality characterized by enhanced selectivity and lack of permanent retinal structural sequelae. These features are particularly desirable when considering macular therapy. Moreover, a high beam velocity enables rapid treatment of relatively large retinal areas. For example, with a beam size of 60 μm, a 15 μs exposure time is achieved with a scanning velocity of 4 m/s. At such speed 24 mm^2 can be treated within 100 ms. For comparison, the total coagulated area using the modified ETDRS or mild macular grid photocoagulation does not exceed 6 mm^2.[54] The entire macula can be treated with a line scanning laser within a time shorter than a single conventional exposure. PASCAL™ laser units, already in widespread clinical use, can be equipped with the line scanning software to provide such treatment.

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employee of OptiMedica Corporation. DP holds a Stanford University patent on patterned scanning laser photocoagulation licensed to OptiMedica Corporation with an associated equity and royalty interest and serves as a consultant for OptiMedica Corporation.

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