(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2017 (26.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/015676 A1

(51) International Patent Classification:
A61N 5/06 (2006.01) *A61B 18/22* (2006.01)
A61B 18/00 (2006.01) *A61N 5/00* (2006.01)
A61B 18/20 (2006.01)

(21) International Application Number:
PCT/US2016/043957

(22) International Filing Date:
25 July 2016 (25.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/196,198 23 July 2015 (23.07.2015) US

(71) Applicant: **HEALTH RESEARCH, INC.** [US/US]; Elm and Carlton Streets, Buffalo, NY 14263 (US).

(72) Inventors: **SHAFIRSTEIN, Gal**; 30 Pennington Court, Amherst, NY 14228 (US). **WRAZEN, Brian**; 43 Lehigh Street, Cheektowaga, NY 14206 (US). **BELLNIER, David, A.**; 62 Allenhurst Road, Buffalo, NY 14214 (US). **DEMMY, Todd**; 15 Pino Verde Lane, Williamsville, NY 14221 (US).

(74) Agents: **CUTAIA, Alfonzo, I.** et al.; Hodgson Russ LLP, The Guaranty Building, 140 Pearl Street, Suite 100, Buffalo, NY 14202-4040 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: SYSTEM AND METHOD FOR ADMINISTERING LIGHT THERAPY TO CURVED AND LARGE SURFACES

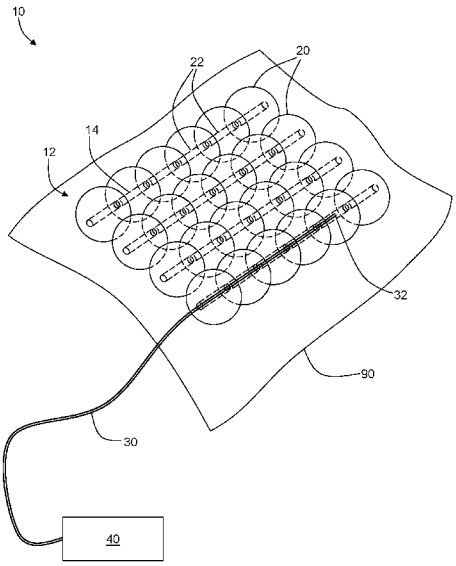

Fig. 1

(57) Abstract: A system and method are disclosed that use a flexible guide (flap) and a scanning method to control the delivery of light dose to a treatment area. This approach overcomes the non-reliable delivery of light dose with a flap that conforms to the target area. Dosimetry control can be improved through the use of a computer controlled motor to move the laser fibers at known speed over the target tissue. In some embodiments, treatment time is reduced and illumination of large surfaces is achieved by using multiple fibers to deliver the light simultaneously.

WO 2017/015676 A1

SYSTEM AND METHOD FOR ADMINISTERING LIGHT THERAPY TO CURVED AND LARGE SURFACES

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 62/196,198, filed on July 23, 2015, now pending, the disclosure of which is incorporated herein by reference.

Field of the Disclosure

[0002] The disclosure relates to administering light therapy to tissue.

Background of the Disclosure

[0003] Minimally-invasive light therapy comprises external beam illumination of the target tissue using, for example, a laser. The laser beam size determines the delivered light fluence or dose (J/cm^2). The target tissue must be illuminated at a prescribed light fluence rate and dose for an effective treatment. Typically, the light illumination is achieved by aiming the laser beam towards the target surface (treatment area). This may be practical when the treatment area is few centimeters in diameter (*e.g.*, 0.5-3 cm) and its surface is relatively flat (as in non-melanoma skin cancer, or early stage oral lesions). In treating curved and larger lesions, the therapeutic illumination is accomplished by manually moving a laser beam over the treated area. The treating physician uses a spot source to treat flat large surfaces, or a balloon (diffused light) to treat large body cavities, such as the thoracic cavity. This technique of manually scanning results in uncontrolled light dose deposition, which in turns may lead to over or under treatment. Others have attempted to address this issue by using woven layers of optical fibers for dose delivery, utilizing motion tracking devices to track the dose administered by a physician, or robotic scans to administer the light dose. These solutions are expensive, cumbersome, and/or do not adequately control the delivery of the light dose.

Brief Summary of the Disclosure

[0004] A system and method are disclosed that use a flexible guide (flap) and a scanning method to control the delivery of light dose to a treatment area. This approach overcomes the non-reliable delivery of light dose with a flap that conforms to the target area. Dosimetry control can be improved through the use of a computer controlled motor to move the laser fibers at known speed over the target tissue. In some embodiments, treatment time is reduced and

illumination of large surfaces is achieved by using multiple fibers to deliver the light simultaneously. In such embodiments, software can be used to synchronize fiber movements through the flap. Control of the light delivery is improved by using detection fibers and/or imaging, to monitor the light fluence rate and fluence distribution during treatment.

Description of the Drawings

[0005] For a fuller understanding of the nature and objects of the disclosure, reference should be made to the following detailed description taken in conjunction with the accompanying drawings, in which:

Figure 1 is a diagram of a system according to an embodiment of the present disclosure;

Figure 2A shows a guide and two treatment fibers disposed in a model of a chest cavity;

Figure 2B shows the guide of Figure 2A with light emitted from the treatment fibers;

Figure 3A shows light emitted from a treatment fiber and diffused through spheres of a guide; and

Figure 3B depicts the intensity of light in Figure 3A;

Figure 4A shows light emitted from a flap that is fed with two 3 cm cylindrical diffusers emitting 630 nm at 400 mW/cm;

Figure 4B depicts the intensity of light in Figure 4A;

Figure 5 depicts a test configuration wherein a flap is disposed between two layers of phantom and a 96 well plate is disposed on a side of one of the phantom layers opposite the side of the flap;

Figure 6 are graphs showing test results of the configuration of Figure 5;

Figure 7 is a graph showing the result of in vivo testing in the chest of an adult pig, showing the achievement of relatively uniform light distribution;

Figure 8 shows a test detection area using 8 fibers in a 4x5 cm area;

Figure 9 shows the test configuration of Figure 8 in a flap, shown under test;

Figure 10 shows a comparison configuration using a balloon, shown under test;

Figure 11 shows the flap configuration of Figure 9 with gold foil;

Figure 12 shows the flap configuration of Figure 9 without gold foil;

Figure 13 is a table showing the results of flap and balloon in comparison tests; and

Figure 14 is a chart depicting a method according to an embodiment of the present disclosure.

Detailed Description of the Disclosure

[0006] The present disclosure uses a template (flap) to guide treatment fibers with diffused working end (for emitting light) through channels that are at known distance from the target tissue. This approach allows:

(1) Improved light dosimetry to the target tissue. Since the distance from the treated surfaces is known and constant, the light dose can be adjusted by delivering more power through the laser fibers, by changing the scanning speed of the fibers, and/or by using multiple fibers.

(2) Light therapy delivered with multiple wavelengths.

(3) Incorporation of diagnosis.

(4) Use of thermal and non-thermal therapies, simultaneously or sequentially.

(5) Increased flexibility of the system compared to alternatives in the market or research.

[0007] In the present approach, a treatment fiber is either pulled or pushed through a channel within the flap, which parallel to the target lesion. The light dose is directly proportional to the rate of fiber movement, which can be controlled by a microprocessor. Well-defined light delivery can be accomplished by, for example, using multiple fibers in several channels or by moving one or more fibers from one channel to another.

[0008] Systems of the present disclosure advantageously allow: (1) Improved accuracy and repeatability of the light delivery to curved and large surfaces (such as, for example, the thoracic cavity); (2) improved control of light dose; (3) treatment of specific regions while sparing others; (4) automation; (5) reduced treatment time; and (6) cost effective and simple treament.

[0009] With reference to Figure 1, in one aspect, the present disclosure is embodied a system **10** for light therapy of a tissue surface **90** (although reference is made herein to treatment of a surface, it should be noted that such treatments may also penetrate to some depth of the tissue beneath the surface). The system **10** comprises a guide **12** that articulates to conform to the surface **90** being treated (the guide is sometimes referred to herein as a "flap"). The guide **12** includes one or more channels **14** having a length. The guide **12** is configured such that, when the guide **12** is conformed to the surface **90**, the channels **14** are substantially a same distance from the surface **90** over the length of the channel **14**.

