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(54) Title: RETINAL REJUVENATION LASER

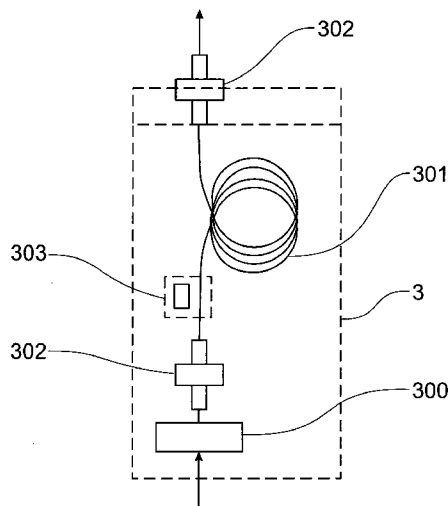


FIG. 3

(57) Abstract: A laser treatment device for use in retinal regeneration. The laser treatment device includes a laser module that delivers a pulse or sequence of pulses having a pulse duration in the range of 50ps to 500ns, a wavelength in the range 500nm to 900nm, and a pulse energy in the range 10μJ to 10mJ. The laser treatment device also includes a uniform irradiance module that modifies an output beam profile of the laser module to produce a uniform treatment effect and a beam delivery and viewing module that delivers the laser pulse or pulses to the retina with a radiant exposure in the range of 8mJ/cm² to 8000mJ/cm² per pulse.

WO 2008/144828 A1

TITLERETINAL REJUVENATION LASERFIELD OF THE INVENTION

This invention relates to a laser treatment device useful for improving
5 the function of the retina of the human eye. This invention may be
beneficially used in the treatment of eye diseases, such as early Age-related
Macular Degeneration (AMD) in which the function of Bruch's membrane has
become impaired as part of a disease pathogenesis, or the treatment of
degradation related to aging.

10 BACKGROUND TO THE INVENTION

The light sensing and signaling processes of the human retina require
a high level of support in terms of energy supply and waste removal to
ensure optimal functionality. A monolayer of epithelial cells, known as the
retinal pigmented epithelium (RPE) separates the light sensing and signaling
15 processes from the blood supply of the choroid and it controls many bi-
directional support functions. The RPE cells are attached to a basement
membrane, known as Bruch's membrane, which is a thin extra-cellular matrix
of collagen layers which act as a semi-permeable barrier between the RPE
cells and blood vessels of the choroid. The work of Marshall, Hussain, Guo
20 and Ahir, [Expression of Matalloproteinases from human retinal pigment
epithelial cells and their effects on the hydraulic conductivity of Bruch's
Membrane, Invest Ophthalmol Vis Sci. 2002 Feb;43(2):458-65] has shown
that degradation of the transport functions of Bruch's membrane is a major
contributor to loss or decline in visual function with normal aging or a more

rapid decline due to diseases such as age-related macular degeneration (AMD). Although these transport functions begin to degrade from birth, serious vision loss may not occur until later in life when the RPE/Bruch's membrane/choroid complex degrades to a point at which it can no longer sustain the neuro-retina, resulting in atrophy of the neuro-retina or stress induced responses such as choroidal new vessel (CNV) growth.

Although changes in diet and environment have been recommended to reduce the rate of age related loss of visual acuity, no direct treatment for the retina exists, and almost all current treatments for AMD are focused on treating late stage complications such as CNV's. Current treatments for CNV's include photo-dynamic therapy (PDT) (as described in United States patent number 5756541 assigned to QLT Phototherapeutics Inc) where a photosensitive drug is administered intravenously and then activated by a light source which is directed at the CNV, and intra-vitreous injections of drugs which inhibit the growth factors which promote new blood vessel growth (anti-VEGF).

Lasers have been used for many years to treat retinal disorders, predominately using their ability to coagulate tissue. The degree of laser energy absorption in retinal layers and structures is highly dependant on the wavelength used and one of the major absorbing chromophores within the retina is the melanin which pigments the RPE cells. Although the current retinal lasers use wavelengths that are strongly absorbed by the melanin of the RPE cells, the duration of the laser pulses which are currently used allows time for thermal diffusion from the RPE cells to adjacent structures

and is particularly damaging to the neuro-retina resulting in permanent loss of visual function at the treatment site. Roider, Norman, Michaud, Thomas, Flotte and Birngruber [Response of the Retinal Pigment Epithelium to Selective Photocoagulation Arch Ophthalmology Vol 110, December 1992] describe that short duration laser pulses can be used to contain the energy within the RPE cells and prevent neuro-retinal damage, using a technique known as selective retinal therapy (SRT). SRT has been applied to a number of late stage retinal diseases with the aim of producing a therapeutic benefit by initiating a wound healing response at the level of the RPE, but with limited success, and the reason why a beneficial effect can be obtained in this way has not been explained.

The SRT method is well described in United States patent application 20040039378 by Lin in which a laser scanning device is used to provide very short irradiance times. While this patent describes the requirement for nanosecond duration exposures it is difficult to achieve the required radiant exposure level using the scanning method described.

OBJECT OF THE INVENTION

It is an object of this invention to provide a laser device to improve the function of the retina of the human eye.

Further objects will be evident from the following description.

DISCLOSURE OF THE INVENTION

In one form, although it need not be the only or indeed the broadest form, the invention resides in a laser treatment device for improving the function of the retina of the human eye comprising:

a **laser module** producing a laser pulse or sequence of laser pulses each having:

a pulse duration in the range of 50ps to 500ns;

a wavelength in the range 500nm to 900nm; and

5 a pulse energy in the range 10μJ to 10mJ;

a **uniform irradiance module** that modifies an output beam profile of the laser module to produce a uniform treatment effect; and

a **beam delivery and viewing module** that delivers the laser pulse or pulses to the retina with a radiant exposure in the range of 8mJ/cm² to
10 8000mJ/cm² per pulse.

Preferably the pulse duration is around 3ns. The wavelength is suitably about 532nm.

The radiant exposure is preferably in the range 20mJ/cm² to 300mJ/cm² per pulse.

15 The laser system is suitable for performing the method of retinal rejuvenation described in our co-pending international patent application number PCT/AU2007/001622.

BRIEF DETAILS OF THE DRAWINGS

To assist in understanding the invention preferred embodiments will
20 now be described with reference to the following figures in which:

FIG 1 is a block diagram of retinal rejuvenation laser;

FIG 2 is a block diagram of a laser module of the retinal rejuvenation laser of FIG 1;

FIG 3 is a block diagram of a uniform irradiance module of the retinal rejuvenation laser of FIG 1;

FIG 4 is a block diagram of a beam delivery and viewing module of the retinal rejuvenation laser of FIG 1;

5 FIG 5 shows the energy distribution profile of laser pulses applied to an aluminium target;

FIG 6 shows the energy distribution profile of the same laser after passing through a uniform irradiance module; and

FIG 7 is a diagrammatic representation of the effect of firing multiple
10 laser pulses with different speckle patterns onto the same target zone.

DETAILED DESCRIPTION OF THE DRAWINGS

In describing different embodiments of the present invention common reference numerals are used to describe like features.

Referring to FIG 1 there is shown a block diagram of a retinal
15 rejuvenation laser 1. The retinal rejuvenation laser 1 consists of a laser module 2 (described in more detail by reference to FIG 2), a uniform irradiance module 3 (described in more detail with reference to FIG 3), and a beam delivery and viewing module 4 (described in more detail with reference to FIG 4). A laser beam 5 is generated by the laser module 2, manipulated
20 for uniform irradiance by the uniform irradiance module 3 and directed to the eye 6 of a patient by the beam delivery and viewing module 4. The beam delivery and viewing module 4 incorporates a coincident viewing path for an operator 7.

Referring now to FIG 2, the preferred embodiment of the retinal rejuvenation laser 1 utilises a Q-switched flashlamp-pumped Nd:YAG laser producing nominally 1064nm laser pulses. The laser cavity 200 is of conventional design having a 100% reflecting end mirror 201 and a partial reflecting output coupler 202. The laser rod 203 is excited by a flashlamp 204 that is energized by a high voltage power supply 205. A passive Q-switch 206 allows the cavity energy to be delivered as very short, high energy pulses. The laser output is converted to about 532nm by a suitable frequency doubling crystal 207.

It will be appreciated that the specific wavelength of the laser output is determined by the laser medium and the optical arrangement. In a preferred embodiment the laser output is nominally 532nm but the actual wavelength may not be exactly 532nm.

Although a flashlamp pumped Nd:YAG laser is the preferred embodiment for the laser cavity the invention is not limited to this particular cavity design. Any laser cavity capable of producing pulses in the 50ps to 500ns range with a wavelength between about 500nm and about 900nm and pulse energy of around 10 μ J to 10mJ will be suitable. This includes other solid stated materials such as Er:YAG, Nd:YLF and Er:YLF. Other elements may also be varied. For instance, an active Q-switch may be used instead of a passive Q-switch.

The beam is directed to an optical attenuator 208 formed from a half wave plate 209 and polarizing optic 210. The optical attenuator allows fine control of the energy delivered from the laser module 2 by rotation of the

half-wave plate 209. The laser module 2 also includes a beam combining optic 211 that combines the output from an aiming laser 212 into the same path as the laser module output (so that the treatment laser beam and the aiming laser beam are co-axial).

5 The treatment laser beam output from the laser module 2 has a non-uniform and slightly variable energy distribution profile. If this was directly used to irradiate a target treatment zone some areas would receive lower radiant intensity while others would receive higher radiant energy. This is demonstrated below with reference to FIG 5 and FIG 6. To address this
10 problem the treatment laser beam and aiming laser beam are directed to the uniform irradiance module 3. The uniform irradiance module 3 includes a fiber focus lens 300 that focuses the treatment laser and aiming laser beams into an optical fiber 301. Each end of the optical fibre 301 is terminated in a movable fitting 302 that facilitates accurate alignment.