[0010] In the exemplary embodiment depicted in Figure 1, the guide **12** is made up of a plurality of spheres **20** arranged in a two-dimensional matrix. Each sphere **20** has a passage **22** disposed therethrough. The plurality of spheres **20** are disposed in one or more rows such that the passages **22** of each sphere **20** of a row are aligned to form a channel **14**. When such a matrix is used, the guide **12** conforms to the surface such that all or substantially all (e.g., more than 80%, 90%, etc.) of the spheres **20** are in contact with the tissue. In this way, in an embodiment where the spheres **20** are 1 cm in diameter, the center of the channel **14** will be 0.5 cm from the tissue along the length of the channel **14**.

[0011] The spheres **20** may be transparent or translucent. The spheres **20** may be made from, for example, silicone rubber, plastic, or other materials. In some embodiments, the spheres **20** may have some treatment—such as, for example, a surface treatment, embedded material, etc.—configured to diffuse light. In this way, light from a small light source within the channel, will be diffused to some extent. Such diffusion can be advantageous in delivering light therapy. Figures 3A and 3B show light diffusion from a fiber located in the channel of an exemplary sphere-based guide. It can be seen that the light emanating from a small source has been diffused by the spheres. In some embodiments, the system **10** may comprise a diffusing sheet configured to diffuse the light from the guide **12**. Such a diffusing sheet may be disposed between the guide **12** and the tissue surface **90** to further diffuse the light. In some embodiments, a diffusing sheet is placed on the opposite side of the guide **12** as the tissue. In this way, light can be reflected back to the tissue. In other embodiments, one or more sheets may be placed such that tissue regions are protected from exposure to light. In such embodiments, a sheet can be used in the form of a mask. Various combinations of sheets can be used. Sheet material can be selected based on the desired function (e.g., light blocking, light diffusing, light reflecting, etc.)

[0012] The system **10** further comprises a treatment fiber **30** having a working end **32** for emitting light. The working fiber **30** is, for example, a light-transmitting fiber with a ball end where light is emitted at the working end **32**. The treatment fiber **30** is configured to be disposed in the channel **14**. For example, the channel **14** may have a diameter of 0.5 mm, and the treatment fiber **30** may have a diameter of 0.98 mm over at least a length of the treatment fiber **30** which is configured to be disposed in the channel **14**. In some embodiments, more than one treatment fiber **30** is used. For example, 2, 3, 4, or more treatment fibers **30** may be used simultaneously, each treatment fiber **30** being disposed in another of the channels **14** of guide **12**. Figures 2A show an exemplary mat placed in a model rib cage of a human and having two

treatment fibers disposed within two of the channels. In figure 2B, the working ends of the fiber are shown emitting light.

[0013] A therapeutic light source **40** is in light-transmitting communication with the working end **32** of the treatment fiber **30**. Where more than one fiber **30** is used, each fiber **30** may be connected to a separate source **40** or two or more of the fibers **30** may be connected with a single source **40**. The source **40** may be, for example, a laser. In other embodiments, the source **40** is a broadband light source which may be unfiltered or filtered to transmit one or more wavelengths of light. It should be noted that a reference to one wavelength of light should be interpreted in view of known practical limits of light transmission, and should be interpreted to mean a narrow band of wavelengths surrounding the single wavelength.

[0014] Through the use of a guide **12** with channels **14**, the working end **32** of the treatment fiber **30** may be moved back and forth within the channel **14** during therapy. In this way, the surface **90** beneath and around a channel **14** will be exposed to light emanating from the working end **32** within that channel **14**, and light can be more uniform because movement of the fiber **30** is constrained to a single degree of freedom—*i.e.*, back and forth within the channel **14**. The doseage is provided according to the speed of movement of the working end **32** (*i.e.*, the time of exposure of a particular portion of the surface) and the intensity of the light.

[0015] In some embodiments, the light source **40** is controlled by a microcontroller such that the intensity can be varied. The light may be varied in accordance with the location of the working end **32** within the channel **14**. In some embodiments, the light is varied according to doseage measured by sensors on the surface. The microcontroller may be programmed to vary the light for any other reasons that will be apparent in light of the present disclosure.

[0016] In some embodiments, the system **10** further comprises an armature or other mover for moving the working end **32** within the channel **14**. In this way, the fiber **30** may be moved by the mover and not be manual operation by a physician or other user. The mover may also be controlled by a microcontroller (which may be the same microcontroller as described above or a different microcontroller). The mover may alter the speed at which the fibers are moved and/or the total duration of treatment time to accomplish the desired therapeutic light dose. In this way, the system **10** may be automated such that once placed into position, control by a physician is not necessary for its continued operation.

[0017] In some embodiments, measurement of the dosage is achieved using a measurement fiber (dosimetry fiber) which can be disposed in the same channel **14** as the treatment fiber **30** or a different channel **14**. More than one dosimetry fiber can be used and the dosimetry fibers can be moved or can be motionless within the channels. Information measured through the use of such fibers can be provided as feedback to the microcontroller such that the light intensity, motion of the treatment fibers **30**, and/or treatment time can be altered accordingly.

[0018] In another aspect of the present disclosure (for example, shown in Figure 14), a method **100** for light therapy of a tissue is provided. The method **100** comprises placing **103** an articulating guide onto the surface such that the guide conforms to the surface. The guide may be configured as in any of the embodiments described above. In some embodiments, the method **100** includes securing **121** the guide onto the surface. For example, the guide may be sutured to the tissue.

[0019] A treatment fiber is inserted **106** into a channel of the guide until a working end of the treatment fiber reaches a first location of the channel. The method **100** comprises causing **109** light to be emitted from the working end of the fiber. For example, a light source connected to the fiber may be energized such that light is transmitted through the fiber (through the axial length of the fiber) and emitted from the working end. The fiber is moved **112** such that the working end of the fiber reaches a second location within the channel.

[0020] In some embodiments, more than one treatment fibers are inserted **106** into channels of the guide. For example, two treatment fibers may be inserted **106**, each fiber being inserted into a separate channel of the guide. Each of the treatment fibers may be moved **112** together with the other treatment fibers (*i.e.*, coordinated) or one or more of the fibers may be moved **112** independently of the other fiber(s).

[0021] The inserted **106** fiber may be moved back and forth within the channel from the first location to the second location (and or other locations) until a sufficient light dose has been received by the surface. As such, the method **100** may comprise measuring **115** a light dose of a location of the tissue surface. Such measurement may be made by, for example, sensors on the surface, a dosimetry fiber inserted **118** into a channel of the guide, or in other ways known for making such dosimetry measurements.

[0022] The fiber may be moved until a desired dosage (*e.g.*, a predetermined dosage) is reached for the tissue at each of one or more locations of the surface. The fiber may then be removed and/or the light emission is ceased.

EXEMPLARY EMBODIMENTS

[0023] In a test configuration shown in Figure 5, Lewis Lung Carcinoma (LLC) cells were seeded into 96-well culture dishes. When cells reached approximately 95% confluence Photofrin was added at 0, 1, 2, 3, 10, and 30 μg/mL. Cells were incubated at 37 °C in the dark for ~24 hours. Media was removed and fresh media added. Immediately after the dishes were positioned over the center of the PDT surface applicator with a layer of ballistic gel tissue phantom between the flap and the culture dish. Two 3 cm long diffusing fibers were placed 6 cm apart in the flap. LLC cells were exposed topo 1.5 J/cm^2 630 nm light from a laser diode. PDT effect was determined 24 hours later using an MTT assay. Results are shown in Figure 6.

[0024] Tests comparing the presently-disclosed flap device with a balloon device were performed using air, water, or 0.01% intralipid media. The tests incorporated a 4x5 cm detection area, IP-85 probes between 2 gel layers, and 400 mW of light at a wavelength 652 nm. Figure 8 shows 8 fibers used in the 4x5 cm area with 3 fibers along two edges and 2 fibers in the middle. A 10x10 cm flap was used with 1-4 cylindrical fibers (see Figure 9). The flap was tested with gold foil (Figure 11) and without (Figure 12). In comparison, a 3 cm balloon was used with a single cylindrical fiber delivering a total of 400 mW (Figure 10). The scans were performed at 1 mm/s, with 0.05 mm steps, at 0.3 cm from the phantom surface. Data was acquired over 50 seconds. Results for both configurations are shown in Figure 13.

[0025] Although the present disclosure has been described with respect to one or more particular embodiments, it will be understood that other embodiments of the present disclosure may be made without departing from the spirit and scope of the present disclosure. Hence, the present disclosure is deemed limited only by the appended claims and the reasonable interpretation thereof.