15 When laser light is directed through an optical fibre, interference between propagation modes can result in a granular spatial distribution of the laser energy at the output which is referred to as speckle. By passing the output of the pulsed laser through an optical fiber as shown in FIG 3 the structure of the energy distribution profile going into the fiber will be lost due
20 to multiple internal reflections along the length of the optical fiber, resulting in a speckle profile at the fiber output. A single pulse such as this can be used for treatment with some areas between the peaks of the speckle pattern receiving low radiant intensity, resulting in a uniform but patchy treatment effect.

However, because the laser has some variability in the energy distribution profile, by producing another pulse which can be directed to the same target treatment zone a different speckle pattern will be produced by the optical fiber. Because of the random nature of the speckle patterns produced by each laser pulse, many of the peaks within the speckle pattern of the second pulse will occur in areas where low irradiance occurred on the first pulse, resulting in improved coverage of the target treatment zone. Subsequent laser pulses directed to the same target treatment zone will further improve the coverage, with successive pulses producing statistically less improvement as the coverage approaches 100%.

By selecting the number of laser pulses with speckle pattern which are delivered it is therefore possible to produce a uniform treatment effect but with a selected coverage of the target treatment zone. The granularity of the laser speckle can also be varied by using optical fibres with different optical characteristics, such as numerical aperture. Selection of coverage of the target treatment zone and speckle granularity, in conjunction with the laser treatment spot size, may be used to optimize the wound healing response and therapeutic benefit. Preferably the number of pulses is within the range of 1 to 5 and the numerical aperture of the fibre is within the range of 0.1 to 0.35.

In a further embodiment of the invention, where the pulsed laser has a non-uniform but stable energy distribution profile, or to improve the probability of different speckle patterns being produced by each pulse, the device can include an optical fiber vibrator 303. The vibrator 303 can be in

the form of a small motor mechanically coupled to the fiber as shown in FIG 3, with an offset shaft load to cause the vibration or alternatively a piezo-electric transducer may be used in the same way. A small amount of continually variable lateral or angular displacement is induced into the fiber by the vibrating means which alters the internal reflections within the fiber and continually alters the speckle pattern. The pulse repetition rate must be low enough to allow sufficient movement of the fiber, by the vibrating means, to produce a randomly different speckle pattern. In the case of a flashlamp pumped laser cavity this pulse repetition rate may be achieved by charging multiple discharge capacitors and then discharging them individually through the flashlamp by means of an electronic switching and control system. For example, a motor with an offset shaft load running asynchronously at 10,000 RPM would produce one shaft rotation approximately every 6ms, so a pulse repetition rate of about 33Hz or less would ensure a different speckle pattern with each pulse.

Vibration of the optical fiber has the added advantage of greatly reducing the speckle pattern of a co-axial aiming laser, traveling through the same optical fiber as the treatment laser beam, thereby improving usability.

The output from the uniform irradiance module 3 is directed to the beam delivery and viewing module 4, shown in FIG 4. The beam delivery and viewing module 4 consists of an optical zoom module 400 that sizes and focuses the treatment laser beam 401 through an objective lens 402 to the retina 403 of the eye 6 of a patient. A contact lens 404 on the cornea 405 of the eye 6 is conventionally used to counteract the cornea and lens of the eye

in the optical path. A binocular viewing microscope 408 is commonly used. A folding mirror 406 is reflective at the wavelength of the treatment laser beam 401 and the aiming laser beam 407 and is situated between the binocular viewing paths. A safety filter 409 protects the user from back scattered laser radiation.

The optical zoom module 400 can be preset to image the optical fibre output onto the retina via the contact lens, or it can be made adjustable to allow treatment spot size selection.

As mentioned above, the output from the laser module 2 is a beam with a non-uniform energy distribution profile. This is shown in FIG 5. The energy distribution profile of a 3ns passively Q-switched, flashlamp pumped Nd:YAG laser pulse is applied to a painted aluminium target to display the non-uniform profile. The target treatment zone is indicated by a circle 50. The damage caused at the target zone for one, two, three, four and five pulses is shown sequentially with the damage from a single pulse shown at the top and at the bottom the damage after five pulses delivered to the same target zone. It can be seen that after five pulses are delivered the target zone approximately 50% of the area has still not been affected.

When the target is a pigmented epithelial cell layer the result will be that a portion of the cells will not receive the full radiant intensity, and even if the energy profile varies slightly with each pulse, applying more pulses to the same area will not greatly improve the coverage.

FIG 6 shows the same result for one, two and three pulses after the laser treatment beam has been passed through the uniform irradiance

module 3 and the beam delivery and viewing module 4. Again the target treatment zone is shown by circle 50. The top image is the damage caused by a single pulse. The second image shows the damage caused by three pulses delivered to the same target area at a high repetition rate but without vibration of the optical fibre. The bottom image is the damage caused by five pulses delivered to the same target zone with lower repetition rate and vibration of the optical fibre, showing that almost 100% of the treatment zone has been affected. The shots are manually controlled to ensure the repetition rate is low compared to the rate of vibration of the fibre.

FIG 7 is a diagrammatic representation of multiple laser pulses (71-74) with different speckle patterns being fired at a common target treatment zone 50 to further explain the image in FIG 6. The speckle pattern peaks are depicted by dark spots 75. The cumulative effect of laser pulses 71 and 72 is shown at 76. The addition of laser pulse 73 results in the image 77 and the addition of laser pulse 74 results in image 78. It can be seen that the cumulative effect of different speckle pattern peaks on each successive pulse results in increasing coverage of the treatment zone, allowing the degree of coverage to be determined by the number of pulses delivered to the target treatment zone.