We claim:

1. A method for light therapy of a tissue surface, comprising:
placing an articulating guide onto the surface such that the guide conforms to the surface;
inserting a treatment fiber into a channel of the guide until a working end of the treatment fiber reaches a first location of the channel;
causing light to emit from the working end of the treatment fiber; and
moving the treatment fiber in the channel until the working end of the treatment fiber reaches a second location.

2. The method of claim 1, wherein more than one treatment fiber is inserted, each treatment fiber being inserted into a corresponding channel of the guide.

3. The method of claim 2, wherein each treatment fiber is moved together with the other treatment fibers.

4. The method of claim 2, wherein at least one of the treatment fibers is moved independently of the another treatment fiber.

5. The method of claim 1, wherein the treatment fiber is alternately moved between the second position and the first position until a sufficient light dose has been received by the surface.

6. The method of claim 1, further comprising measuring a light dose of a location of the surface.

7. The method of claim 6, further comprising inserting a dosimetry fiber into the channel of the guide.

8. The method of claim 1, further comprising securing the guide onto the surface.

9. The method of claim 8, wherein the guide is secured to the surface by way of suturing.

10. The method of claim 1, wherein the treatment fiber is moved at a speed corresponding to a desired light dosage rate.

11. The method of claim 1, further comprising varying the intensity of light.

12. The method of claim 1, wherein the emitted light comprises more than one wavelength.

13. A system for light therapy of a tissue surface, comprising:

an articulating guide having a channel having a length, the guide configured to conform to the surface such that the channel is substantially a same distance from the surface over the length of the channel;

a treatment fiber having a working end for emitting light, the treatment fiber configured to be at least partially disposed in the channel; and

a light source in light-transmitting communication with the working end of the treatment fiber.

14. The system of claim 13, wherein the guide comprises a matrix of spheres having a passage therethrough, the spheres disposed in rows, wherein the passages of each sphere of a row are aligned to form a channel.

15. The system of claim 14, wherein the spheres are translucent.

16. The system of claim 15, wherein the spheres are made from silicone rubber.

17. The system of claim 14, wherein the spheres are 1 cm in diameter.

18. The system of claim 14, wherein the passages of each sphere are pass through a diameter of the sphere.

19. The system of claim 13, further comprising a sheet disposed between the guide and the surface.

20. The system of claim 13, wherein a sheet is disposed on a side of the guide opposite the tissue surface.

21. The system of claim 13, further comprising a microprocessor in operable communication with the light source and configured to control the intensity of the light source.