When this technique is applied to the treatment of pigmented cell layers such as the RPE of the human eye the pulse separation can be chosen so that there is no additive effect between pulses, so peaks in the speckle pattern that occur in the same position on subsequent pulses do not cause an increased treatment effect in those areas. For example, if a 3ns

laser pulse duration and 1kHz pulse repetition rate is used, no additive thermal effect will occur with multiple pulses. If a passively Q-switched, flashlamp pumped laser is used as shown in Fig 2, multiple pulses may be obtained by increasing the energy which is discharged through the flashlamp, or by charging multiple discharge capacitors and then discharging them individually through the flashlamp by means of an electronic switching and control system.

By using pulse durations within the 50ps to 500ns range RPE cells can be killed or altered by explosive bubble formation around melanosomes within the cells and thermal effects are fully contained within the cells, preventing collateral damage to surrounding cells or structures. At pulse lengths less than about 50 picoseconds the laser pulse is so short that all the pulse energy is deposited in less than the time required for an acoustic wave to traverse the optical path causing mechanical damage such as photodisruption along the beam path. At pulse durations longer than about 500 nanoseconds it may not be possible to fully contain the thermal effects within the cells, particularly where melanosomes are congregated around the interface with the photoreceptors, which could result in permanent damage to the RPE/photoreceptor interface.

The retinal rejuvenation laser described may be used to improve the function of the retina of the human eye in the following manner. A variety of diagnostic techniques can be applied, depending on the retinal disease that is being treated, to select patients that are suitable for the laser treatment and to determine the laser treatment areas. For example, for diabetic

macular edema it is useful to use scanning laser ophthalmoscopy and optical coherence tomography to identify the region of edema, while for early AMD dark adaptation tests and autofluorescence imaging can be used to identify compromised retinal function.

5 As this technique relies on the migration and division of RPE cells it is important to treat areas where RPE cells are healthy, rather than targeting areas where poor retinal function is identified. For example, if autofluorescence imaging identified an area of hyperfluorescence, indicating compromised RPE function, laser treatment would be carried out on the
10 periphery of the area, rather than the center.

 A 1X Mainster Retinal Contact Lens, or similar, would then be applied to the patients eye. An energy of approximately 0.1mJ would be selected and a retinal treatment spot size of approximately 400 micron selected. The laser would be fired around the treatment area, with the treatment spots spaced
15 apart by approximately half a spot diameter. Energy can be incrementally titrated to just below the visible bubble formation threshold. The number of laser pulses delivered to each target treatment zone can be selected to provide the best therapeutic outcomes and optimum wound healing response.

20 The inventors envisage that the retinal rejuvenation laser will be useful for a wide range of procedures. The foregoing description is offered as an example of the use of the laser and is not meant to suggest that the use of the laser is limited to this procedure. Persons skilled in the field will be aware of specific optical elements that may be substituted for one or more of the

elements described for the preferred embodiment without departing from the spirit and scope of the invention. Throughout the specification the aim has been to describe the invention without limiting the invention to any one particular combination of preferred features or embodiment.

CLAIMS

1. A laser treatment device comprising:
a laser module producing a laser pulse or sequence of laser pulses
each having:
 - 5 a pulse duration in the range of 50ps to 500ns;
 - a wavelength in the range 500nm to 900nm; and
 - a pulse energy in the range 10μJ to 10mJ;
a uniform irradiance module that modifies an output beam profile of
the laser module to produce a uniform treatment effect; and
- 10 a beam delivery and viewing module that delivers the laser pulse or
pulses to the retina with a radiant exposure in the range of 8mJ/cm² to
8000mJ/cm² per pulse.
2. The laser treatment device of claim 1 wherein the laser module
produces from 1 to 5 laser pulses.
- 15 3. The laser treatment device of claim 1 wherein the laser module
produces 3 pulses.
4. The laser treatment device of any preceding claim wherein pulse
duration is around 3ns.
5. The laser treatment device of any preceding claim wherein the laser
- 20 module comprises a Q-switched solid state laser.
6. The laser treatment device of any preceding claim further comprising
a frequency doubling crystal.
7. The laser treatment device of any preceding claim wherein the
wavelength is about 532nm.

8. The laser treatment device of any preceding claim producing a radiant exposure in the range $20\text{mJ}/\text{cm}^2$ to $300\text{mJ}/\text{cm}^2$ per pulse.
9. The laser treatment device of any preceding claim wherein the laser module contains an optical attenuator.
- 5 10. The laser treatment device of claim 9 wherein the optical attenuator comprises a half wave plate and a polarizing optic.
11. The laser treatment device of any preceding claim wherein the uniform irradiance module comprises an optical fibre.
12. The laser treatment device of claim 11 wherein the optical fibre has a
10 numerical aperture in the range 0.1 to 0.35.
13. The laser treatment device of claim 11 wherein the uniform irradiance module further comprises an optical fibre vibrator.
14. The laser treatment device of claim 11 wherein the uniform irradiance module further comprises a motor with an offset load shaft that mechanically
15 vibrates the optical fibre.
15. The laser treatment device of any preceding claim wherein the beam delivery and viewing module includes an optical zoom module.