22. The system of claim 13, further comprising an armature configured to move the treatment fiber within the channel.

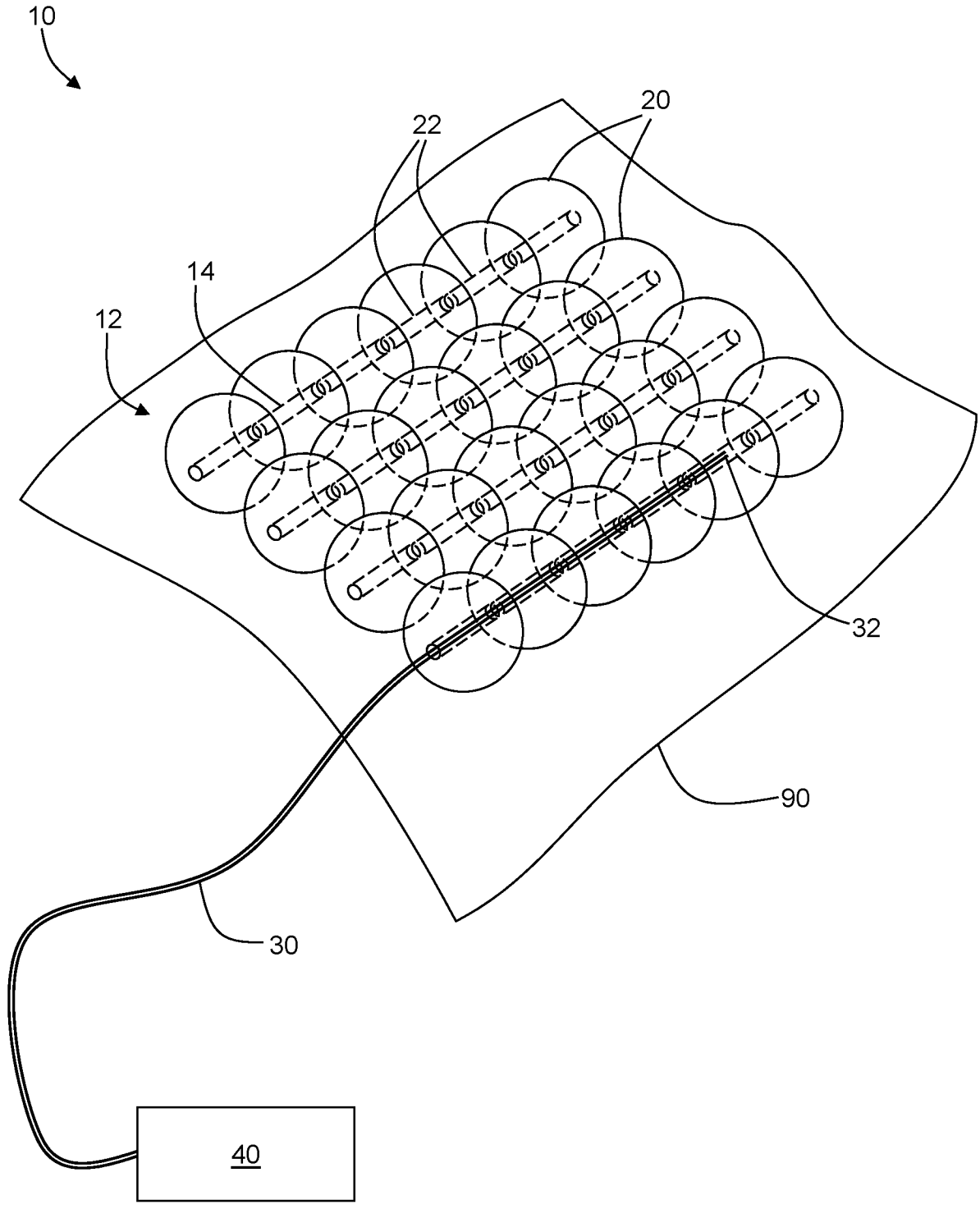

Fig. 1

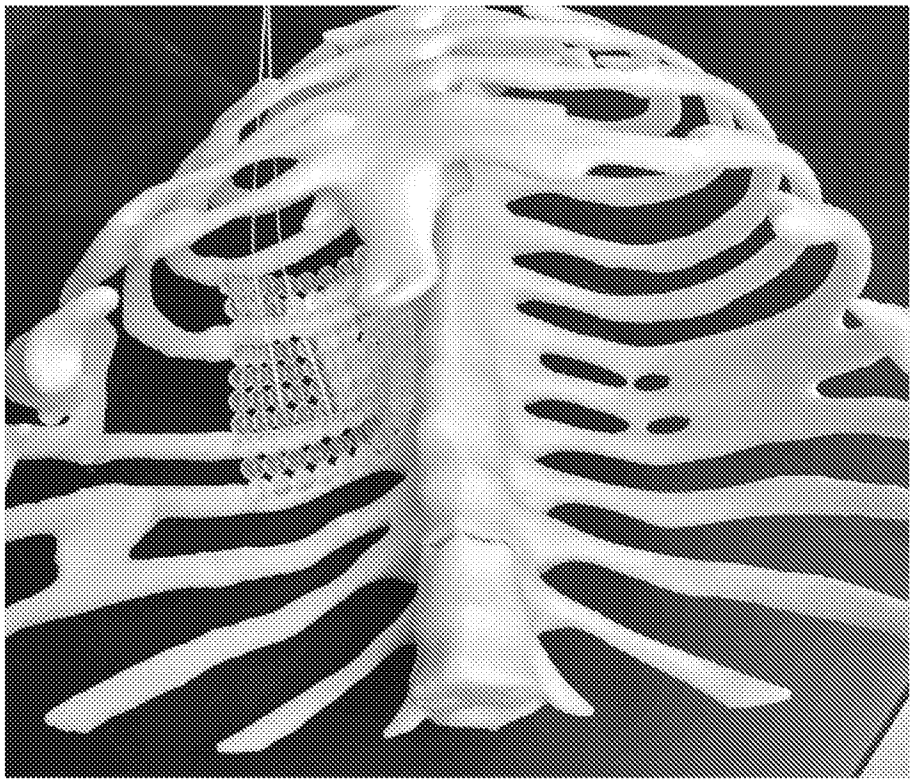

Fig. 2A

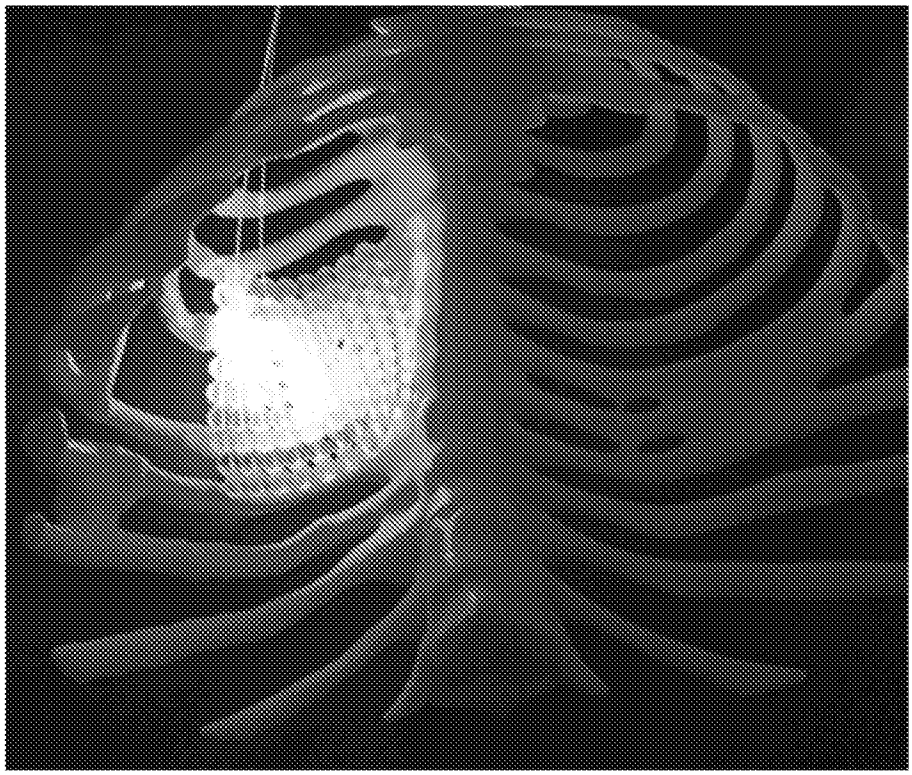

Fig. 2B

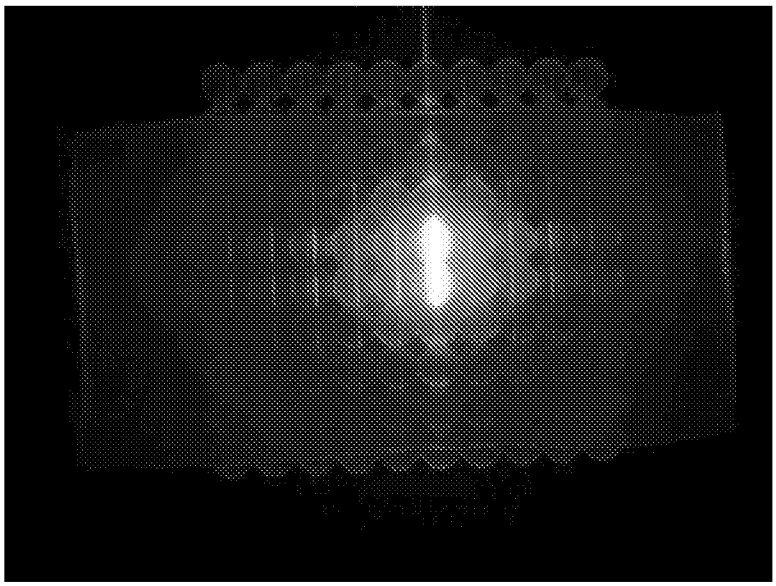

Fig. 3A

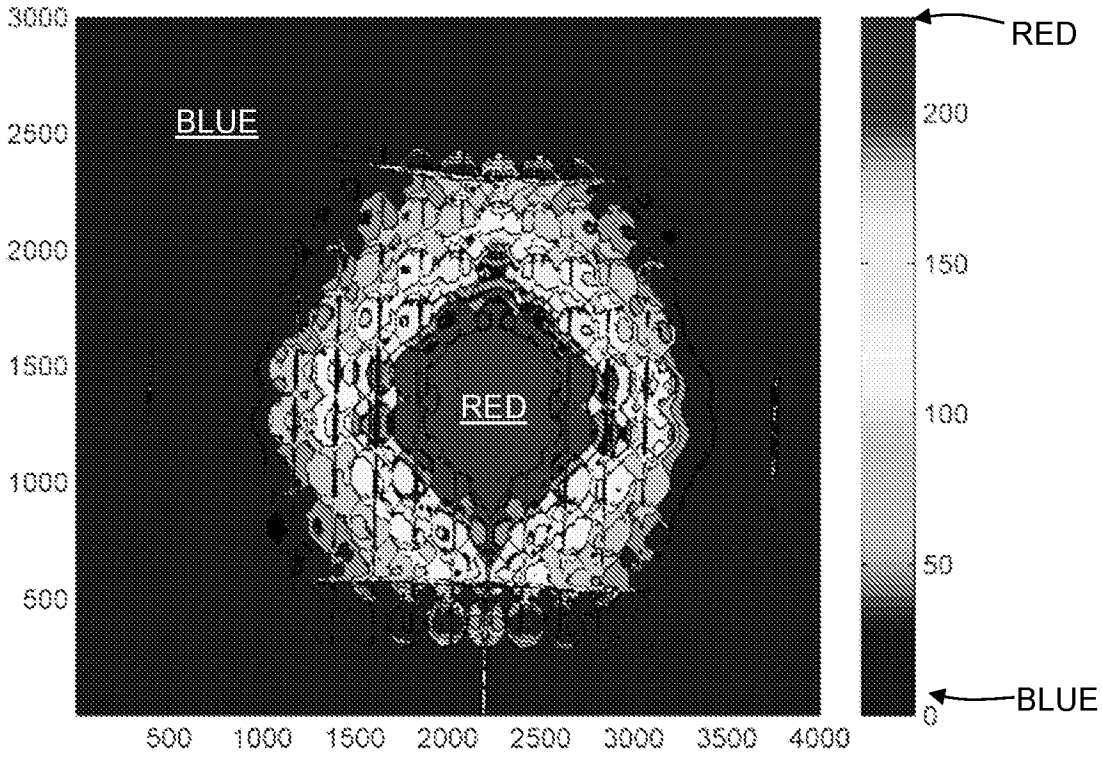
3000
2500
2000
1500
1000
500
BLUE
RED
500
1000
1500
2000
2500
3000
3500
4000
RED
200
150
100
50
0
BLUE

Fig. 3B

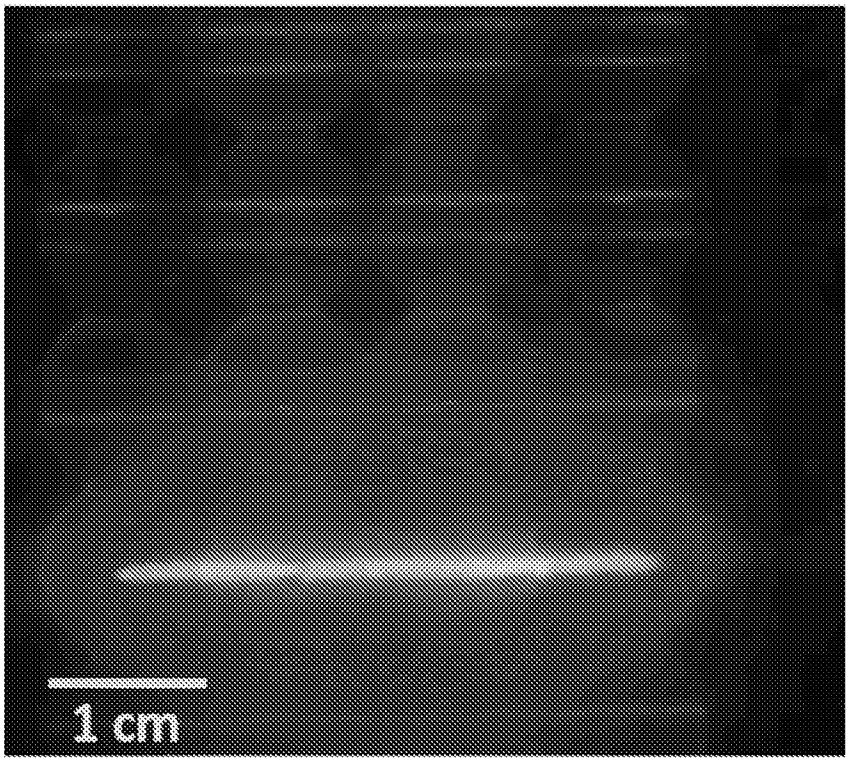

Fig. 4A

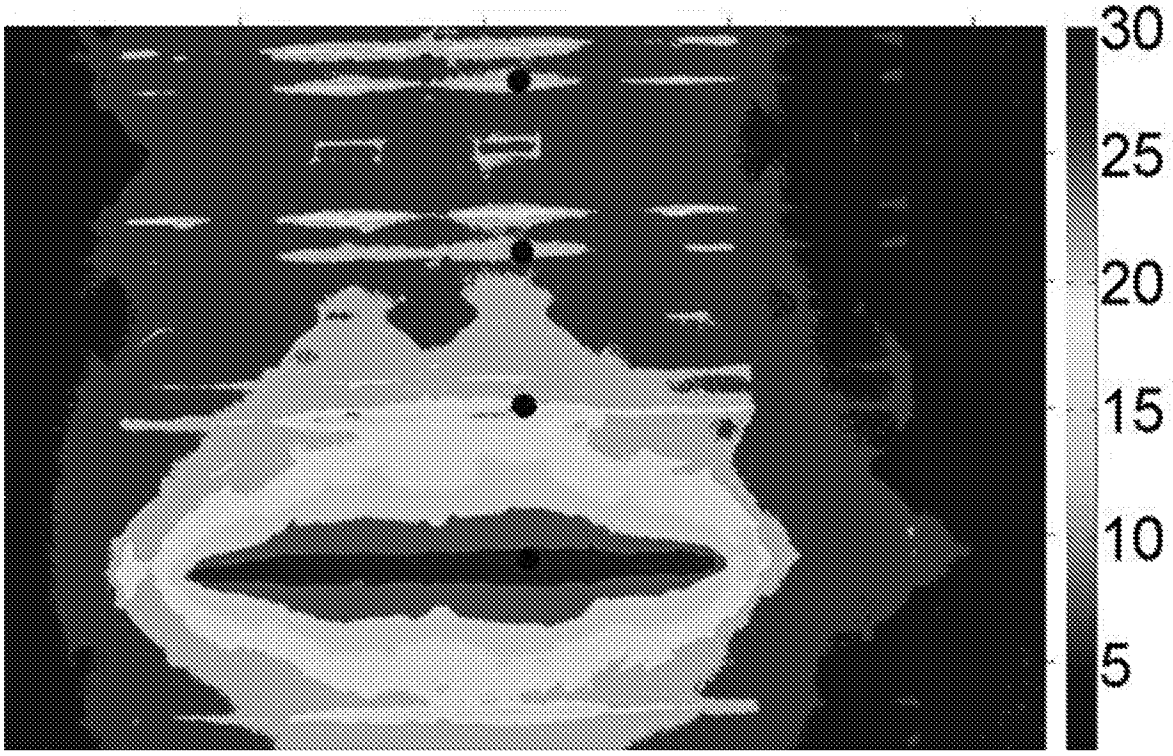

Fig. 4B

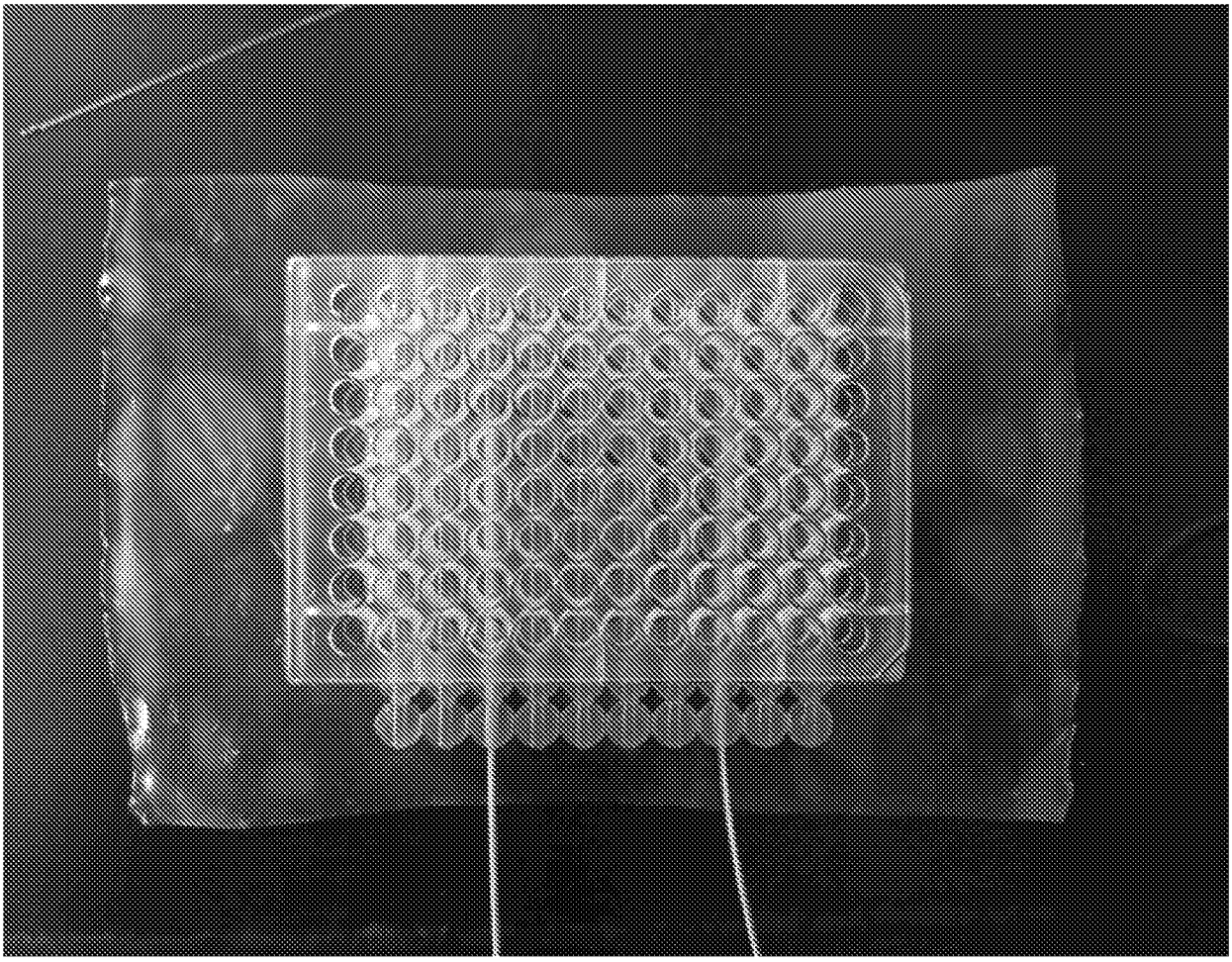

Fig. 5

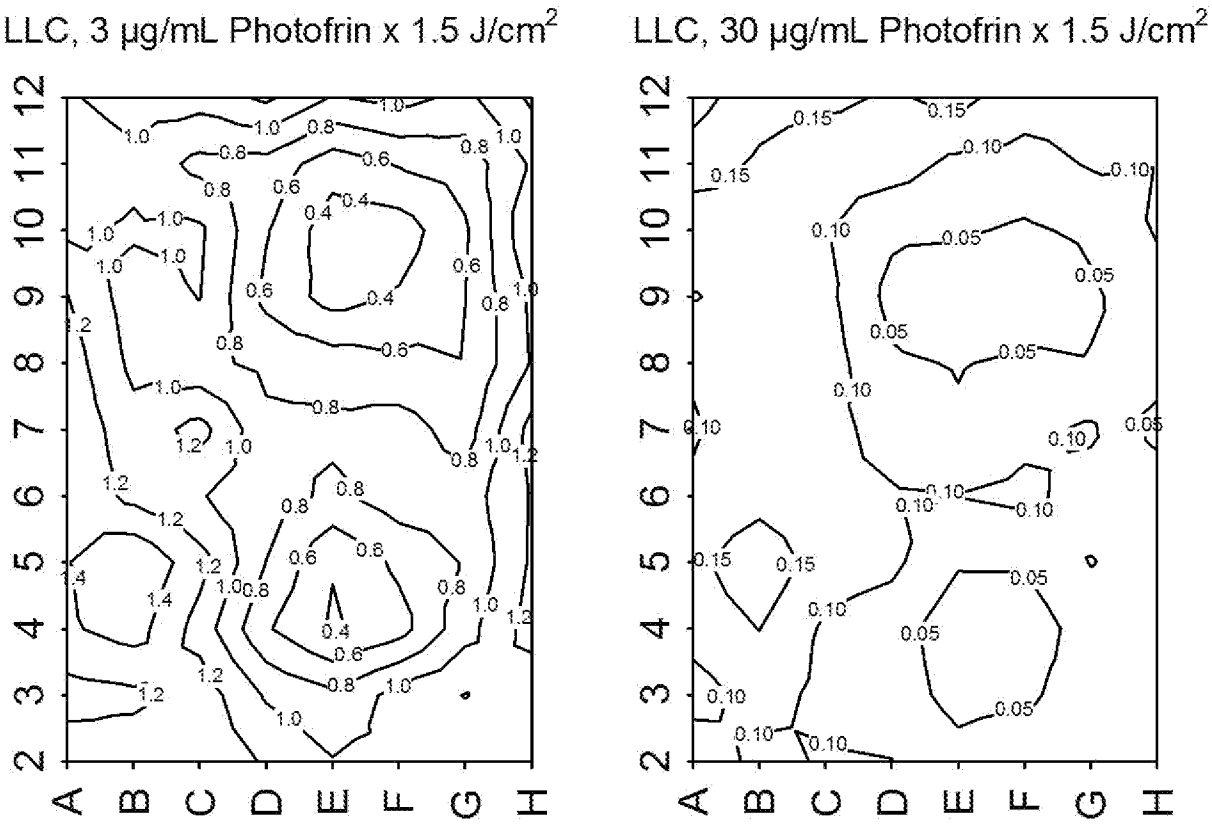
LLC, 3 µg/mL Photofrin x 1.5 J/cm2