1 / 5

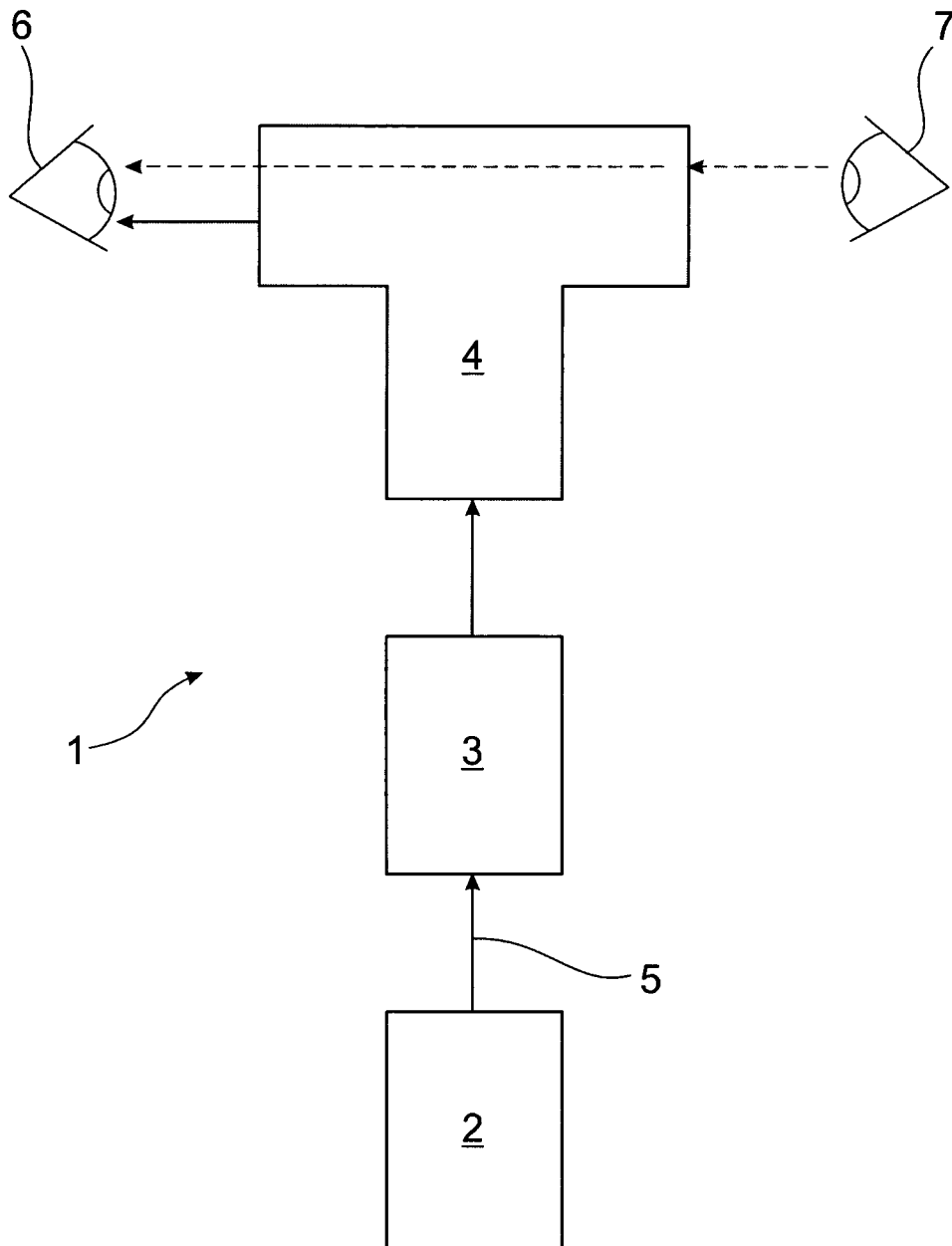


FIG. 1

2 / 5

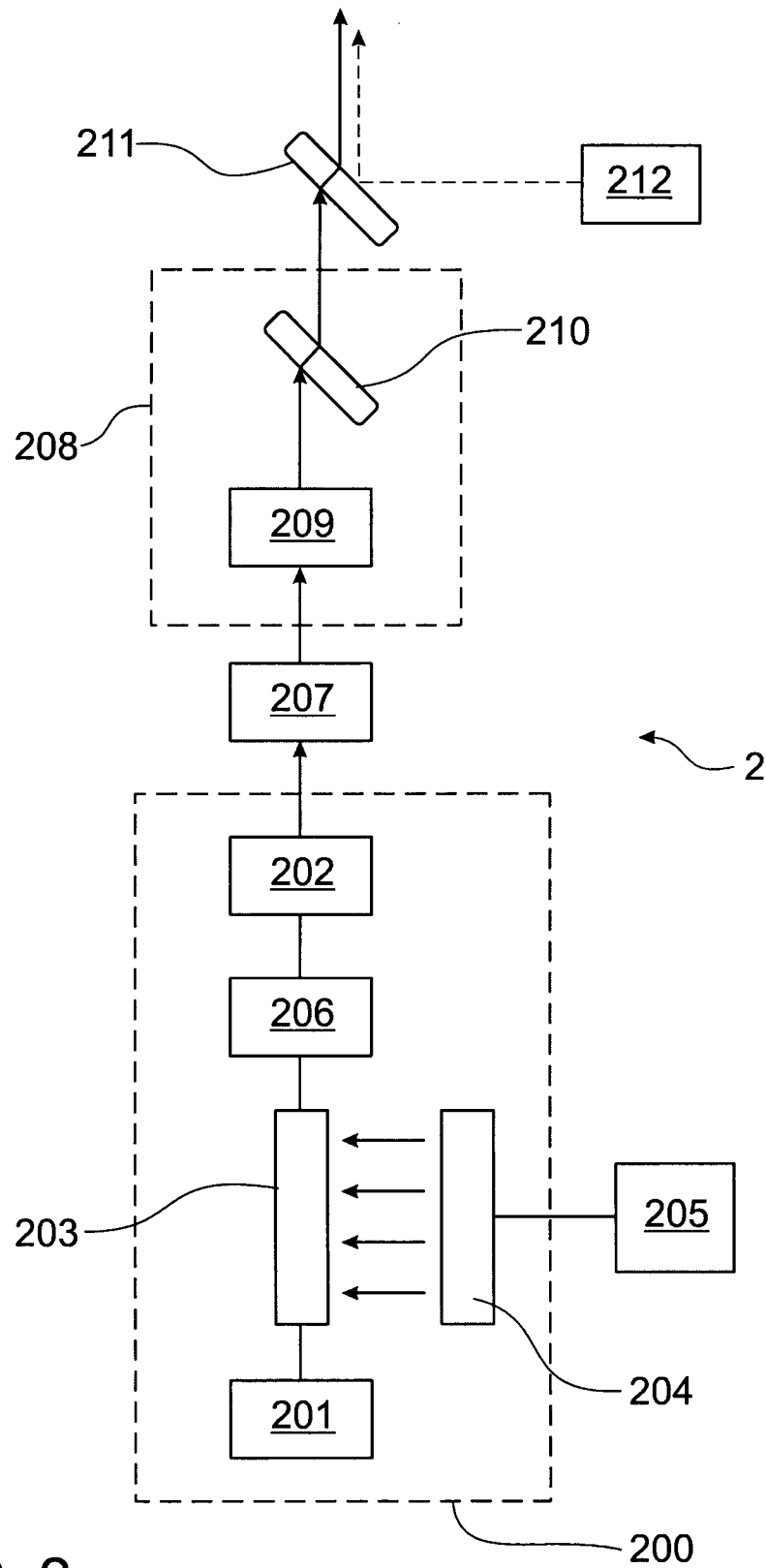


FIG. 2

3 / 5

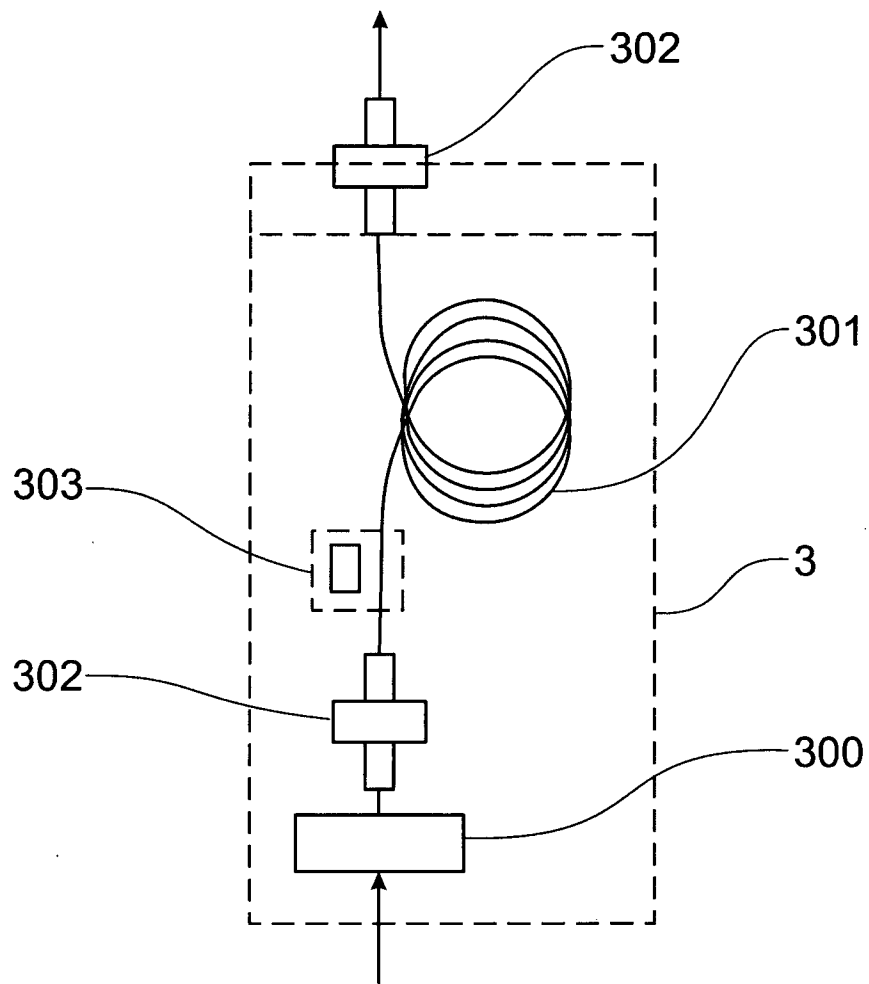


FIG. 3

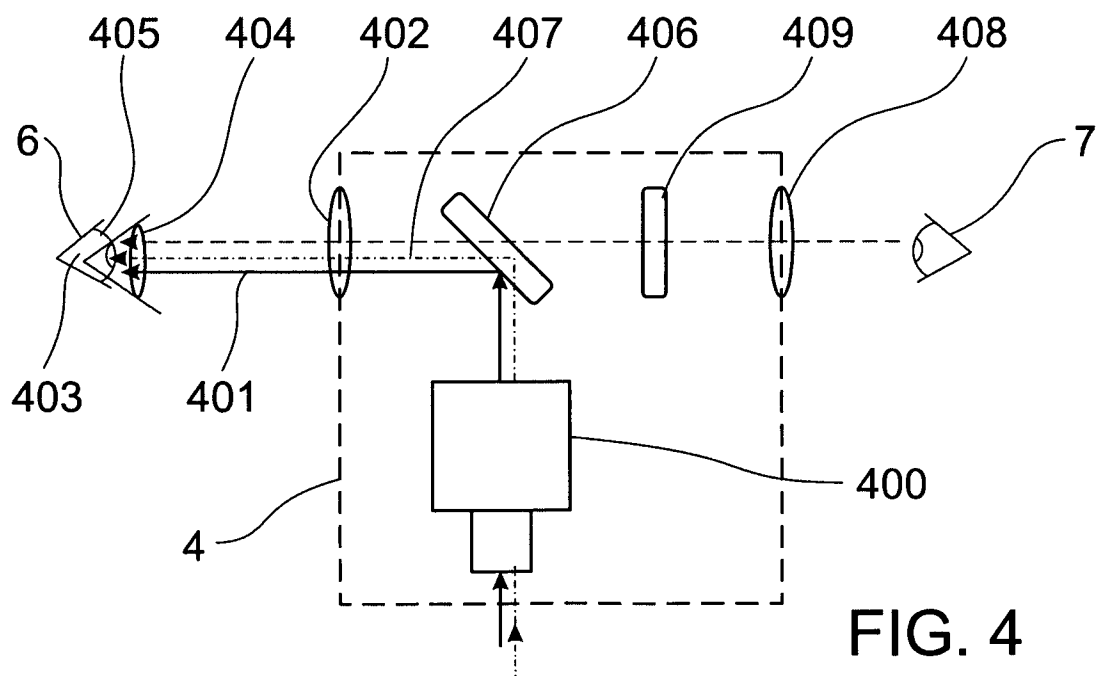


FIG. 4

4 / 5

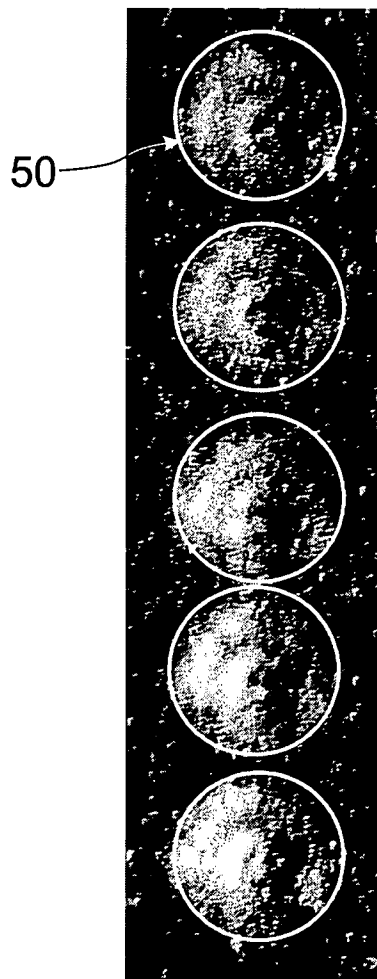


FIG. 5

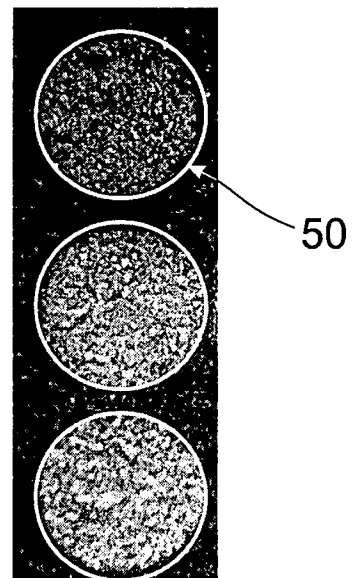


FIG. 6

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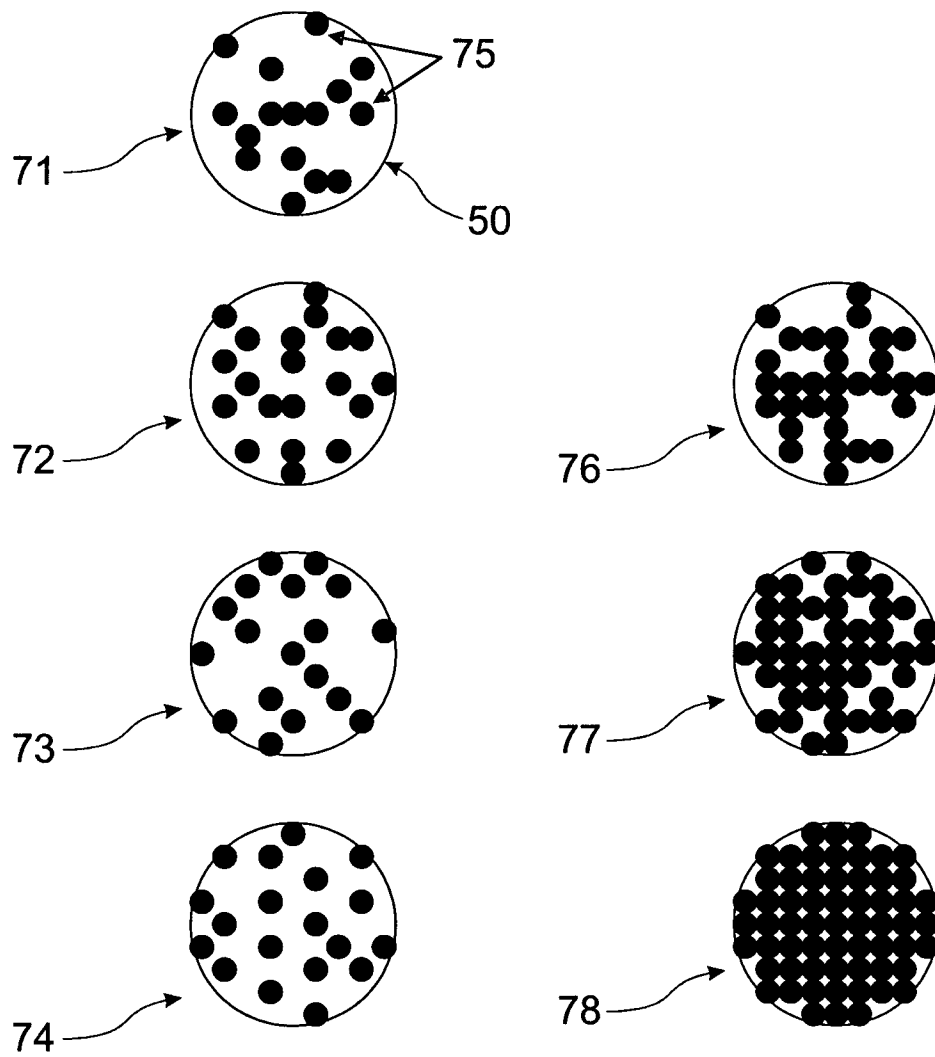


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000763

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. A61F 9/008 (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) DWPI. IPC: A61F and keywords: laser, retina, macula, rejuvenate, uniform, consistent and similar words.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5549596 A (LATINA) 27 August 1996 See whole document especially: Column 2 lines 5-6, 9-10 and Column 4 lines 54-57	1-15
Y	US 2005/0027288 A1 (OYAGI et al) 3 February 2005 See whole document.	1-15
A	US 2006/0111697 A1 (BRINKMANN et al.) 25 May 2006 Whole document	1-15
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Date of the actual completion of the international search 15 August 2008		Date of mailing of the international search report 28 AUG 2008
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. +61 2 6283 7999		Authorized officer C FLORES AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 7964

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2008/000763

C (Continuation).

DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US.2003/0179344 A1 (VAN DE VELDE) 25 September 2003 Whole document	1-15
A	US 6671043 B1 (HUETTMAN) 30 December 2003 Whole document	1-15

INTERNATIONAL SEARCH REPORT

International application No.
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		EP	1226150	EP	1887082
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	US	2005184619	US	2007197949	US	2007238835	
	US	2008019465	WO	0129056	WO	9509898	
	WO	9513851	WO	9600118	WO	9814133	
	WO	9942120					
US	2006111697	AU	2004257388	CA	2532233	DE	10331792
		EP	1643924	WO	2005007002		
US	2003179344	EP	0973432	EP	1082048	EP	1194066
		EP	1562468	US	5892569	US	5923399
		US	5943117	US	6186628	US	6789900
		US	7374287	US	2006176448	WO	0071019
		WO	9822016	WO	9958047	WO	2004043234
US	6671043	DE	19932477				
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.							
END OF ANNEX							