LLC, 30 µg/mL Photofrin x 1.5 J/cm2
A B C D E F G H
2 3 4 5 6 7 8 9 10 11 12

Fig. 6

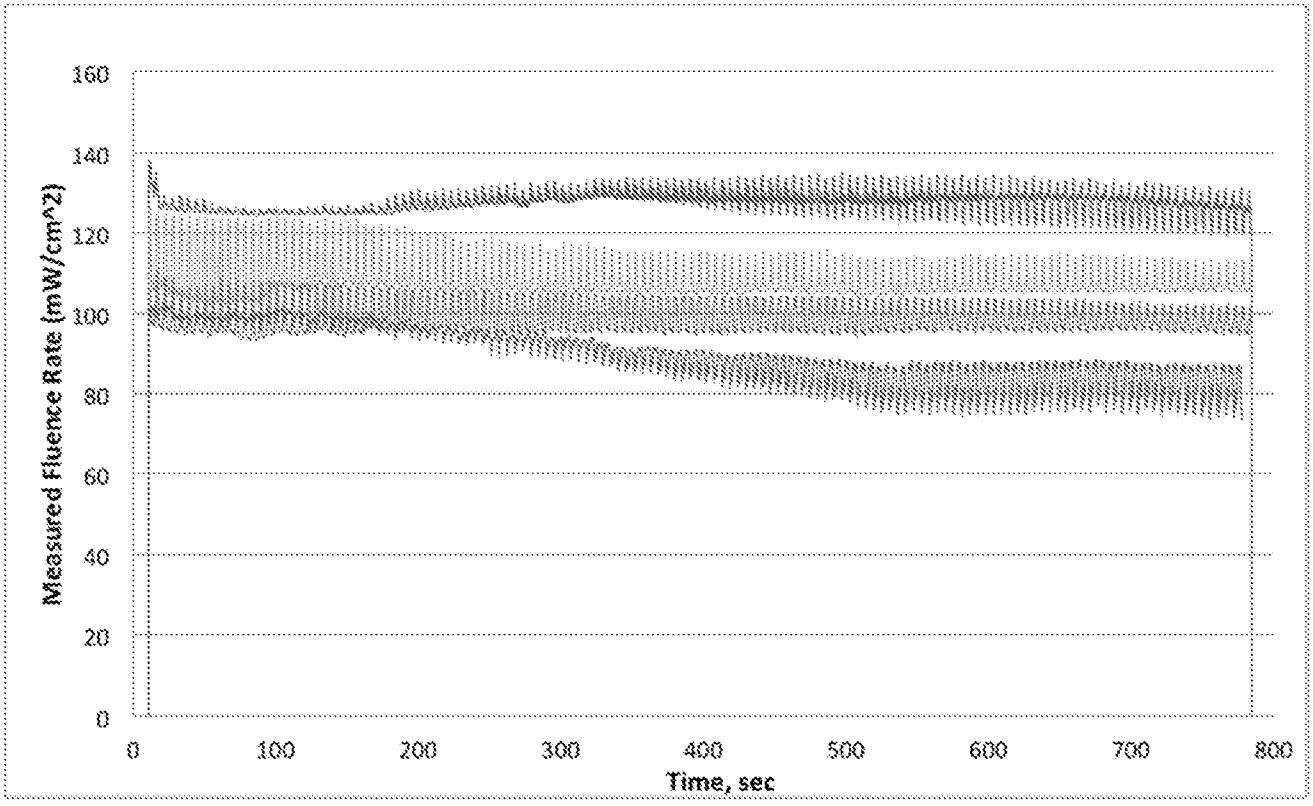
Measured Fluence Rate (mW/cm^2)
Time, sec
0 20 40 60 80 100 120 140 160
0 100 200 300 400 500 600 700 800

Fig. 7

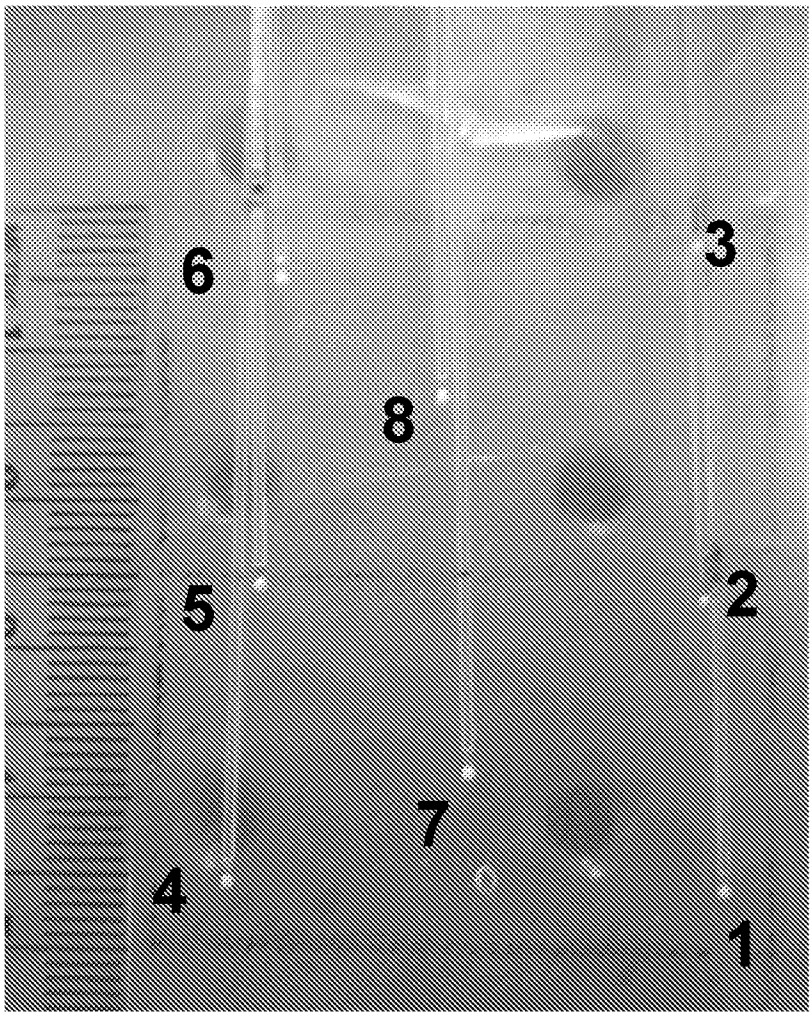

Fig. 8

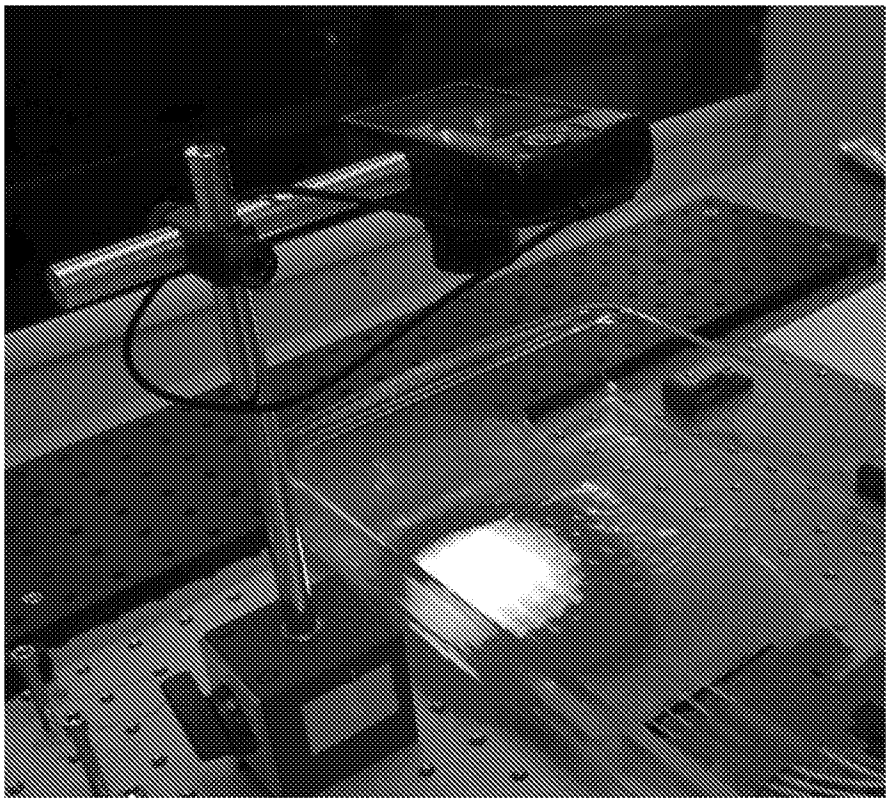

Fig. 9

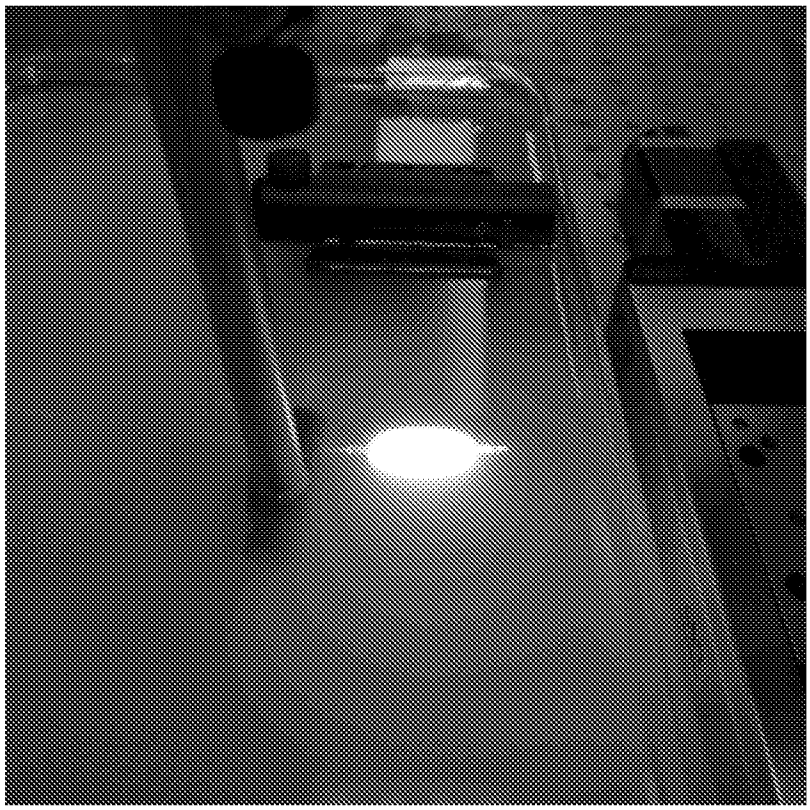

Fig. 10

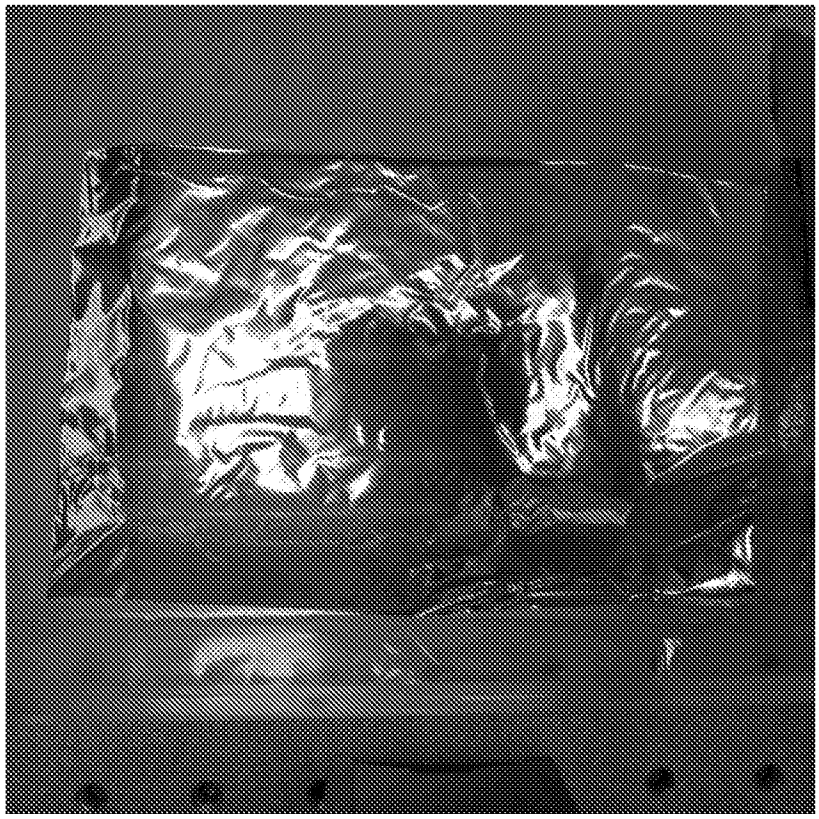

Fig. 11

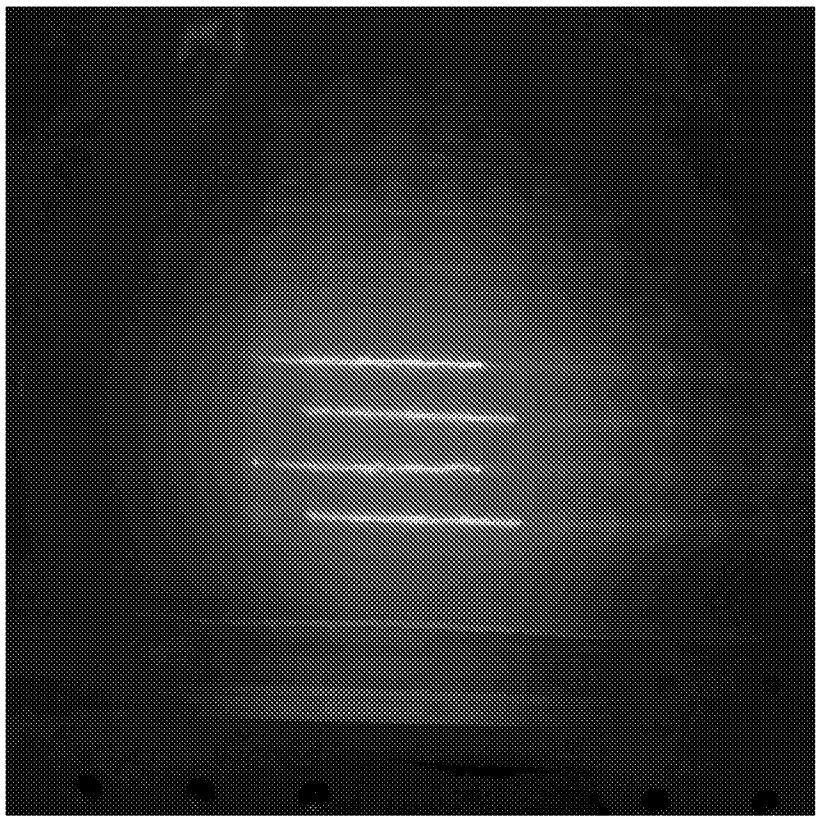

Fig. 12

Flap Configuration

	AIR mW/cm^2	WATER mW/cm^2	0.01% Lip. mW/cm^2
1 diffuser in middle	6.10	4.52	3.76
2 diffusers in middle	5.74	4.19	3.97
4 diffusers	5.46	3.87	3.97
1 diff. in middle & Gold Foil	8.29	6.32	6.46
2 diff. in middle & Gold Foil	9.17	6.38	6.88
4 diffusers & Gold Foil	9.30	6.73	7.16

Balloon Configuration

	AIR mW/cm^2	WATER mW/cm^2	0.01% Lip. mW/cm^2
3 mm above surface	3.14	2.76	3.12

Fig. 13

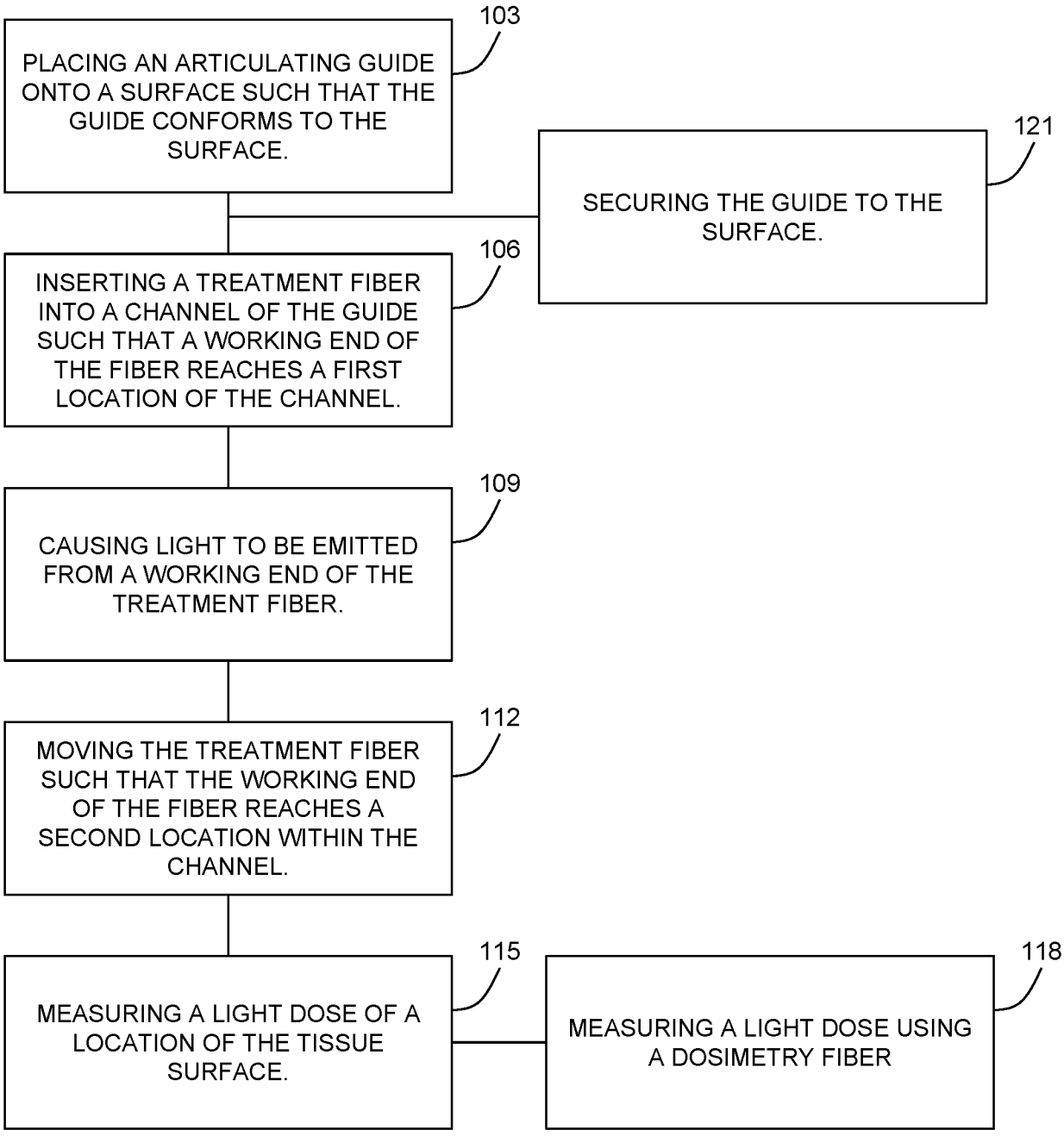
103
PLACING AN ARTICULATING GUIDE ONTO A SURFACE SUCH THAT THE GUIDE CONFORMS TO THE SURFACE.
121
SECURING THE GUIDE TO THE SURFACE.
106
INSERTING A TREATMENT FIBER INTO A CHANNEL OF THE GUIDE SUCH THAT A WORKING END OF THE FIBER REACHES A FIRST LOCATION OF THE CHANNEL.
109
CAUSING LIGHT TO BE EMITTED FROM A WORKING END OF THE TREATMENT FIBER.
112
MOVING THE TREATMENT FIBER SUCH THAT THE WORKING END OF THE FIBER REACHES A SECOND LOCATION WITHIN THE CHANNEL.
115
MEASURING A LIGHT DOSE OF A LOCATION OF THE TISSUE SURFACE.
118
MEASURING A LIGHT DOSE USING A DOSIMETRY FIBER

Fig. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/043957

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 5/06; A61B 18/00; A61B 18/20; A61B 18/22; A61N 5/00 (2016.01)
CPC - A61N 5/06; A61B 18/20; A61B 18/22; A61B 18/201; A61N 5/0601; A61N 5/062 (2016.08)
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)
IPC - A61B 18/00; A61B 18/20; A61B 18/22; A61N 5/00; A61N 5/06
CPC - A61B 18/00; A61B 18/20; A61B 18/22; A61B 18/201; A61N 5/00; A61N 5/06; A61N 5/0601; A61N 5/062; A61N 5/0622

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 604/20; 604/21; 606/11; 607/88; 607/89 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar, ProQuest.
Search terms used: light, therapy, tissue, channel, guide, fiber, move, position, sphere, control, conform.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2007/0032845 A1 (NEUBERGER) 08 February 2007 (08.02.2007) entire document	1-3, 8, 13, 19, 20 — 4-7, 9-12, 14-18, 21, 22
Y	US 2006/0111762 A1 (STERENBORG et al) 25 May 2006 (25.05.2006) entire document	4-7, 10
Y	US 2015/0057724 A1 (KONINKLIJKE PHILIPS N.V.,) 26 February 2015 (26.02.2015) entire document	7, 11, 12
Y	US 5,766,234 A (CHEN et al) 16 June 1998 (16.06.1998) entire document	9
Y	US 5,212,749 A (HUGGINS et al) 18 May 1993 (18.05.1993) entire document	14-18
Y	US 2006/0173514 A1 (BIEL et al) 03 August 2006 (03.08.2006) entire document	21
Y	US 2011/0144503 A1 (DEBRECZENY et al) 16 June 2011 (16.06.2011) entire document	22
A	US 2014/0188035 A1 (ABBOTT CARDIOVASCULAR SYSTEM, INC.) 03 July 2014 (03.07.2014) entire document	1-22
A	US 5,997,569 A (CHEN et al) 07 December 1999 (07.12.1999) entire document	1-22
A	US 2008/0082091 A1 (RUBTSOV et al) 03 April 2008 (03.04.2008) entire document	1-22
A	US 2013/0144364 A1 (WAGENAAR CACCIOLA et al) 06 June 2013 (06.06.2013) entire document	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2016	06 OCT 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774